

Squamous cell carcinoma in the head and neck

Head and neck cancers are responsible for 10% of male cancers in the UK, and used to be six or seven times more common in men than women. Now these cancers are only about twice as common among men. This article reviews the presentation and management of these cancers.

Squamous cell carcinoma represents more than 90% of all head and neck cancers (the other 10% include adenocarcinoma, lymphoma and poorly differentiated sarcoma). The behaviour of squamous cell cancer depends on its site of origin. Each anatomical site has its own particular spread pattern and prognosis. Squamous cell carcinoma of the head and neck is difficult to diagnose and treat and hard for the patient to bear. It affects parts of the body that can't be hidden, and impairs key activities: after treatment the patient may be disfigured, have impaired speech, and can sometimes eat and drink only with difficulty.

Incidence

Squamous cell carcinoma is by far the most common malignant neoplasm of the head and neck, excepting those of the skin (Burris et al, 1998). Those arising from the upper aerodigestive tract account for around 2.4% of all new cancers in men, and 0.7% of all new cancers in women. Male:female incidence rates are greater than 2:1. The discrepancy in the male:female ratio is even more pronounced in laryngeal tumours, in which carcinoma is 4–5 times more common in men. This ratio has declined in the last 20 years, possibly reflecting the increased number of women using tobacco products during this period. There are three main specialities dealing with this disease, ear, nose and throat (or otolaryngology), oral/maxillofacial, and plastic surgeons in order of number of new cases seen per year. In the longer term it seems likely that regional centres combining all three modalities in the same therapeutic team, along with radiotherapy and support services will treat the majority of cases, in accordance with the Department of Health guidelines for cancer treatment (Califano et al, 1996).

Aetiology

A number of factors have been implicated in the aetiology of squamous cell carcinoma of the head and neck.

The use of alcohol and tobacco in combination results in a multiplicative risk of squamous cell carcinoma in persons who are both heavy smokers and heavy drinkers, the risk of squamous cell carcinoma may be 200 times that of persons who neither smoke nor drink (Goldenberg et al, 2004). The probable reason for the change in the proportion of men to women who develop squamous cell carcinoma of the head and neck is that younger women are smoking and drinking more whereas fewer men smoke. It has been proposed that the increase in oral sex over the last generation might be a relevant factor. Human papillomavirus, the wart virus responsible for cervical and some other genital cancers, was also found in 7–10% of tonsils removed because of malignancy (Klussmann et al, 2003). There are many other co-factors, including causes of chronic irritation such as poor dental hygiene, syphilis, candidiasis, erosive lichen planus, iron deficiency anaemia, betel nut chewing and acquired immune deficiency syndrome (AIDS).

Histology

The tumours originate from squamous epithelial cells lining the upper aerodigestive tract. Their appearance may vary, from an exophytic (verrucous) pattern to an invasive pattern with diffuse tissue infiltration and ulceration. The hallmark of these tumours on pathological examination is the presence of well-formed desmosomal attachments and intracytoplasmic bundles of keratin. Depending on the degree of expression of these characteristics, the tumours can be classified into different levels of differentiation from well-differentiated to poorly differentiated tumours.

Those tumours that cannot be classified in this way by light microscopy should be analysed by electron microscopy and immunochemistry, since if they are of a squamous origin, intracytoplasmic keratin will be found. Poorly differentiated tumours behave in a more aggressive manner than well-differentiated tumours, although the higher replication rate that presumably causes their increased aggression also makes them more sensitive to some forms of treatment such as radiotherapy.

Clinical presentation

Squamous cell carcinomas usually begin as surface lesions with erythema and slight elevation. These lesions

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are termed erythroplasia and require a biopsy. These early red lesions are asymptomatic and may be either carcinoma in situ or invasive carcinoma. One third of lesions are pure white; they are known as leukoplakia but only 10% of them are carcinoma in situ or invasive carcinoma. The most common sites for squamous cell carcinoma are the floor of the mouth, the tongue, soft palate, anterior tonsillar pillar, and the retromolar trigone. Tender, painful lesions usually are suggestive of perineural invasions. When lesions become palpable masses, symptoms such as a vague persistent sore throat or ear infection occur.

In more advanced cases, dissemination to ipsilateral submandibular and jugulodigastric nodes is common, and the patient may present with a mass in the neck (*Figure 1a and b*). When lymph node or remote bone and organ metastases are associated with an early oral primary lesion, often a second, more advanced primary upper aerodigestive or lung cancer is responsible for the metastases.

Staging

The tumour node metastasis (TNM) staging system used for head and neck cancers is a clinical staging system that allows physicians to compare results across patients, assess prognosis, and design appropriate treatment regimens. T refers to tumour size at the primary

site, N refers to the status of the cervical chain of lymph nodes, and M refers to the presence or absence of distant metastases. This method of staging is somewhat artificial and rather subjective, but it is nonetheless a universally accepted yardstick that needs to be retained until a better method comes along.

T = Extent of the primary tumour

N = State of regional lymph nodes

M = Metastases.

The same system is used for laryngeal tumours. The basic premise of these systems is that smaller cancers with no nodal disease have a better prognosis than a larger lesion with positive neck nodes.

Tumour site and lymphatic drainage

The lymphatic drainage of each tumour depends on the tumour site, as detailed below:

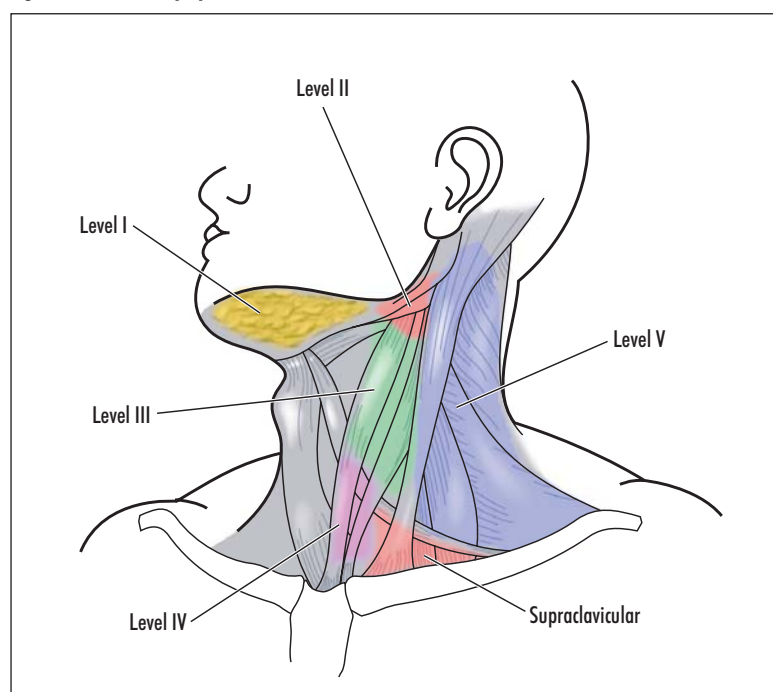
- Anterior tongue to subdigastric, submaxillary or mid-jugular nodes (*Figure 2*)
- Floor of mouth to subdigastric, submaxillary or mid-jugular nodes
- Gingival to jugulodigastric, submaxillary or midjugular nodes
- Buccal mucosa to submaxillary, preparotid or jugular nodes
- Hard palate to submaxillary or jugulodigastric.

The pharynx consists of the oropharynx, nasopharynx, and hypopharynx. The most common sites of cancer in the oropharynx are the tonsillar fossa, soft palate, and base of tongue, followed by the pharyngeal wall. The hypopharynx is divided into the pyriform sinus (most common site of tumour involvement), posterior pharyngeal wall and postcricoid region.

Figure 1. a and b. Squamous cell carcinoma of a cervical lymph node.



Figure 2. Levels of lymph nodes in the neck.



Treatment

Treating cancer always necessitates a balance between eradicating the disease and preserving function and appearance, and this equilibrium is particularly achieved through a multidisciplinary approach. This involves a team comprising an oncologist, histopathologist and a radiologist with a special interest in head and neck.

Different methods for treatment of cancer of the head and neck are acceptable, including surgery, radiotherapy, chemotherapy, and combinations of these. New investigative treatments include immunotherapy and gene therapy. Factors that influence the choice of treatment are the site, grade, and stage of the primary tumour, the patient's age and general medical condition. Goals of treatment generally consist of removal of cancer load, maintenance of quality of life, and prevention of subsequent primaries.

Medical therapy

Early detection and treatment by multiple modalities is important for better prognosis in head and neck cancer.

Radiotherapy

Nearly all patients with advanced disease require adjuvant radiotherapy, preoperatively or postoperatively. Preoperative radiotherapy has the risk of increased complications of surgery. Radiation dosage in excess of 6000 cGy is recommended with a boost to areas of high risk.

Indications for radiotherapy include a bulky tumour with significant risk of recurrence (T3 and T4), histologically positive margins, and perineural or perivascular invasion of tumour. For the neck, indications for radiotherapy include elective treatment of the N0 neck not treated surgically where risk of micrometastasis is high, gross residual tumour in the neck following neck dissection, multiple positive lymph nodes and extranodal extension of tumour.

Chemotherapy

Adaptation of traditional chemotherapeutics to local and regional administration techniques in treating head and neck cancers is being actively pursued to provide higher local concentrations of otherwise systemically toxic drugs. Bleomycin with or without electroporation has been used. Cisplatin is another chemotherapeutic drug of choice for head and neck cancers. Although cisplatin is one of the most successful agents in the treatment of cancer, it produces major toxicities in normal cells and organs at the concentrations necessary for effective treatment of malignancies. A combination of cisplatin with interstitial laser therapy has been reported (Vokes and Stenson, 2003; Clark et al, 2006). Hyperthermia produced by the laser augments cytotoxic effects of both radiation therapy and some chemotherapy drugs. Temperatures above 38°C enhance cisplatin therapy.

Surgical therapy

Surgical resection remains the criterion standard for treatment of head and neck cancer. Management of all but the earliest confirmed neck metastases is best achieved with surgical removal. The literature reports radiation therapy for patients with no evidence of lymph node involvement or an involvement of a mobile homolateral regional lymph node and concludes that radiation or surgery can treat them equally well (Guardiola et al, 2006; Lim et al, 2006). Because patients with cancers of the head and neck often have had previous radiation therapy, flaps must have an adequate blood supply.

Photosensitizers and interstitial laser therapy

Photosensitizing drugs that concentrate in cancer cells form the basis for photodynamic therapy. Activation of the drug with light results in cancer cell death. Laser photothermal ablation may be an alternative to surgery for the palliative treatment of head and neck cancer because of its tissue-sparing access, the possibility of repeated treatment, and experimental evidence suggesting lower recurrence at tumour margins compared with surgery (Lim et al, 2006). The combination of interstitial laser therapy with regional chemotherapy agents that are activated by light or heat is under investigation as a combined therapeutic regimen.

Immunotherapy

Recruitment of immune cells and administration of stimulatory immune factors to augment treatment of cancer through the host immune response have been advocated but have had little success to date in treating head and neck cancers. Non-specific immunoadjuvant systemic treatments with factors, such as levamisole or bacillus Calmette–Guérin (BCG), or targeted treatment with purified or recombinant factors, such as interferons or interleukin-2 (IL-2), have not improved either response rate or duration. Severe toxicities also are associated with the systemic use of these factors.

Gene therapy

Gene therapy involves a variety of delivery vehicles that can transfer therapeutic genes to target cells. Therapeutic genes may encode a product that induces a biological response, such as activation of the immune system with transferred interleukin sequences. Head and neck cancers are known to have high levels of p53 mutations. Normal functions of p53 are cell growth regulation. Insertion of the p53 gene into a variety of tumour cell lines in vitro and into animal models in vivo has resulted in suppressed cell growth through cell cycle arrest and apoptosis. Head and neck cancers are accessible to injection therapy and are good candidates for trials of p53 gene therapy.

Another form of therapeutic gene delivery is the adenovirus vector, which uses a genetically engineered virus that is replication incompetent.

Prodrug gene therapy, also known as suicide gene therapy, is designed to induce negative selection of cancer cells. By transducing cancer cells with a gene encoding an enzyme that metabolizes a non-toxic prodrug into its toxic form, cancer cells can be selectively killed.

Herpes simplex virus is a common human virus that produces a unique thymidine kinase. This viral enzyme preferentially phosphorylates the prodrug ganciclovir, a guanine nucleoside analogue, to produce a metabolite that, after cellular phosphorylation, is incorporated into replicating DNA, inhibiting DNA polymerase and ultimately killing the cell. This therapy is most effective in treating cancer cells growing in tissues where normal cells are not proliferating.

Many phase I and II trials are being pursued, and may ultimately provide non-toxic, tumour-specific, locally and regionally active, and biologically active injectable modalities that add therapeutic advantages to the existing treatment of head and neck cancers.

Cause of death

Studies of patients dying from head and neck cancer have shown that approximately 30% of uncured patients have uncontrolled disease at the primary site and about 70% have uncontrolled local lymphatic or soft tissue spread.

Conclusions

Squamous cell carcinoma is by far the most common malignant neoplasm of the head and neck. The aetiology of the disease have been linked to a number of factors most importantly cigarette smoking and alcohol intake. Patient with squamous cell carcinoma of the head and neck can present late with dissemination to a regional

lymph node or even a distant organ metastases. It has an excellent prognosis when treated in its early stages. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Squamous cell carcinoma of the head and neck account for 90% of all head and neck cancers.
- The incidence of head and neck squamous cell carcinoma is increasing in females.
- Smoking, alcohol and oral sex are all risk factors for the disease.
- Squamous cell carcinoma has a good prognosis if treated in the early stages.