Head and neck cancer
An update

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Recent changes in the area of head and neck cancer include an increase in cases in young nonsmoking, nonalcohol-drinking patients caused by human papillomavirus infection, new diagnostic modalities, such as PET scanning, and new treatments, such as transoral laser and robotic surgery, intensity modulated radiation therapy and targeted molecular therapy.

The term head and neck cancer describes a wide range of malignancies that arise from the mucosa of the upper aerodigestive tract and salivary glands, as well as the skin and lymphatic system of the head and neck region (Figures 1a and b). Around 4000 people in Australia are diagnosed with head and neck cancer each year (70% men and 30% women). Head and neck mucosal squamous cell carcinoma (HANMSCC) arises from the squamous mucosal cells that line the upper aerodigestive tract and accounts for around 90% of head and neck cancers. It is the focus of this article.

Exposure to carcinogens such as tobacco smoke and alcohol are well known risk factors for HANMSCC. However, research over the past decade has strongly implicated human papillomavirus (HPV) as a major causative agent in oropharyngeal (tonsil and tongue base) carcinoma. Epidemiological studies in Western countries have shown that there has been a gradually decreasing incidence of laryngeal and hypopharyngeal cancer, almost certainly attributable to reducing smoking rates, simultaneous with a rising incidence of HPV-related oropharyngeal cancers.

Treatment decisions in HANMSCC are often complex and involve input from multiple specialists, such as medical and radiation oncologists, head and neck surgeons, plastic surgeons and oral and maxillofacial surgeons.

GPs are responsible for detecting most head and neck cancers in patients in the community and play a crucial role in co-ordinating their treatment.

Key points
- Around 4000 people are diagnosed with head and neck cancer each year in Australia.
- Well-known risk factors include smoking and excess alcohol use; human papillomavirus infection has now been identified as the major risk factor for oropharyngeal cancer.
- Early diagnosis and treatment improve outcomes; GPs play a crucial role in detecting most head and neck cancers in patients in the community.
- Persistent upper aerodigestive tract symptoms, a nonhealing ulcer in the oral cavity or a persistent neck lump warrant further investigation and patient referral to an ENT, head and neck surgeon.
- Treatment is often complex, and patients are best evaluated in multidisciplinary head and neck clinics, located in most major teaching hospitals.

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investigation, treatment and long-term follow up.

**WHAT ARE THE RISK FACTORS?**

Smoking and excessive alcohol consumption are the major risk factors for HANMSCC. Chronic exposure of the mucosa of the upper aerodigestive tract to chemical carcinogens such as tobacco smoke and alcohol results in the accumulation of genetic alterations within epithelial cells. This leads to progressive phenotypic changes, ranging from hyperplasia to various degrees of dysplasia and eventually invasive squamous cell carcinoma (SCC).

The term ‘field cancerisation’ refers to the widespread genetic change that results from ongoing carcinogen exposure. This change creates a molecularly altered preneoplastic field in the epithelium of the aerodigestive tract, from which multiple tumours may develop. Early intervention to address risk factors may halt the progression and accumulation of genetic aberrations before the mucosa becomes ‘condemned’.

**Tobacco smoking**

Tobacco smoking is the most important aetiological factor in HANMSCC. More than 80% of all head and neck cancers occur in smokers. The risk of developing HANMSCC correlates with both the duration a person smokes and the quantity of tobacco they consume. Heavy smokers have up to 20 times greater risk of developing laryngeal cancer than lifetime nonsmokers.

Quitting smoking significantly reduces the risk of developing HANMSCC, and the risk of cancer declines to that of nonsmokers about 10 years after smoking cessation. Patients treated for HANMSCC who continue to smoke have reduced survival rates compared with those who quit smoking.

**Alcohol consumption**

Alcohol consumption is the second most important risk factor for HANMSCC. Consumption of 50 grams of alcohol per day (approximately three standard drinks) results in a two to three times greater risk of developing HANMSCC compared with nondrinkers.

Smoking and drinking are synergistic risk factors so that people who smoke and drink heavily have a significantly higher risk of developing HANMSCC than those who either just smoke or just drink heavily. For heavy drinkers who are also heavy smokers, the risk of oral cancer is over 35 times that of people who neither smoke nor drink; the pattern is similar for laryngeal cancer.1,2

**Epstein–Barr virus**

Epstein–Barr virus (EBV) is ubiquitous in nasopharyngeal SCC, a tumour that is endemic in Southern Chinese, Hong Kong and Korean populations. Ingested carcinogenic nitrosamines, which are commonly found in salted preserved foods, are thought to interact with EBV in genetically predisposed populations to account for this marked geographic bias.

Nasopharyngeal SCC is unrelated to smoking and drinking and generally affects a younger population than cancer at other head and neck subsites.
Human papillomavirus
HPV, mainly HPV type 16 and to a lesser extent type 18, is a newly identified cause of HANMSCC. It is mainly associated with oropharyngeal (tonsil and tongue base) cancers. HPV cancers occur more frequently in younger patients who are nonsmokers and nonalcohol drinkers.

The incidence of oropharyngeal cancer, particularly tonsil cancer, is rising steadily, which is almost certainly due to the increasing prevalence of HPV infection thought to be linked to changes in sexual practices. The incidence of HPV-associated oropharyngeal cancers is four times higher among men than among women, and higher among young adults and people with a higher lifetime number of sex partners (vaginal and oral). HPV infection is the most commonly transferred sexual infection. In most people the virus is cleared by the immune system in less than two years. It is not known why HPV persists in the throat in a small proportion of patients, resulting in an increased risk of oropharyngeal cancer. There is no approved HPV test to determine whether a patient has HPV in their oropharynx.

HPV causes oropharyngeal cancer in a similar way to cervical cancer. The viral DNA integrates into human DNA in the nuclei of healthy epithelial cells and uses the epithelial cell machinery to produce two oncogenic proteins, E6 and E7, both of which bind to shut down the crucial suppressor proteins p53 and pRb, resulting in uncontrolled tumour cell growth. Patients with HPV-positive tumours seem to have a better prognosis than those with HPV-negative tumours irrespective of the treatment strategy used.

Other risk factors
Other risk factors for HANMSCC include the following.

- **Occupational exposure to wood dust** is a risk factor for sinonasal adenocarcinoma. Certain other industrial exposures, such as to asbestos, may be associated with an increased risk of laryngeal cancer (although this association remains controversial).
- **Chewing tobacco and betel quid** (a preparation of tobacco and betel palm seeds wrapped in a betel leaf) is a major risk factor for cancer of the oral cavity in certain South-East Asian populations.
- **Radiation exposure** to the head and neck is associated with an increased risk of salivary gland and thyroid cancers.
- **Diet** may be a risk factor. Epidemiological studies suggest that diets high in fresh fruit and vegetables are associated with a reduced risk of HANMSCC, although the relative risk of diet is difficult to quantify.
- **Sun exposure** is a risk factor for lip cancer.

### Nasal and paranasal
- Nasal obstruction
- Epistaxis
- Persistent facial pain
- Facial numbness

### Oral cavity
- Persistent pain, ulceration, induration, white or red lesion of the tongue, buccal mucosa, floor of mouth or palate (Figures 2 and 3)
- Loose teeth
- Unexplained trismus (reduced mouth opening)
- Numbness of the lip
- Difficulty chewing
- Dysphagia
- Neck lump

### Posterior tongue
- Persistent tongue pain
- Dysphagia, odynophagia
- Ear pain
- Neck lump

### Tonsil
- Unilateral tonsillar hypertrophy
- Ulceration
- Pain, dysphagia, odynophagia
- Ear pain
- Neck lump

### Larynx
- Hoarseness
- Stridor
- Persistent cough
- Haemoptysis
- Dysphagia

### Nasopharynx
- Persistent nasal obstruction
- Unilateral middle ear effusion
- Neck lump
- Epistaxis
- Persistent pain in the head and neck region
- Cranial nerve palsies

### Hypopharynx
- Persistent pain in the throat
- Dysphagia
- Hoarseness
- Referred ear pain
- Neck lump
vigilant in patients presenting with unexplained or persistent throat symptoms, particularly if they have significant risk factors for head and neck cancer.

The common presenting symptoms and signs for head and neck cancer at different sites are listed in Box 1. In addition, some symptoms and signs can indicate a head or neck cancer at any of a number of sites.

- **A neck lump due to cervical metastatic disease** may be the presenting sign of SCC affecting any head and neck subsite (Figure 4). It is the most common presenting sign in patients with nasopharyngeal cancer and is also common in those with oropharyngeal malignancy. HPV oropharyngeal cancers often present with cystic metastases to upper cervical lymph nodes. These cystic nodes may be misdiagnosed as benign branchial cysts on imaging studies. Hence, a high index of suspicion is required when evaluating an adult with a lateral cystic neck mass.

- **Persistent unexplained otalgia** can sometimes be referred from the larynx or pharynx. If there is no otological explanation for persistent otalgia then further investigation of the head and neck is warranted.

- **Weight loss** due to anorexia and dysphagia can also occur with any head and neck cancer and is often a sign of advanced disease.

### HOW SHOULD YOU EXAMINE THE PATIENT?

Although the oral cavity is easily amenable to office examination, other regions of the upper aerodigestive tract are difficult to examine without specialised equipment. It is therefore imperative that GPs maintain a high index of suspicion when evaluating patients with persistent throat symptoms.

- **Oral cavity**

  Oral lesions are easily identifiable using a bright light and tongue depressor, which provides excellent access to the mouth and oropharynx. Tips for examining the oral cavity are shown in Box 2.

  Mouth cancers typically present as exophytic masses or infiltrating ulcers with irregular rolled edges and sometimes a granulatizing base (Figures 2 and 3). Tonsillar cancers may present as ulceration involving the tonsillar surface or as unilateral tonsillar hypertrophy.

Leucoplakia is a descriptive clinical term for a white lesion of the oral mucosa that cannot be scraped off (unlike oral thrush). Leucoplakia results from chronic irritation of the oral mucous membranes. Common causes include smoking, alcohol and irritation from sharp teeth or ill-fitting dentures. Most leucoplakia lesions are benign, but biopsy is important to exclude dysplasia and malignancy. Dysplasia is graded as mild, moderate or severe; the degree of dysplasia helps predict the risk of future malignant transformation. The overall risk of malignant transformation for all leucoplakia lesions has been estimated as 1 to 3%.

Erythroplakia (also known as erythroplasia) refers to a persistent flat red patch or red lesion of the oral cavity. It appears as a well-circumscribed red plaque often with a soft velvety texture. Erythroplakia

### 2. TIPS FOR EXAMINING THE ORAL CAVITY

- Remove the patient’s dentures if possible
- Using a head light is always preferable
- Examination is much easier if both hands are free. One hand can grasp the tongue using a gauze swab while the other hand holds a tongue depressor. Alternatively, the index finger can be used to palpate the tongue, floor of mouth and buccal mucosa
- Be systematic. Start with the lips and move onto other areas in an ordered sequence so that all subsites of the oral cavity are examined
3. CRITERIA FOR INVESTIGATION AND REFERRAL*

- A persistent lump anywhere in the head and neck
- A persistent ulcer or discoloured lesion in the oral cavity
- Persistent unexplained mouth or throat pain
- Persistent difficulty swallowing (dysphagia) or pain on swallowing (odynophagia)
- Persistent hoarseness
- Recurrent haemoptysis
- Persistent unilateral ear pain (otalgia) with no obvious cause
- Unilateral unexplained pain in the head or neck region for more than four weeks, especially if associated with ear pain without evidence of an ear abnormality
- Recurrent unexplained blood-stained mucous expectoration (can sometimes be associated with a laryngeal or pharyngeal cancer)
- Persistent unexplained nosebleeds (warrant referral to exclude an intranasal polyp or tumour)

* Persistence of any of these for more than three to four weeks should prompt further investigation and referral to an ear, nose, throat, head and neck surgeon.

Other areas of the aerodigestive tract
Indirect laryngoscopy using a mirror allows examination of the tongue base, epiglottis and larynx. Indirect laryngoscopy has been replaced by modern endoscopy, which can be performed using a small flexible endoscope that is generally inserted through the nose under topical anaesthesia. Nasoendoscopy is quick and provides state of the art visualisation of the nasal cavity, postnasal space and the entire upper aerodigestive tract. It also allows excellent functional assessment of the vocal cords.

External neck
It is important to always examine both sides of the neck when evaluating a patient with possible head and neck cancer. Transient upper cervical lymphadenopathy in children and young adults is commonly associated with an upper respiratory tract infection, such as acute tonsillitis or a viral illness. The presence of a neck lump in an adult with no obvious inflammatory cause should alert the GP to the possibility of cancer. A persistent neck lump in an adult warrants further investigation to exclude cancer.1

Most head and neck tumours follow predictable lymphatic drainage pathways, with oral cancers tending to spread to submental and submandibular nodes, and laryngeal and lower pharyngeal cancers tending to spread to lymph nodes along the internal jugular vein, which are felt along the course of the sternocleidomastoid muscle. Nasopharyngeal cancers may also metastasise to the posterior triangle nodes, which are located behind the sternomastoid muscle.

An enlarged lymph node in the supraclavicular fossa should raise the possibility of a primary tumour site below the clavicles. Breast, lung, stomach, kidney and prostate cancer should be considered when the patient presents with an enlarged supraclavicular node. Similarly, thyroid cancers often metastasise to lower cervical nodes.

When is referral to a surgeon necessary?
Signs and symptoms that should prompt referral to an ear, nose, throat (ENT), head and neck surgeon are listed in Box 3. As a general rule, persistence of any of these signs or symptoms for more than three to four weeks should prompt further investigation and referral.

What investigations are used?
When head and neck cancer is suspected, investigations are required to:
- identify the primary tumour
- evaluate its relationship to surrounding structures
- evaluate the degree of cervical lymph node involvement
- exclude the presence of distant metastatic lung disease prior to commencement of curative therapy.

Biopsy
Primary tumour biopsy
Biopsy of the primary tumour can be performed under local anaesthetic for lesions in the oral cavity and tonsil region. Patients with lesions in most other locations require a general anaesthetic for tumour biopsy.

Fine needle aspiration biopsy
Fine needle aspiration biopsy (FNAB) is a very useful diagnostic tool and is frequently used to evaluate neck lumps. Ultrasound-guided FNAB can be performed in radiology centres. The diagnostic accuracy depends on the clinician’s skill in performing the FNAB, in addition to the cytopathologist’s experience.

Imaging
CT scanning
CT scanning of the head and neck soft tissues (from skull base to mediastinum with intravenous contrast) is the most commonly used initial investigation in patients with, or suspected to have, HANMSCC. It provides valuable information on the extent of the primary tumour (Figures 5a and b). It also helps evaluate the cervical lymph nodes. Once a diagnosis of SCC is made, a CT scan of the lungs is also indicated to exclude pulmonary metastases.

MRI scanning
MRI scanning is sometimes required to provide more accurate soft tissue delineation, particularly when surgical resection of large complex tumours is
being considered (Figure 6). MRI is also invaluable when assessing for perineural infiltration or skull base erosion and complements CT imaging when evaluating certain head and neck malignancies, such as nasopharyngeal cancer or advanced sinonasal cancer.

**PET scanning**

PET scanning involves the use of a positron emission scanner, which detects a radiotracer that is injected into the patient’s bloodstream. The tracer used is 18F-fluorodeoxyglucose, which is derived from glucose and a small amount of radioactive fluorine. Because cancer cells tend to have a very high metabolic rate, they take up more glucose than normal cells and appear very bright or ‘hot’ on a PET scan (Figure 7).

**PET–CT scanning**

PET–CT is a combination of PET scanning and CT scanning that fuses the functional images provided by the PET scan with cross-sectional images obtained by the CT scan (Figure 8). PET–CT scanning is one of the most significant advances in head and neck imaging in recent years.

PET scans can:
- help to diagnose and stage head and neck cancer
- help to exclude distant metastatic disease before therapy is begun
- assist in evaluating a patient’s response to therapy
- help to detect tumour recurrence.

**Chest x-ray and/or chest CT scan**

Imaging of the chest with an x-ray or CT scan is mandatory when head and neck cancer has been confirmed for several reasons, noted below.
- Imaging of the chest helps to exclude lung metastatic disease, which has major implications for the patient’s treatment.
- Most patients with head and neck cancer smoke heavily and hence are also at high risk of a synchronous primary lung tumour.
- Patients who are heavy smokers often have respiratory compromise. Chest imaging provides useful information on their respiratory status, particularly before general anaesthesia and major surgery.

**How is HanMscC treated?**

Successful management of patients with head and neck cancer requires a multidisciplinary cooperative approach with input and expertise from multiple medical and allied health professionals. These include:
- GP
- head and neck surgeon
- medical oncologist
- radiation oncologist
- dental surgeon or oromaxillary surgeon
- plastic surgeon
- speech pathologist
- specialised head and neck nurses
- dietitian
- social worker.

Patients diagnosed with HanMscC are best evaluated in specialised multidisciplinary team (MDT) head and neck cancer clinics, which are present in most major teaching hospitals. These clinics not only facilitate patient clinical management but also provide supportive care to patients and their families.

The treatment plan needs to be individualised for each patient. It depends on careful consideration of numerous factors, including:
- the age and general health of the patient
- the site and TNM stage of the head and neck tumour
- the wishes of both the patient and their family.

Head and neck MDT clinics usually have treatment protocols and algorithms for most head and neck cancers. It is
important that patients are informed of the nature of their disease and the various treatment options available so they are able to participate in treatment planning.

Treatment of patients with head and neck cancer may include surgery, radiotherapy, chemotherapy or a combination of these treatments. It is beyond the scope of this article to outline all the treatment options for the various head and neck tumours. Detailed guidelines that are continually updated are available from the US National Comprehensive Cancer Network (www.nccn.org).

Surgery
Surgical resection of a primary tumour may be required for definitive initial treatment or for salvage treatment when disease persists after nonsurgical therapy. When determining a patient’s candidacy for surgery, the functional consequences of the resection (voice, swallowing and breathing) as well as patient comorbidities that affect their ability to tolerate surgery need to be assessed.

Neck dissection is commonly performed if lymph nodes are known to be involved (therapeutic neck dissection) or if the incidence of occult micrometastases is high (selective neck dissection).

Recent advances in head and neck surgery include:
- **Endoscopic laser resection**, which has gained wide acceptance as a mainstream alternative treatment to radiotherapy for early laryngeal and certain pharyngeal cancers. Laser resection is generally performed as a day-surgery procedure.
- **Transoral robotic surgery**, which allows oropharyngeal and other pharyngeal tumours to be removed via robotic instruments that are placed through the mouth. The surgery is performed under three-dimensional magnified vision by a surgeon who sits at a separate console in the operating room. Reconstruction is required when large tumours are removed leaving defects that are unsuitable for primary closure and cannot safely be left to granulate and heal by secondary intention. Plastic surgeons have a myriad of flap options available to repair head and neck defects, ranging from local rotation flaps to microvascular free flap reconstruction. Free flap reconstruction involves harvesting tissue from another area of the body (forearm, leg, abdominal wall or even the small intestine) and transplanting it into the head and neck defect using microsurgery to reanastomose its blood supply to neck vessels so that the tissue remains viable.

Radiotherapy
Radiotherapy plays an important role in the management of patients with head and neck cancer. External beam radiotherapy may be given following surgery (adjuvant treatment) for advanced stage cancers or alternatively it can be used as primary treatment, sometimes in combination with chemotherapy for certain head and neck cancer sites.

Intensity modulated radiation therapy (IMRT) is a recent advance. This is an advanced form of high precision radiotherapy that delivers radiation more accurately and precisely to the tumour with less radiation to surrounding normal tissues. IMRT is proving to be as effective as conventional radiotherapy, with reduced long-term toxicity.

Chemotherapy
Traditionally, chemotherapy has been used in the palliative setting for patients with unresectable or recurrent head and neck cancer. There is no evidence supporting the use of chemotherapy alone as a curative therapy for HANMSCC. However, advances over the past decade have seen the role of chemotherapy increased in patients with advanced stage head and neck cancers, and multiple trials are ongoing.

Chemotherapy may be used as:
- neoadjuvant or induction
chemotherapy, which refers to its use (sometimes combined with radiotherapy) to shrink large tumours prior to surgery
- adjuvant chemotherapy, which refers to its use (sometimes combined with radiotherapy) after radical surgery
- concurrent chemoradiotherapy, which involves the administration of radiation therapy combined with chemotherapy. This is an accepted treatment for certain patients with advanced laryngeal cancer who wish to avoid total laryngectomy. It is also the standard of care for patients with nasopharyngeal SCC and is commonly used to treat advanced oropharyngeal cancers (as an alternative treatment to surgery).

**Targeted molecular therapy**
Advances in tumour biology research over the past 15 years have dramatically improved our understanding of the molecular mechanisms and basic pathways involved in the pathogenesis of HANMSCC. This has spurred interest in targeted therapies at the molecular level that specifically aim to inhibit tumour cell growth and metastases by targeting the tumour microenvironment or vasculature. These therapies focus on specific proteins or signal transduction pathways that cause HANMSCC to grow and spread.

Examples of targeted therapies currently under investigation for HANMSCC include:
- drugs that target epidermal growth factor receptor (e.g. cetuximab)
- drugs that block the growth of blood vessels supplying tumours, such as vascular endothelial growth factor receptors inhibitors (e.g. sorafenib).

Ongoing clinical trials are currently evaluating these and new emerging agents and their combination in the treatment of HANMSCC.

**Gene therapy**
Gene therapy for HANMSCC is a rapidly evolving field that has spurred an enormous amount of research in recent years. It remains confined to clinical trials at present, but future progress in this exciting field may translate to clinical use in combination with conventional treatment modalities.

**Palliative care**
Fortunately, most patients diagnosed with HANMSCC are initially treated with curative intent. Palliation is required when:
- the tumour burden is so advanced or is associated with distant metastatic disease, making cure impossible
- the patient’s medical comorbidities preclude standard therapies
- the patient elects not to pursue conventional treatment and prefers to accept palliation to maintain their comfort and
upper aerodigestive tract separate from their initial tumour. It is imperative to educate patients and their families about the importance of implementing preventive strategies, such as ceasing smoking and heavy drinking, to reduce the chance of disease recurrence or a second primary cancer.

WHAT CAN BE DONE TO PREVENT HANMSCC?

Prevention is clearly the key to reducing the incidence of HANMSCC. Making certain lifestyle changes can significantly lower the risk of developing head and neck cancer. Preventive strategies are listed in Box 4.

The risk of HPV infection of the mouth and throat is associated with increased oral sex practice and/or multiple sex partners. Hence safe sex practices may decrease risk. HPV vaccination has been shown to reduce the risk of cervical and anal SCC and it is hoped that vaccinating boys and girls before they become sexually active will also reduce the risk of HPV-induced HANMSCC in the future. HPV vaccines are effective only if given before a person becomes infected with HPV.

Reports over recent years have raised concern about a potential link between alcohol-based mouthwashes and HANMSCC. Although further studies are required to prove the link, it seems prudent to avoid long-term overuse of these mouthwashes.

CONCLUSION

The rising incidence of HPV-related oropharyngeal cancer means that GPs need to remain vigilant when patients, even those who do not smoke or drink, present with persistent unexplained throat symptoms or a persistent neck mass. The prognosis for patients with HANMSCC correlates with tumour stage at diagnosis, and hence early detection and referral to an ENT, head and neck surgeon is important. Although advances in treatment continue to evolve, prevention is the key to reducing the incidence of HANMSCC, and GPs play a crucial role in reducing patients’ risk through education.

WHAT ABOUT FOLLOW UP?

Patients treated for head and neck cancer require long-term follow up. It is important that patients are followed up by their treating surgeons and/or radiation oncology colleagues so that local recurrence can be detected early. For the first few years, follow up is generally required every two to three months. If patients are disease-free after two years then the interval between follow-up visits is gradually increased.

Living with the effects of head and neck cancer can sometimes be difficult for both patients and their carers. Side effects from surgery and radiotherapy can result in significant difficulties with speaking, eating and swallowing. These patients require specialised support, not only from their treating physicians but also allied health professionals, such as speech pathologists, specialist nurses and dietitians. It is important that GPs have direct access to all of these health professionals so that communication channels are maintained, which facilitates the patient’s ongoing care and rehabilitation.

Like patients with cutaneous skin cancers, those with HANMSCC are always at risk of developing a new primary cancer in another region of the quality of life while allowing ‘nature to take its course’. 

REFERENCES


COMPETING INTERESTS: None.