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Head and neck cancer

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Abstract

Most head and neck cancers are squamous cell carcinomas that develop in the upper aerodigestive epithelium after exposure to carcinogens such as tobacco and alcohol. Human papillomavirus has also been strongly implicated as a causative agent in a subset of these cancers. The complex anatomy and vital physiological role of the tumour-involved structures dictate that the goals of treatment are not only to improve survival outcomes but also to preserve organ function. Major improvements have been accomplished in surgical techniques and radiotherapy delivery. Moreover, systemic therapy including chemotherapy and molecularly targeted agents—namely, the epidermal growth factor receptor inhibitors—has been successfully integrated into potentially curative treatment of locally advanced squamous-cell carcinoma of the head and neck. In deciding which treatment strategy would be suitable for an individual patient, important considerations include expected functional outcomes, ability to tolerate treatment, and comorbid illnesses. The collaboration of many specialties is the key for optimum assessment and decision making. We

review the epidemiology, molecular pathogenesis, diagnosis and staging, and the latest multimodal management of squamous cell carcinoma of the head and neck.

Introduction

Head and neck cancer is a broad term that encompasses epithelial malignancies that arise in the paranasal sinuses, nasal cavity, oral cavity, pharynx, and larynx. Almost all of these epithelial malignancies are squamous cell carcinoma of the head and neck (SCCHN), for which the most important risk factors are tobacco and alcohol consumption.[1] However, increasing evidence has documented human papillomavirus (HPV) as a cause of specific subsets of SCCHN.[2] About two-thirds of patients with SCCHN present with advanced stage disease, commonly involving regional lymph nodes. Distant metastasis at initial presentation is uncommon, arising in about 10% of patients.[3]

Treatment decisions in SCCHN are often complicated, involving many specialists, including head and neck surgeons, medical oncologists, radiation oncologists, radiologists, plastic surgeons, and dentists. Primary tumour site, stage and resectability, and patient factors — including swallowing and airway considerations, desire for organ preservation, and comorbid illnesses— are used to guide appropriate management. Surgery and radiotherapy have long been the major treatment approaches. Improved surgical and radiation treatment approaches and incorporation of systemic agents into curative therapy have improved clinical outcomes. A new class of agents, the epidermal growth factor receptor (EGFR) inhibitors, has shown clinical benefit in this disease.

SCCHN survivors face lifetime risks of dying from cardiac and respiratory illnesses, and second primary tumours,[4] which are commonly related to smoking. Second primary tumours develop at rates of 3–5% every year and can affect the entire aerodigestive tract.[5] Presently, no established biomarker or evidenced-based imaging for patient surveillance exists, and no chemopreventive agent is of proven benefit. Despite promising early data, several well designed randomised clinical trials that assessed the effect of retinoids in chemoprevention yielded negative results.[5] Continued smoking and alcohol use is harmful and should be avoided.[6] Further elucidation of molecular events in SCCHN development are expected to accelerate the development of novel, potentially efficacious anticancer agents and identification of biomarkers, which could optimise treatment.

This Seminar provides an update on epidemiology, pathogenesis, diagnosis and staging, and latest treatment for SCCHN. Our primary focus is the four common sites of head and neck— ie, oral cavity, oropharynx, hypopharynx, and larynx. We exclude nasopharyngeal cancer, which is examined as a separate clinicopathological entity and reviewed separately.[7]

Epidemiology and risk factors

Head and neck cancer is the sixth most common type of cancer, representing about 6% of all cases and accounting for an estimated 650 000 new cancer cases and 350 000 cancer deaths worldwide every year.[8] High-risk regions for oral cavity cancer include Melanesia (a subregion of Oceania, northeast of Australia) and southcentral Asia (including in women),

western and southern Europe, and southern Africa, and for laryngeal cancer southern and eastern Europe, South America, and western Asia.[8] In the USA alone, an estimated 45 660 new cases and 11 210 deaths caused by head and neck cancer occurred in 2007[9] The median age for diagnosis is in a patient's early 60s, with a male predominance, especially in laryngeal cancer.[3,8] A slight decrease in the overall incidence of head and neck cancer has been detected in the past two decades;[3] however, an increase in cancer in the base of tongue and tonsillar cancer has been noted,[10] which could be more pronounced in young adults in the USA and European countries.[11,12] The 5-year survival for all stages combined on the basis of Surveillance Epidemiology and End Results (SEER) data is about 60%; survival is worse for specific primary sites such as the hypopharynx.[3]

Tobacco and alcohol consumption are implicated in 75% of all SCCHN and have a multiplicative combined effect.[13–15] In people who have never smoked, substantial alcohol consumption (ie, three or more drinks per day) has been associated with an increased risk of SCCHN.[16] Selected genetic polymorphisms in enzymes that metabolise tobacco and alcohol have been linked with an increased risk for SCCHN.[16,17] Smokeless tobacco and chewing of betel quid—a preparation of various ingredients, including tobacco and the seeds of the betel palm (betel or areca nut), wrapped in a betel leaf—are well recognised risk factors for cancer of the oral cavity.[18,19] Consumption of fruits and vegetables has been associated with a reduced risk of SCCHN.[20] Additionally, the role of specific anthropometric variables[21] and occupational factors have also been assessed.[22,23] Although SCCHN arises sporadically, familial inheritance has been noted.[24] Furthermore, the risk for SCCHN increases in individuals with cancer susceptibility syndromes, such as hereditary non-polyposis colorectal cancer, Li-Fraumeni syndrome, Fanconi's anaemia, and ataxia telangiectasia.[25,26]

HPV, mainly HPV type 16 and to a lesser extent type 18, is a newly identified causal factor for SCCHN.[2] Oncogenic HPV subtypes can be detected with in-situ hybridisation and p16 immunohistochemistry. About 25% of SCCHN contain HPV genomic DNA.[27] The association between HPV and SCCHN is strongest for cancers of the tonsil, intermediate for the rest of the oropharynx, and weakest for the oral cavity and larynx.[28] With in-situ hybridisation, HPV16 genomic DNA can be detected in up to 72% of oropharyngeal cancers.[2] HPV-related SCCHN occurs more frequently in individuals who are not smokers, drinkers, or immunosuppressed, and are often poorly differentiated and of basaloid histology. The role of HPV16 in SCCHN might be independent of other carcinogens.[2] Some sexual practices, because of their higher risk for transmission of HPV infection, were also noted to be risk factors for oropharyngeal cancer.[2,29] High-risk oncogenic HPV types (eg, HPV16, HPV18) mediate their carcinogenic effect through E6 and E7 viral oncoproteins, which inactivate the tumour-suppressor proteins, P53 and PRb, respectively.[30] Substantial differences in gene expression profiles and chromosomal defects have been documented between HPV-positive and HPV-negative tumours.[31]

The association between HPV and SCCHN has potentially important implications for prevention, treatment, and prognosis. HPV positivity is a favourable prognostic factor in SCCHN.[32] HPV-positive tumours have better responsiveness to radiation, chemotherapy, or both, and might be more susceptible to immune surveillance of tumour-specific antigens than are HPV-negative tumours. Therefore, HPV status is an important predictive biomarker

that should be taken into consideration in the design of prospective clinical studies in SCCHN. For example, it is possible that patients with locally advanced, HPV-positive SCCHN could do well with standard therapy, but might not benefit from treatment intensification. Finally, vaccination against HPV has shown efficacy in the prevention of cervical cancer and is of potential interest for prevention of SCCHN.

Pathogenesis

A plethora of genetic events leading to the inactivation of tumour-suppressor genes or activation of proto-oncogenes, or both, govern the development of SCCHN. Molecular techniques can identify genetic and epigenetic alterations in premalignant and invasive lesions, and allow the delineation of a hypothetical progression model for SCCHN carcinogenesis (figure 1).[33–35] Stromal and immune or inflammatory cells contribute to carcinogenesis and treatment resistance. Telomerase, which is involved in telomere maintenance and immortalisation (thus protecting the acquired genetic changes), has been found to be reactivated in 90% of SCCHN and in premalignant lesions.[36] The loss of 9p21 is a very common genetic aberration, because it is seen in 70–80% of SCCHN.[37] Inactivation of *p16*, which is caused by homozygous deletion, point mutations, or promoter hypermethylation, and loss of 3p, could be early events in SCCHN carcinogenesis.[34,38] Loss of heterozygocity of 17p and *TP53* point mutations are seen in over 50% of cases of SCCHN.[39] The prognostic significance of *TP53* mutations is rather controversial; however, disruptive *TP53* mutations in the DNA of the tumour were shown to be associated with reduced survival after surgical treatment of SCCHN.[40] Amplification of 11q13 and overexpression of cyclin D1 are also detected in SCCHN, and could correlate with more aggressive tumour behaviour.[41,42]

Leukoplakia and erythroplakia are clinically detected lesions that can histologically represent hyperplasia, dysplasia, and even in-situ or invasive carcinoma.[43] A subsequent invasive cancer might develop at the site of a known dysplastic lesion or at other mucosal sites; the reported risk depends on histology and length of follow-up, and varies considerably between studies (10–40%).[44] Although standard treatment options for head and neck epithelial dysplasia range from watchful waiting to laser surgery and aggressive resection, none of these approaches are of clear clinical benefit in preventing malignant transformation.[45] Chemoprevention (topical or systemic) has been used to prevent the evolution of premalignant lesions into invasive SCCHN, with variable results.[46]

EGFR is a member of the ErbB growth factor receptor tyrosine kinase family, which is central to SCCHN biology.[47] Ligand binding (eg, epidermal growth factor) results in EGFR homodimerisation or heterodimerisation with other members of the ErbB family. Thus, a molecular cascade is triggered, activating the receptor-linked tyrosine kinase and many downstream pathways, which regulate cell proliferation, apoptosis, metastatic potential, and angiogenesis (figure 2). EGFR activation can be also achieved through cross-talk with other receptors—eg, G-protein-coupled, platelet-derived growth factor, insulin-like growth factor, and hormone receptors.[47] EGFR protein expression is seen in 90% or more of cases of SCCHN.[48] Many retrospective analyses have shown poor outcome for patients with SCCHN

that overexpress EGFR.[49] Targeting of this receptor has been successfully exploited for therapeutic purposes.[47]

Angiogenesis is fundamental to cancer growth and metastasis, and is regulated by many endogenous proangiogenic and antiangiogenic factors—the most important being the vascular endothelial growth factor (VEGF) and its receptors.[50] VEGF can be upregulated and has prognostic significance in SCCHN.[51] Antiangiogenesis therapeutic strategies have been extensively studied in other solid tumours[50] and are under assessment in the treatment of SCCHN (figure 2).

Malignant cells, including SCCHN, escape from immune-mediated destruction not only by evading immune recognition but also by directly inhibiting or exploiting antitumour immune defences. Patients with SCCHN showed reduced peripheral blood concentrations of CD3+, CD4+, and CD8+ T cells, which might persist even several years after curative surgery.[52] Many mechanisms for immune evasion have been proposed, including escape from immune recognition and elimination caused by tumour factors,[53,54] impaired T-lymphocyte activity, activity of immunosuppressive cells, and cytokines mediating local and systemic effects.

Diagnosis and staging

Early recognition of symptoms and signs of SCCHN is important for prompt diagnosis (panel 1 and figure 3). No proven screening methods, except population screening with oral visual inspection in high-risk regions for oral cavity cancer, are known to exist.[55] Referral criteria have been developed to expedite specialist assessment for biopsy of suspected malignant lesions, which is always needed to confirm the diagnosis.[56] Histological variants of SCCHN are rare and include verrucous, basaloid, spindle cell, and adenosquamous carcinomas. Poorly differentiated or undifferentiated carcinomas of the head and neck are managed in a manner similar to SCCHN.

Accurate staging is the most important factor that guides therapeutic decision making. Staging methods include examination by a head and neck surgeon and radiological assessment that usually entails imaging of the neck with CT or MRI, or both. The most common site of distant metastasis is the lung, followed by the mediastinal lymph nodes, liver, and bones. Chest imaging is routinely done at initial assessment, and might detect a second primary lung cancer or, especially in locally advanced SCCHN, the presence of lung metastasis. The sixth edition of the American Joint Committee on Cancer (AJCC) staging classification is widely used;[57] staging criteria vary according to the primary site. Although the AJCC system is helpful in defining the anatomical extent of cancer, it does not include pathological or biological parameters of tumour behaviour.

PET scanning with [^{18}F]fluoro-2-deoxyglucose is increasingly used, especially for the detection of nodal or distant metastasis, or both.[58] Combined PET and CT scans are more accurate than either method alone[59] for identifying malignant lesions in the head and neck.[59] PET-CT scanning is also potentially valuable for assessment of response (figure 4) and detection of persistent or recurrent SCCHN.

Patients might also present with neck lymphadenopathy without an apparent primary tumour. Endoscopic assessment and biopsy of Waldeyer's ring (nasopharynx, tonsil, and base of tongue), including tonsillectomy, along with PET, could identify the occult primary tumour.[60] However, in up to 5% of cases of SCCHN the primary site remains unknown. Management of this entity is controversial, but prognosis seems favourable.[61]

Innovations in treatment

Surgery

Surgery is a standard treatment for SCCHN but is frequently limited by the anatomical extent of tumour and desire to achieve organ preservation. Advances in microsurgical free tissue transfer for reconstruction of surgical defects have made major reconstructive procedures commonplace at many centres, helping in the resection of locally advanced tumours. By use of modern surgical techniques, substantially improved functional outcomes are often possible for patients who need extensive surgical resections, even in the setting of salvage surgery after failure of organ-preserving treatment. No uniform unresectability criteria exist, but most surgeons accept invasion of the carotid artery, base of the skull, or prevertebral musculature as unresectable.

Surgical management provides pathological staging of primary tumour and regional nodes, often upstaging clinically uninvolved neck (ie, clinical stage N0) by histological identification of micrometastasis,[62] which will guide adjuvant treatment decisions. For small, transorally accessible cancers of the oral cavity, pharynx, and larynx, surgical excision can be achieved with functional preservation of much of the involved organ and good oncological results.[63,64] Microsurgical treatment, which uses endoscopic laser or robotic techniques and high resolution magnified optics, has become technically feasible and could be cost saving compared with open surgical procedures or radiotherapy for early stage laryngeal cancer with acceptable voice outcomes.[65]

When surgery is the primary treatment, neck dissection is carried out as part of surgical management. However, after treatment with primary chemoradiotherapy, neck dissection is usually recommended when residual disease is suspected, whereas its role remains controversial in the setting of complete response.[66,67] The adaptation of less morbid selective neck dissection procedures is yielding important staging information for guiding therapy and assessing prognosis.[68] Selective neck dissection is also a reasonable therapeutic procedure for clinically uninvolved necks, which can harbour micrometastasis in up to a third of cases,[62] and clinically N1 disease in the absence of adverse histological features.[69,70] Sentinel lymph node biopsy has gained attention for its ability to reliably detect nodal metastasis in oral and oropharyngeal SCCHN, and was validated by a large multi-institutional trial done by the American College of Surgeons' Oncology Group. In the future, risk of metastasis could be ascertained through molecular gene signatures in the sentinel lymph node[70] or in the primary tumour.[71,72]

Radiotherapy

Radiotherapy is an integral part of primary or adjuvant treatment of SCCHN. Radiotherapy alone results in high tumour control and cure rates for early stage glottic, base of tongue, and tonsillar cancer. Advances in imaging and radiation delivery have dramatically changed management approaches. Planning CT scans are now frequently combined with diagnostic CT, MRI, or PET datasets to improve tumour delineation in three dimensions. Intensity-modulated radiation therapy represents an advanced form of radiation in three dimensions. A computer-controlled treatment machine is used to produce many radiotherapy beams in which the intensity is optimised to deliver a high dose of radiation to specified volumes, while reducing the dose and, theoretically, the toxic effect on adjacent non-target tissues. Intensity-modulated radiation therapy uses inverse planning to protect healthy tissue from chronic damage by limiting the dose delivered to areas such as the salivary tissue. Another advantage of this technique is that it allows for delivery of a synchronous integrated boost in which treatment field modifications, such as off-cord laterals and posterior electron strips, are no longer needed. Although initial clinical results of intensity-modulated radiation therapy in the treatment of SCCHN are very promising,[73] several issues have to be addressed before its use becomes widespread, either as a single treatment method or in combination with chemotherapy.[74,75] Additional advances in radiotherapy include tomotherapy (integration of CT or PET-CT technology into a linear accelerator) heavy particle radiation, proton therapy, neutron beam radiation, brachytherapy, and stereotactic radiosurgery; however, in most instances these methods have not been validated in prospective clinical trials.[76,77]

Radiation therapy for treatment of SCCHN is typically given in daily fractions of 2·0 Gy, 5 days a week, up to a total dose of 70 Gy over 7 weeks. Higher dose per fraction schemas have been attempted for early-stage laryngeal SCCHN, with excellent results (2·25 Gy per fraction) and no increase in late toxic effects.[78] Postoperatively, radiation doses of 60–66 Gy are usually prescribed; increasing the total dose to at least 63 Gy improves locoregional control when extracapsular extension is present.[79]

Long-term interruptions to radiotherapy or delays in starting postoperative radiotherapy are potentially harmful, presumably because of repopulation of cancer cells.[80–82] To address tumour cell kinetics and exploit differences in damage repair between healthy and tumour cells, altered fractionation radiotherapy regimens were introduced. Two major fractionation variants that make it possible for multiple fractions per day to be delivered have been tested: hyperfractionation and accelerated fractionation.[83]

Hyperfractionation was designed to improve effectiveness by delivering two to three fractions every day with a reduced dose per fraction (usually 1·10–1·25 Gy), while maintaining or improving the chronic toxic effect profile of standard fractionation, despite an increased total dose. Accelerated fractionation was designed to increase radiation dose intensity by delivering fractions of 1·6–1·8 Gy more than once daily with a planned dose of 10 Gy per week in a reduced time period compared with hyperfractionation, but maintaining the same or slightly reduced dose of conventional radiation treatment.[84] Phase III trials showed that altered fractionation improves locoregional control with increased infield toxic effects but with marginal effects on survival, compared with conventional radiotherapy.[85] A

meta-analysis of 15 randomised trials with more than 5000 participants, mostly with oropharyngeal and laryngeal SCCHN, showed that altered fractionation radiotherapy yielded an absolute 5-year survival benefit of 3·4% (HR 0·92, 95% CI 0·86–0·97; p=0.004).[86] Additionally, the combination of altered fractionation schedules and chemotherapy has been tested in clinical trials with promising results (table 1). The results of a completed phase III trial (Radiation Therapy Oncology Group [RTOG] 01-29) that compared conventional fractionation with accelerated boost fractionation in patients receiving concurrent cisplatin are pending.

Chemotherapy and novel agents

The role of chemotherapy in SCCHN treatment has evolved from palliative care to a central component of curative programmes for locally advanced SCCHN.[87] Various classes of agents such as platinum compounds, antimetabolites, and taxanes have shown single-agent activity against SCCHN.[88] The platinum compound cisplatin is regarded as a standard agent in combination with radiation or with other agents. Carboplatin is well tolerated but less active than cisplatin as a component of combination regimens,[89,90] although the radiosensitising properties of the two platinum agents could be comparable.[91] Taxane-based combinations are very active and have been tested in the induction chemotherapy of locally advanced SCCHN.[92] Moreover, EGFR inhibition has emerged as a novel treatment strategy for SCCHN, and cetuximab is the first molecularly targeted agent that has been introduced into standard practice.[47] Other ways of targeting EGFR and other dysregulated molecular pathways in SCCHN, using monoclonal antibodies, single-selective or multi-selective tyrosine kinase inhibitors, and nucleic acid-directed approaches, are also being explored (figure 2). The combination of EGFR inhibitors with other molecularly targeted agents (eg, angiogenesis inhibitors) has surfaced as a novel strategy, whereas the combination of these novel agents with chemotherapy and radiotherapy is under investigagion.

Treatment of early stage disease

About a third of all patients with SCCHN present with stage I or II disease. These patients are treated with surgery or radiation therapy with the intent of curing the disease, which is achieved in up to 90% of patients with stage I disease and about 70% of those with stage II disease. Treatment approaches differ according to the primary tumour site. In early stages of SCCHN in the oral cavity, surgery or radiotherapy could be used. Although efficacy is comparable between the two methods, surgery is usually preferred so that the late toxic effects of radiation can be avoided and so the most accurate staging can be obtained. Elective functional neck dissection of ipsilateral cervical lymph nodes in the clinically uninvolved neck remains a standard procedure in patients with a high risk for occult neck lymphadenopathy.[93] Radiotherapy, as well as open or endoscopic surgery that spare the larynx, are acceptable options for treatment of early-stage laryngeal SCCHN; the treatment choice depends on tumour location, the treating centre's expertise, and patient preference.[94–96] For early-stage oropharyngeal and hypopharyngeal carcinomas, radiotherapy generally represents the first option since it results in cure rates comparable with surgery and is usually associated with lower morbidity.[97,98]

Treatment of locally advanced disease

Surgery, radiotherapy, and chemotherapy are the main means for curative management of locally advanced SCCHN (ie, stage III or IV). A major advancement in the treatment of this stage of disease has been the introduction of concurrent administration of chemotherapy and radiotherapy (chemoradiotherapy). Adequate preclinical and clinical rationales exist to support the use of chemoradiotherapy.[99] Several phase III clinical trials have shown that chemoradiotherapy yields better results than radiotherapy alone or the sequential administration of chemotherapy and radiotherapy (table 1).[100–116] The survival advantage that was noted with chemoradiotherapy over radiotherapy alone could, in most cases, be attributed to improved locoregional control.[100–116] Benefit from chemoradiotherapy has also been documented in the postoperative setting. After encouraging preliminary data,[117,118] phase III trials compared postoperative radiotherapy with or without concurrent chemotherapy with cisplatin[100–102] or cisplatin and fluorouracil[103] in patients with high-risk resected SCCHN (table 1). The definition of high-risk pathological features was not uniform in these studies and included the involvement of many lymph nodes, extracapsular extension, and involved margins. These studies show that the addition of cisplatin-based chemotherapy to radiotherapy can improve locoregional control, disease-free survival, or survival. A combined analysis of two of these studies suggested that the addition of cisplatin to postoperative radiotherapy was most beneficial when extracapsular spread or positive margins were present.[119]

A meta-analysis of 63 trials with nearly 11 000 patients with SCCHN showed that the addition of chemotherapy to locoregional treatment resulted in an absolute survival benefit of 4% at 5 years (HR 0·90, 95% CI 0·85-0–94; $p<0.0001$).[120] This benefit was confined to chemoradiotherapy (HR 0·81, 95% CI 0·76–0·88; $p<0.0001$) that resulted in an absolute survival improvement of 8% at 5 years,[120] which was also supported by an updated meta-analysis that included 24 additional studies.[121] Treatment benefit was maintained in stage III or IV disease, each major primary site, definitive or postoperative radiotherapy, and when altered fractionation radiotherapy was used in the control arm.[121] However, chemoradiotherapy has an insignificant effect on distant recurrence rate and results in increased acute complications including mucositis, dermatitis, and myelosuppression. Nevertheless, being cured is of paramount importance to patients, overshadowing potential toxic effects.[122]

In patients with unresectable, locally advanced SCCHN chemoradiotherapy is standard,[106] unless the addition of chemotherapy is not indicated because of poor performance status or comorbid illnesses. In patients with resectable, locally advanced SCCHN, surgery usually followed by postoperative chemoradiotherapy or chemoradiotherapy alone could be the primary treatment choice. Guidelines that provide useful practical approaches have been developed.[66] Although an important treatment goal is organ preservation, physicians recognise that such attempts might leave an anatomically intact but dysfunctional organ. No conclusive data exist regarding quality of life in surgical versus non-surgical approaches. In general, oral cavity primaries are usually treated with surgery, since the cosmetic and functional result is regarded as satisfactory and patients might be spared aggresive chemoradiotherapy. However, locally advanced oropharyngeal primaries are usually treated

with chemoradiotherapy with good efficacy and functional results.[123] Patients with locally advanced hypopharyngeal and laryngeal primaries should be considered for organ preservation.

In the 1990s, induction chemotherapy followed by radiotherapy in responders offered comparable survival rates to laryngectomy.[124,125] However, only a few patients with T4 tumours were enrolled in these two randomised trials. In bulky T4 tumours, especially with baseline organ dysfunction, many experts advocate upfront surgery because of high failure rates with non-surgical approaches and questionable benefit from preservation of a poorly functional larynx. A randomised trial (RTOG 91-11) assessed the optimum non-surgical treatment of patients with locally advanced laryngeal cancer, using organ preservation as the primary endpoint (table 1).[107,108] Although no survival difference was evident between the three arms in the study, which could be partially attributed to the effect of salvage laryngectomy,[126] the laryngeal preservation rate was highest in patients given chemoradiotherapy with radiation and concurrent cisplatin.

Although various chemoradiotherapy regimens are being used, cisplatin-containing regimens are generally viewed as standard and have been studied extensively. Moreover, even though chemoradiotherapy with two-drug combinations has produced promising data,[127] it has not yet proved better than chemoradiotherapy with one chemotherapy agent alone in randomised comparisons.[120,121] Cetuximab, an IgG1 chimeric monoclonal antibody directed against EGFR, is the first molecularly targeted agent to yield positive survival data in SCCHN. The combination of radiation and cetuximab was compared with radiation alone in patients with locally advanced SCCHN and showed improved locoregional control (47% *vs* 34% at 3 years; HR 0·68, 95% CI 0·52–0·89; p=0·005), progression-free survival (42% vs 31% at 3 years; HR 0·70, 95% CI 0· 54–0· 90; p=0·006), and overall survival (55% *vs* 45% at 3 years; HR 0·74, 95% CI 0·74–0·97; p=0·03) but not distant control (17% *vs* 16% at 2 years).[128] Although results with cetuximab were comparable with those achieved with platinum-based regimens, no randomised trial has yet compared radiation plus cetuximab versus radiation plus cisplatin. Radiation plus cetuximab is an alternative to chemoradiotherapy that should be strongly considered in patients who cannot tolerate chemotherapy, since this regimen is not associated with increased myelosuppression or mucositis, although side-effects due to inhibition of EGFR are seen (eg, rash and hypomagnesaemia). A focus of continuing investigation is the incorporation of EGFR inhibitors into various chemoradiotherapy regimens. A phase II study assessed the combination of cetuximab with cisplatin and accelerated boost radiotherapy with promising preliminary efficacy, but there were also concerns about possibly enhanced toxic effects.[129] An ongoing phase III trial by the RTOG is comparing this regimen with radiation and cisplatin alone.

Role of induction chemotherapy

Induction (neoadjuvant) chemotherapy has the potential to reduce the incidence of distant metastases, which are increasingly recognised as sites of disease recurrence, as a result of improved locoregional control with chemoradiotherapy.[130] SCCHN is a highly responsive malignancy at initial presentation; cisplatin-based induction chemotherapy has produced response rates of 80–90%, with complete response rates of 20–40% in locally advanced

SCCHN.[92] Despite high antitumour activity, many phase III trials that compared induction chemotherapy followed by locoregional treatment (surgery or radiotherapy, or both) with locoregional treatment alone failed to show survival benefit,[92] except for two studies in which benefit was shown, although one in a subset analysis only (table 2).[131–133] Many of these trials reported a reduction in the risk of distant metastases in patients given induction chemotherapy, but the effect on locoregional control was insignificant. In a meta-analysis, induction chemotherapy resulted in a non-significant survival improvement of 2% at 5 years (HR 0·95, 95% CI 0·88–1–01; p=0·10).[120] However, in the 15 trials with a platinum agent plus fluorouracil, a marginal survival benefit was evident (HR 0·88, 95% CI 0·79–0·97; p=0·05).[120] The introduction of more active, taxane-containing chemotherapy combinations has strengthened the rationale for using induction chemotherapy. In phase III clinical trials, a taxane (docetaxel or paclitaxel) plus cisplatin and fluorouracil resulted in improved survival or organ preservation compared with cisplatin and fluorouracil alone (table 2).[134–137] However, induction chemotherapy is not yet regarded a standard treatment for locally advanced SCCHN. Several randomised trials comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone are underway.

Acute and late complications

Patients with SCCHN develop acute and late complications as a result of their disease and its treatment. Common acute toxic effects associated with radiation are mucositis (which is severe in 50% or more of patients receiving chemoradiotherapy), increased secretions, dysphagia, occasionally with aspiration, loss of taste, hoarseness caused by laryngeal oedema, and dermatitis.[138,139] Supportive care during chemoradiotherapy is often demanding and includes oral and skin care, narcotic analgesics, intravenous hydration, and enteral nutrition, as necessary. Swallowing function and quality of life usually improve in the first year after treatment, but swallowing dysfunction might be permanent.[140,141] Other possible late sequelae of treatment include osteoradionecrosis, dental caries, subcutaneous fibrosis, trismus, thyroid dysfunction, sensorineural hearing loss, pharyngeal or oesophageal stenosis (figure 5), and myelitis. Radiation-induced xerostomia is universal in long-term survivors, which is moderate or severe in about 60% of patients.[142] Several strategies seek to prevent xerostomia, including surgical transfer of salivary glands, radioprotectants (eg, amifostine), and radiation techniques that spare the salivary glands.[143] Supportive care measures include oral hygiene with fluoride agents and antimicrobials to prevent dental caries and oral infections, saliva substitutes, and cholinergic stimulants (eg, pilocarpine). Treatment and disease-induced anatomical and functional defects might lead to many social and psychological problems;[141,144] thus, patients with SCCHN should be cautiously monitored and encouraged to participate in long-term supportive care programmes.

At present, there is no radioprotectant with proven efficacy in decreasing the severity of mucositis during chemoradiotherapy for SCCHN. Granulocyte-macrophage colony stimulating factor or granulocyte colony stimulating factor has been investigated for amelioration of radiation mucositis without convincing results; moreover, there are concerns about poor disease control when such factors are added to radiation.[115,145] Erythropoietin could also have an adverse effect on survival presumably because of the presence of erythropoietin receptors in cancer cells.[146] Therefore, the use of cytokines during curative

radiation or chemoradiotherapy should be generally avoided. Many novel agents with potential cytoprotective effect, such as palifermin (recombinant human keratinocyte growth factor), are under assessment in clinical studies.

Recurrent or metastatic disease

At least 50% of patients with locally advanced SCCHN develop locoregional or distant relapses, which are usually detected within the first 2 years of treatment. Salvage surgery is a likely curative option for the few patients with potentially resectable locoregional recurrence.[126] Investigators have also studied re-irradiation alone or in combination with chemotherapy for patients with locoregionally recurrent SCCHN. A randomised study that assessed re-irradiation combined with chemotherapy compared with observation after salvage surgery reported an improvement of progression-free survival (HR 1·6, 95% CI 1· 1– 2 ·4; p=0·01) with acceptable toxic effects.[147] However, chemotherapy remains a standard-of-care treatment option for patients with recurrent or metastatic SCCHN. The main objective in these patients is not only to provide symptom palliation but also to extend survival. Methotrexate, bleomycin, carboplatin, and fluorouracil are active as single agents in recurrent or metastatic SCCHN.[88] Well designed randomised trials to compare chemotherapy versus supportive care have not been done. In a small study, cisplatin monotherapy resulted in a 10-week prolongation in median survival, compared with no treatment.[148] Two-drug combinations improved response rates but not overall survival in randomised trials.[88] Cisplatin plus fluorouracil has been widely accepted as a reference regimen in patients with recurrent or metastatic SCCHN; however, single-agent cisplatin or methotrexate are acceptable alternatives. Among the new drugs, taxanes have substantial activity as monotherapy.[88] Phase II and III studies assessed the combination of taxanes with platinum compounds and showed promising results, although they were not better than cisplatin plus fluorouracil.[149] At present, there is no standard second-line chemotherapy regimen for the treatment of recurrent or metastatic SCCHN.

A randomised, placebo-controlled, trial compared cisplatin with or without the EGFR inhibitor cetuximab as first-line treatment of 123 patients with recurrent or metastatic SCCHN.[150] This trial showed significant improvement in response rates (p=0·03) with a trend towards improved progression-free survival (p=0·09) with the addition of cetuximab; however, it was underpowered. A phase III trial with a larger sample size (420 patients) than the previous trial investigated the combination of a platinum agent (cisplatin or carboplatin) and fluorouracil with or without cetuximab. Preliminary results showed survival benefit with the addition of cetuximab, with an improvement of median survival from 7 · 4 months to 10·1 months (HR 0·797, 95% CI 0·64–0·98; p=0·036).[151] Finally, cetuximab showed activity either as a single agent[152] or in combination with platinum-based regimens in patients with platinum-refractory SCCHN,[47] however, it has not been assessed in comparison with other agents or with best supportive care in patients with previously treated recurrent or metastatic SCCHN.

EGFR-tyrosine kinase inhibitors, gefitinib or erlotinib, have shown modest activity when given alone, with response rates of 1–11%, disease control rates of 34–53%, and median overall survival of 5 ·5–8· 1 months in patients with recurrent or metastatic SCCHN.[47] A

multicentre phase III trial showed that gefitinib (at either 250 mg or 500 mg per day) is not better than methotrexate in terms of overall survival.[153] A phase III, placebo-controlled study, which is in progress in the USA (Eastern Cooperative Oncology Group, E1302), is comparing docetaxel with or without gefitinib as first-line or second-line treatment in recurrent or metastatic SCCHN.[47]

Future perspectives

Clinical investigations in SCCHN now being actively pursued include the use of induction chemotherapy and the incorporation of EGFR, angiogenesis inhibitors, and other molecularly targeted agents (figure 2) in the treatment of locally advanced SCCHN. Treatment intensification is expected to not only improve the locoregional and distant control, but also improve the overall survival of potentially curable patients with SCCHN. Consequently, an important area of investigation is focused on ways of ameliorating treatment-induced toxic effects. New, more accurate, radiation delivery methods and radioprotectant agents are being tested. Additionally, the understanding of the molecular changes that underlie SCCHN development has created optimism that more effective strategies for chemoprevention could be developed. Although many clinicopathological variables and molecular markers (eg, EGFR and HPV) are of prognostic value (panel 2), wide heterogeneity in clinical outcomes is seen. Certainly, there is an unmet need for identification of biomarkers that will guide treatment decisions. Advances in basic research and application of genomic and proteomic profiling are expected to provide powerful methods for the individualisation of treatment approaches in patients with SCCHN.

Acknowledgments

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Search strategy and selection criteria

We did an extensive search of the English-language publications on head and neck cancer through Medline (1966–2007), Cochrane Library (1990–2007), and EmBase (1998–2007). Search terms included "head and neck cancer", "head and neck squamous cell carcinomas", "oral cavity", "pharynx", "larynx", "surgery", "radiotherapy", "chemotherapy", "chemoradiotherapy", "clinical trials", "randomised clinical trials", "meta-analysis", "epidemiology", "chemoprevention", "molecular biology", "EGFR", "predictive factors", "prognostic markers", "supportive care", and "novel agents". Additionally, we manually reviewed relevant bibliographies for extra material. We prioritised the selection of randomised clinical trials. Further information was obtained in oral and abstract form from recent pertinent conferences, such as the American Society of Clinical Oncology (ASCO) and American Association for Cancer Research (AACR) annual meetings. Published National Comprehensive Cancer Network (NCCN) and ASCO guidelines were also reviewed. We largely selected recent publications and preferentially included original articles, but reviews and book chapters were also cited to provide readers with more details.

Panel 1:

Diagnostic considerations in squamous cell carcinoma of the head and neck

Symptoms

Hoarseness, sore throat, tongue pain, mouth ulcer, poorly fitting dentures, otalagia, dysphagia and odynophagia, cough, mouth bleeding, stridor

Physical examination findings

Mass or ulceration in oral cavity or oropharynx, neck mass, vocal cord paralysis, swallowing dysfunction

Staging and assessment

Office nasopharyngeal examination, imaging studies (chest radiograph, CT, MRI, PET), direct laryngoscopy and oesophagoscopy, bimanual examination under anaesthesia, barium swallow, creation of tumour map, biopsy of tumour and adjacent sites, chemistry and complete blood count

Panel 2:

Prognostic factors in squamous cell carcinoma of the head and neck

Locally advanced

- Patient characteristics: performance status, haemoglobin

- Tumour characteristics: T and N stage, site of primary tumour, tumour differentiation, involved margins of resection, extracapsular spread, perineural invasion

- Molecular markers: epidermal growth factor receptor, human papillomavirus

Recurrent or metastatic

- Clinical characteristics: performance status, weight loss, time of recurrence, prior treatment (radiotherapy, chemotherapy)

- Tumour characteristics: tumour differentiation, site of primary tumour
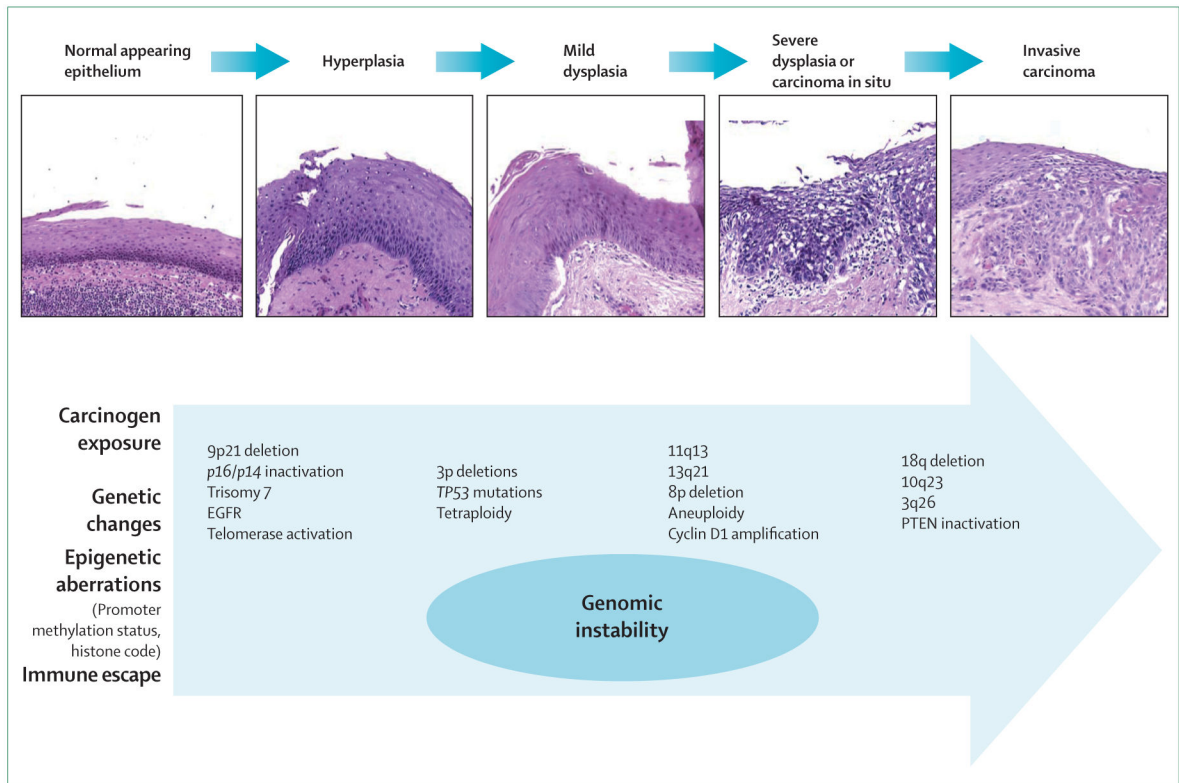
Figure 1: Presentation of phenotypical progression and accumulated molecular alterations in head and neck carcinogenesis

Histological evolution shown in haematoxylin and eosin specimens (×200) parallels genetic and epigenetic events. Modified from references 33 and 34. EGFR=epidermal growth factor receptor. PTEN=phosphatase and tensin homologue.
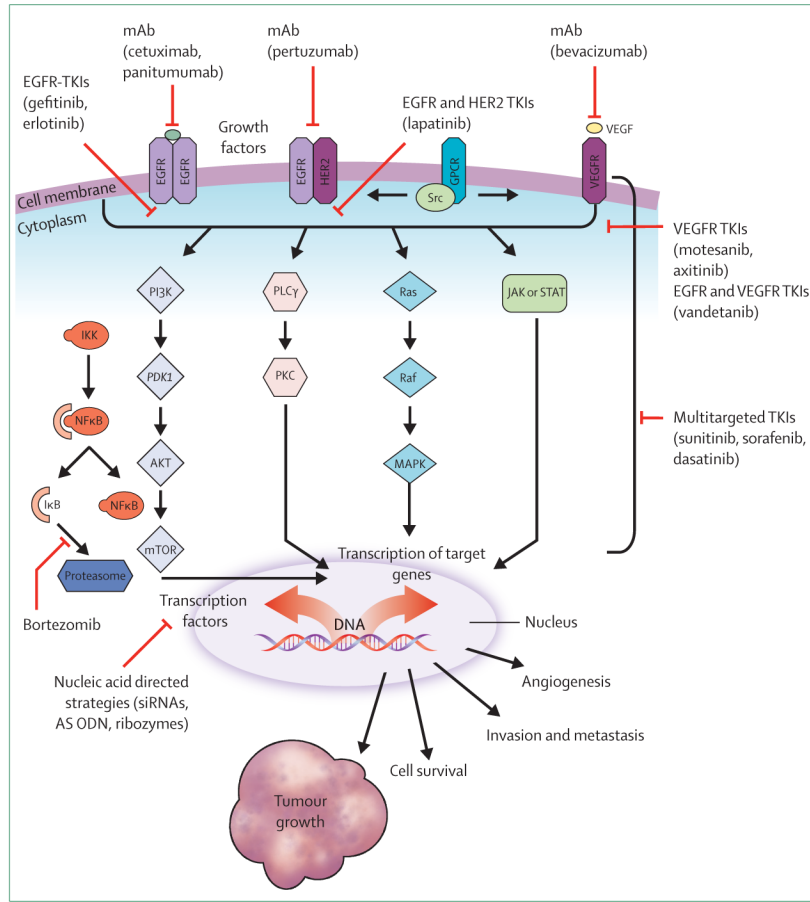
Figure 2: Molecular signalling pathways and novel targeted agents for the treatment of SCCHN
There is considerable cross-talk between various signalling pathways. Various strategies have been developed to inhibit these pathways, such as mAbs; single-selective, dual-selective, or multi-selective tyrosine kinase inhibitors; and nucleic acid-directed gene silencing molecules (eg, AS ODN and RNA interference—siRNA and ribozymes). Representative agents that are used in human beings are listed in the figure. AS ODN=antisense oligodeoxynucleotide. EGFR=epidermal growth factor receptor. GPCR=G-protein-coupled receptor. HER2= human epidermal receptor 2. IKK=inhibitor κB. JAK=Janus kinase. mAb=monoclonal antbodies. MAPK=mitogen-activated protein kinase. mTOR=mammalian target of rapamycin. NF=nuclear factor. PDKI=pyruvate dehydrogenase kinase, isozyme 1. PI3K=phosphatidylinositol-3-kinase. PLCγ=phospholipase-Cγ. PKC=protein kinase. SCCHN=squamous cell carcinoma of the head and neck. STAT=signal transducers and activators of transcription. TKI=tyrosine kinase inhibitor. VEGFR=vascular endothelial growth factor receptor.
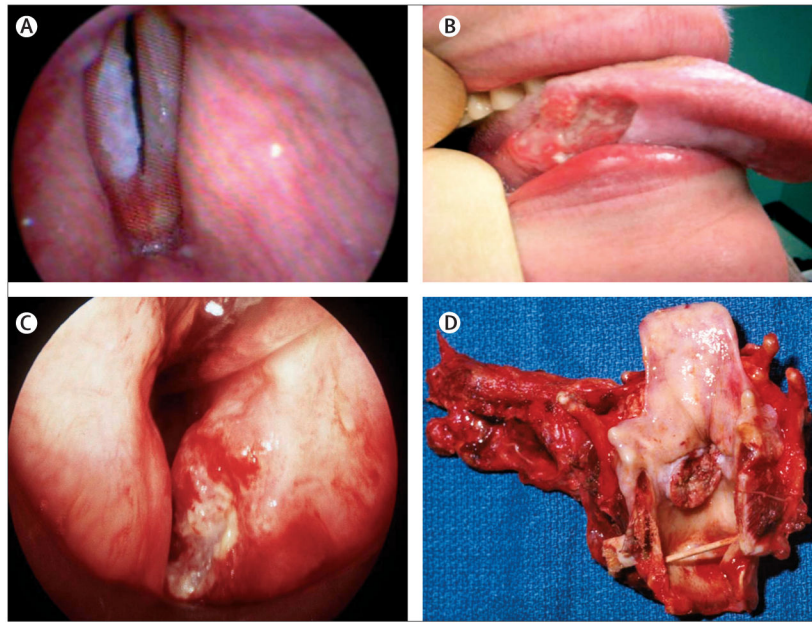
Figure 3: Various stages of squamous cell carcinoma of the head and neck
(A) Premalignancy evidenced by leukoplakia on the right true vocal fold; (B) early oral tongue cancer in a young, non-smoking woman; (C) stage T2 laryngeal carcinoma, potentially treatable with radiation or surgery; and (D) pathology specimen post-total laryngectomy, which is a standard procedure for large volume, destructive laryngeal cancers.
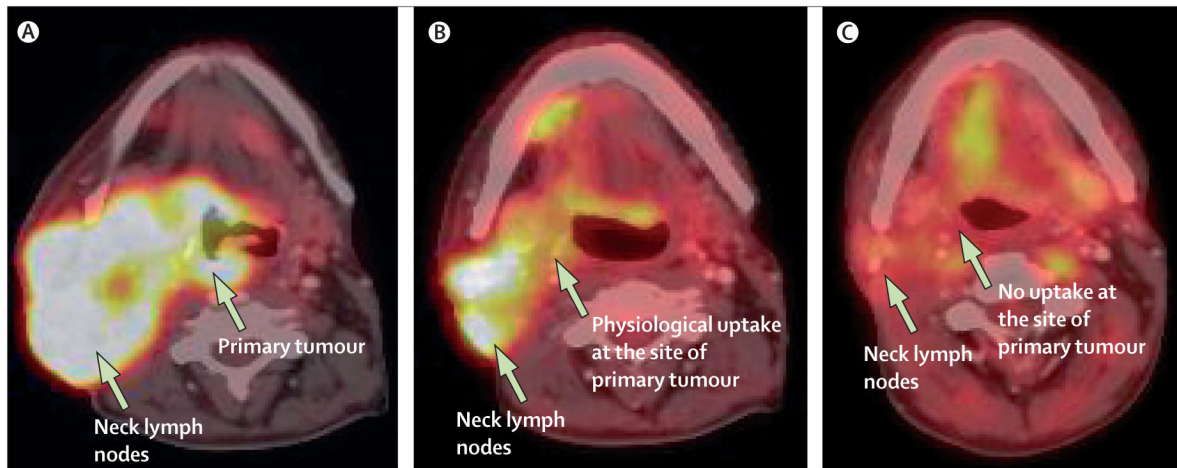
Figure 4: Combined PET-CT scan used for staging and response assessment in locally advanced squamous cell carcinoma of the head and neck

Axial fused images showing (A) locally advanced oropharyngeal squamous cell carcinoma with massive lymphadenopathy, staged as T4N3; (B) induction treatment with cisplatin, docetaxel, and cetuximab (on a research protocol) resulted in complete response in the primary and partial response in regional lymph nodes; and (C) further improvement after completion of radiotherapy with concurrent cisplatin and cetuximab. Physiological uptake is seen in the floor of the mouth. Subsequent neck dissection and biopsy of primary tumour showed a complete pathological response.
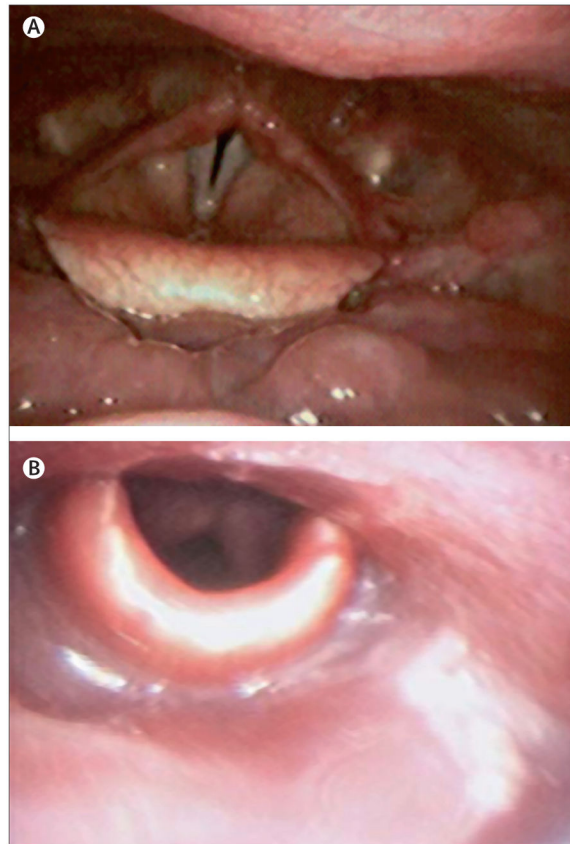
Figure 5: Late effects of radiation might result in poor organ function and quality of life
Laryngoscopic view of (A) normal pharynx; and (B) pharynx with severe fibrosis several years after curative chemoradiotherapy.

Table 1:

Selected randomised phase III studies with concurrent chemoradiotherapy in locally advanced SCCHN

	Number of patients	Treatment schedule	Control arm	Primary endpoint	Treatment outcome
Chemoradiotherapy vs conventional radiotherapy alone as postoperative treatment					
Oral cavity, oropharynx, hypopharynx, larynx[100]	334	Radiotherapy+C (100 mg/m²) d 1,22,43	Radiotherapy	Progression-free survival	47% vs 36% at 5 years, p=0·04 Overall survival 53% vs 40% at 5 years, p=0·04
Oral cavity, oropharynx, hypopharynx, larynx[101,102]	416	Radiotherapy+C (100 mg/m²) d 1,22,43	Radiotherapy	Locoregional control	HR 0·61, 95% CI 0·41–0·91; p=0·01 Updated HR 0·72, 95% CI 0·48–1·06; p=0·08
Oral cavity, oropharynx, hypopharynx, larynx[103]	444	Radiotherapy+C (20 mg/m² ci)+F (600 mg/m² ci) d 1–5, 29–33	Radiotherapy	Locoregional control	88·3% vs 61·9% at 5 years, p=0·0006 Overall survival 58·1% vs 48·6%, p=0·11
Chemoradiotherapy vs conventional radiotherapy alone as primary treatment					
Oropharynx[104,105]	222 (unresectable)	Radiotherapy+Cb (70 mg/m², d 1–4)+F (600 mg/m² ci; d 1–4) for 3 cycles	Radiotherapy	Overall survival	51% vs 31% at 3 years, p=0·02 22·4% vs 15·8% at 5 years, p=0·05
Oral cavity, oropharynx, hypopharynx, larynx[106]	295 (unresectable)	Radiotherapy+C (100 mg/m²) d 1,22,43 (A) or Radiotherapy split course+C (75 mg/m² d 1)+F (1000 mg/m² ci, d 1–4) for 3 cycles (B)	Radiotherapy (C)	Overall survival	(A) 23% vs (C) 37% (p=0·014) vs (B) 27% (p=NS) at 3 years
Larynx[107,108]	510 (resectable)	Radiotherapy+C (100 mg/m²) d 1,22,43 (A) or radiotherapy alone (B)	C (100 mg/m² d 1)+F (1000 mg/m²/d ci d 1–5) for 3 cycles followed by radiotherapy alone in responders (C)	Laryngeal preservation	(A) 84% vs (B) 66% (p=0·00017) vs (C) 70% (p=0·0029), at 5 years
Chemoradiotherapy vs altered fractionation radiotherapy alone as primary treatment					
Oral cavity, oropharynx, hypopharynx, larynx[109]	270 (unresectable)	Hfx radiotherapy+C (60 mg/m², d 1)+F (350 mg/m² bolus, d 2)+Fo (50 mg/m² bolus, d 2) or F (350 mg/m² ci, d 2–5)+Fo (100 mg/m² ci, d 2–5) for 3 cycles	Hfx radiotherapy	Locoregional control	35% vs 17% at 3 years, p<0·004 Overall survival 49% vs 24%, p<0·0003
Oral cavity, oropharynx, hypopharynx, larynx[110]	116 (62 unresectable)	Hfx radiotherapy (70 Gy)+C (12 mg/m², d 1–5)+F (600 mg/m² ci, d 1–5) weeks 1,6	Hfx radiotherapy (75 Gy)	Locoregional control	70% vs 44% at 3 years, p<0·01 Overall survival 55% vs 34%, p=0·07
Oral cavity, oropharynx, hypopharynx, larynx[111]	130	Hfx radiotherapy+C (6 mg/m²) per day	Hfx radiotherapy	Overall survival	46% vs 25% at 5 years, p=0·0075
Oropharynx[112]	192 (unresectable)	Radiotherapy (66–70 Gy)+Cb (75 mg/m², d 1–4)+F (1000 mg/m² ci, d 1–4) for 3 cycles	Conventional radiotherapy or Hfx Acc radiotherapy (64–67·2 Gy)	Overall survival	51% vs 40% at 2 years, p=0·129
Oral cavity, oropharynx, hypopharynx, larynx[113]	224 (78 unresectable)	Hfx radiotherapy+C (20 mg/m², d 1–5) for 2 cycles	Hfx radiotherapy	Time to treatment failure	27% vs 24% at 5 years, p>0·05 Overall survival 46% vs 32% at 5 years, p=0·15

	Number of patients	Treatment schedule	Control arm	Primary endpoint	Treatment outcome
Chemoradiotherapy _vs_ conventional radiotherapy alone as postoperative treatment					
Oral cavity, oropharynx, hypopharynx[114]	384 (unresectable)	Hfx Acc radiotherapy (70·6 Gy)+F (600 mg/m^2 ci, d 1–5)+M (10 mg/m^2 bolus) d 1,36	Hfx Acc radiotherapy (77·6 Gy)	Locoregional control	49·9% _vs_ 37·4% at 5 years, p=0·001 Overall survival 28·6% _vs_ 23·7% at 5 years, p=0·023
Oropharynx, hypopharynx[115,116]	240 (unresectable)	Hfx Acc radiotherapy+Cb (70 mg/m^2 d 1–4)+F (600 mg/m^2 ci, d 1–4) for 2 cycles	Hfx Acc radiotherapy	Locoregional control	22·7% _vs_ 12·6% at 5 years, p=0·01 Overall survival 26·1% _vs_ 13% at 5 years, p=0·008

Acc=accelerated. C=cisplatin. Cb=carboplatin. ci=continuous infusion. d=day of treatment cycle. F=fluorouracil. Fo=folinate. Hfx=hyperfractionated. HR=hazard ratio. M=mitomycin. NS=not significant. SCCHN=squamous cell carcinoma of the head and neck. Unresectable (inoperable) SCCHN is not defined uniformly; it is associated with worse outcomes _vs_ resectable (operable) SCCHN.

Table 2:

Selected phase III randomised trials of cisplatin-based induction chemotherapy in locally advanced SCCHN

	Number of patients	Treatment schedule	Control arm	Primary endpoint	Treatment outcome
Induction chemotherapy followed by locoregional treatment vs locoregional treatment alone					
Larynx[124]	332 (resectable)	C (100 mg/m² ci, d 1)+F (1000 mg/m² ci, d 1–5) every 3 weeks for 3 cycles followed by radiotherapy in responders	Surgery (followed by radiotherapy)	Survival or laryngeal preservation	64% of survivors achieved laryngeal preservation. No difference in overall survival
Hypopharynx[125]	194 (resectable)	C (100 mg/m², d 1)+F (1000 mg/m² ci, d 1–5) every 3 weeks for 3 cycles followed by radiotherapy in responders	Surgery (followed by radiotherapy)	Efficacy equivalence	35% laryngeal preservation at 5 years. Overall survival 57% vs 43% at 3 years (favouring induction)
Oropharynx[133]	318	C (100 mg/m², d 1)+F (1000 mg/m² ci, d 1–5) every 3 weeks for 3 cycles followed by surgery or radiotherapy, or both	Surgery or radiotherapy, or both	Overall survival	Median survival, 5·1 years vs 3·3 years, p=0·03
Oral cavity, oropharynx, hypopharynx, paranasal sinus[131,132]	237 (171 unresectable)	C (100 mg/m², d 1)+F (1000 mg/m² ci, d 1–5) every 3 weeks followed by surgery or radiotherapy, or both	Surgery or radiotherapy, or both	Overall survival	In unresectable, at 5 years, 21% vs 8%; 16% vs 6%, at 10 years, p=0·04 No statistically significant differences in resectable
Taxane plus cisplatin or fluorouracil vs cisplatin or fluorouracil alone					
Oral cavity, oropharynx, hypopharynx, larynx[135]	382 (248 unresectable)	P (175 mg/m² d 1)+C (100 mg/m², d 2)+F (500 mg/m² ci, d 2–6) every 3 weeks for 3 cycles	P (100 mg/m² d 1)+C (100 mg/m² ci, d 1–5) every 3 weeks for 3 cycles	Complete response rate	33% vs 14%, p<0·001 Overall survival 66·5% vs 53·6% at 2 years, p=0·06
Oral cavity, oropharynx, hypopharynx, larynx[137]	358 (unresectable)	D (75 mg/m² d 1)+C (75 mg/m², d 1)+F (750 mg/m² ci, d 1–5) every 3 weeks for 4 cycles followed by radiotherapy	C (100 mg/m² d 1)+F (1000 mg/m² ci, d 1–5) every 3 weeks for 4 cycles followed by radiotherapy	Progression-free survival	Median progression-free survival, 11 months vs 8·2 months, p=0·007 Overall survival 37% vs 26% at 3 years, p=0·02
Oral cavity, oropharynx, hypopharynx, larynx[136]	501 (176 unresectable)	D (75 mg/m², d 1)+C (100 mg/m², d 1–4) every 3 weeks for 3 cycles followed by radiotherapy+Cb (AUC=1·5) every week	C (100 mg/m², d 1)+F (1000 mg/m², d 1–5) every 3 weeks for 3 cyles followed by radiotherapy+Cb (AUC=1·5) every week	Overall survival	Median overall survival, 71 months vs 30 months, p=0·006,62% vs 48% at 3 years
Hypopharynx, larynx[134]	220 (resectable)	D (75 mg/m² d 1)+C (75 mg/m² d 1)+F (750 mg/m² ci, d 1–5) every 3 weeks for 3 cycles followed by radiotherapy for responders	C (100 mg/m² d 1)+F (1000 mg/m² ci, d 1–5) every 3 weeks for 3 cycles followed by radiotherapy for responders	Laryngeal preservation rate	73% vs 63% at 3 years, p=0·036

C=cisplatin. Cb=carboplatin. ci=continuous infusion. d=day of treatment cycle. D=docetaxel. F=fluorouracil. P=paclitaxel. HR=hazard ratio. SCCHN=squamous cell carcinoma of the head and neck.
Unresectable (inoperable) SCCHN is not defined uniformly; it is associated with worse outcomes versus resectable (operable) SCCHN.