Current clinical outcomes demand new treatment options for SCCHN

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Head and neck cancer can be a devastating disease. The mainstays of treatment for early stage disease are either radiotherapy or surgery. However, although disease responds well at this stage, the risk of a second primary cancer is high, with a development rate of about 4% per year. Advanced diseases are treated either by surgery with postoperative radiotherapy or by definitive radiotherapy, with surgery in reserve for salvage if necessary. Over the past two decades major advances have been made in surgery (reconstructive surgery, non-mutilating surgery). Either definitive or postoperative, radiotherapy is an integral part of the treatment for the majority of non-metastatic stages of disease and ways of improving the effects of radiotherapy are constantly being explored. Good activity has been reported for the use of altered radiation fractionation regimens, which allow the delivery of intensified radiation doses. In addition, in recent years randomized trials and meta-analyses have confirmed the survival benefit of adding chemotherapy to radiotherapy in a number of different settings. Cisplatin-based regimens have been identified as the most active and are now standard treatment choices. The survival benefits of chemotherapy appear to be limited to concomitant administration and do not extend to neoadjuvant administration, although this has demonstrated clinical utility in preserving organ function. Platinum-based combination chemotherapy is by many clinicians considered the standard approach to the treatment of recurrent/metastatic disease for patients who are able to tolerate such regimens, but the prognosis for these patients remains poor; this is particularly true for those whose disease progresses on such therapy. This paper discusses current approaches and recent advances in the treatment of head and neck cancer, specifically squamous cell carcinoma, and suggests future management aims for the different disease stages.

Key words: chemoradiotherapy, chemotherapy, head and neck cancer, locally advanced, radiotherapy, recurrent/metastatic

Introduction

Head and neck cancers (comprising cancers of the oral cavity, nasopharynx, pharynx and larynx), make up around 6% of all cancers worldwide (excluding non-melanoma skin cancers) [1]. In most countries they are more common in men than in women. In Europe alone in 2002, the estimated incidence was around 143 000, with over 68 000 deaths [1]. Tobacco and alcohol are major contributors to the development of head and neck cancers. They also generate notable comorbidities, in terms of pulmonary, cardiovascular, hepatic or neurological disorders.

The main histological subtype within head and neck cancers is squamous cell carcinoma (SCCHN). Up to 40% of patients with SCCHN present with metastatic disease, and the main sites of metastases are the lung, mediastinal nodes, liver and bone. The survival of patients with head and neck cancers depends on a number of factors, the most important being disease stage and patient performance status. In a retrospective study of over 3000 mucosal cancers, utilising the fifth edition of the Tumour Node Metastasis (TNM) classification, 5-year survival rates were 91% for stage I disease, 77% for stage II, 61% for stage III, 32% for stage IVa, 25% for stage IVb and less than 4% for stage IVc disease. Survival rates are reduced in patients with comorbidities. Head and neck cancers are characterized by a relatively high risk of a secondary primary cancer, with a constant development rate of approximately 4% per year [3].

General treatment principles

For non-metastatic diseases, whatever the stage, radiotherapy plays an integral part of the treatment strategy plan in the vast majority of the cases. Improvements in delivery methods, such as the use of altered fractionation regimens, have been shown to increase locoregional control both in patients not undergoing resection [4] and in the post-surgical setting [5]. The benefits of chemotherapy are also being increasingly recognized in both resectable and unresectable disease, and the value of adding chemotherapy to radiotherapy in several settings has been confirmed in two meta-analyses [6, 7]. Bourhis et al. showed that

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among 87 trials, the use of chemotherapy was associated with a survival advantage of 5% at 5 years [7]. This benefit was confined mainly to the use of concurrent chemotheraphy and radiotherapy (chemoradiotherapy), which was shown to give an 8% survival advantage at 5 years. The use of chemotherapy in the neoadjuvant setting did not confer a survival benefit [8].

Early stage (stage I and II) disease

Early stage disease is often treated with single modality therapy, namely open or endoscopic surgery, brachytherapy or external beam radiotherapy. In stage I disease, surgery and radiotherapy produce quite similar results. It is generally accepted that treatment of early stage disease should be individualized to the patient and should be based primarily on the disease and the patient’s clinical characteristics, including tumour site and size, and the patient’s age, performance score, cardiovascular and pulmonary functions and wishes. In addition, the patient’s occupation and access to medical resources should also be taken into account. Importantly, the intention of treatment should be determined, i.e. initial cure, ultimate cure (salvage therapy, if any), or cosmetic and optimal functional outcome (quality of life).

In view of the high risk of development of a second primary tumour, which is particularly common in tobacco-exposed tissue, lifestyle changes, for example avoidance of alcohol and tobacco, are advised as a way of helping to reduce this risk, although the extent of any benefit is uncertain. Another way of potentially reducing the risk of second primaries is by the use of chemoprevention, which has been attempted in a number of malignancies, with notable success in some (for example the use of tamoxifen in breast cancer) [9]. In head and neck cancers, retinoids are some of the most extensively investigated compounds and high dose treatment may be effective against premalignant oral lesions. However, recent results from a phase III randomized study in patients with radically treated SCCHN failed to show a significant chemopreventive effect of 13-cis retinoic acid, with no differences between the treatment groups in overall or relapse-free survival [10]. Another large randomized study showed no significant activity of N-acetylcycteine and vitamin A, either alone or in combination, in preventing the development of second primary tumors, compared with no intervention [11]. Novel molecular targets, such as the epidermal growth factor receptor and cyclo-oxygenase-2, appear to be attractive options for chemoprevention and further investigation should help to define their role [9].

Non-metastatic locally advanced disease

For patients with resectable disease, treatment with surgery and post-operative radiotherapy is considered a standard approach. At this stage, as radical resection is the aim, surgery is often extensive. In our experience, the 5-year survival of patients treated in this way is between 35% and 65%. Wherever possible, however, organ preservation is also a desirable aim, and balancing these two goals is difficult. In terms of the success of resection, positive steps have been made with advances in surgical techniques and pre-surgical tumour mapping. However, limitations continue to exist in the form of technical obstacles, patient characteristics (predominantly performance status) and potential cosmetic and functional sequelae.

Despite the use of post-operative radiotherapy following resection, there is a relatively high risk of tumour recurrence (locoregionally or at distance). Combining chemotherapy with radiotherapy was postulated to reduce this risk and this was recently confirmed in two randomized trials, both using cisplatin chemotherapy. In a US trial, 459 patients who had undergone tumour resection were randomized to receive radiotherapy (60 to 66 Gy in 30–33 fractions over 6–6.6 weeks) either alone or in combination with cisplatin (100 mg/m², days 1, 22, and 43) therapy [12]. After a median follow-up of nearly 46 months, the rate of local and regional control was significantly higher in patients receiving chemoradiotherapy than in those receiving radiotherapy alone (hazard ratio 0.61, \( P = 0.01 \)). Disease-free survival was significantly longer with chemoradiotherapy than with radiotherapy alone (\( P = 0.04 \)) but there was no significant difference in overall survival. The second trial, a European trial in 334 patients, was of a similar design [13]. After a median follow-up of 60 months, the incidence of local and regional relapse was significantly lower in the chemoradiotherapy group (\( P = 0.007 \)) and the rate of progression-free survival was significantly higher (\( P = 0.04 \)), with 5-year estimates of 47% and 36% for chemoradiotherapy and radiotherapy alone, respectively. In this study, the rate of overall survival was also significantly longer with chemoradiotherapy (\( P = 0.02 \)), with 5-year estimates of 53% and 40% (Figure 1). Although the efficacy of chemoradiotherapy was clearly demonstrated by these trials, there are some toxicity concerns relating to this treatment approach. In both trials, there was a significant increase in the incidence of acute grade 3/4 adverse events. In the US trial, the incidence of acute grade 3/4 adverse events with chemoradiotherapy was 77% compared with 34% for radiotherapy alone (\( P < 0.001 \)) [12]. In addition, there were four treatment-related deaths in the chemoradiotherapy arm. In the European trial, the corresponding figures for grade 3/4 adverse events were 41% and 21% (\( P = 0.001 \)). However, there was no increase in the incidence of late adverse events which are in general more problematic with postoperative chemoradiotherapy [13].

![Figure 1. Chemoradiotherapy significantly prolongs survival compared with radiotherapy alone [13]. Copyright © 2004 Massachusetts Medical Society. All rights reserved.](image-url)
The value of neoadjuvant chemotherapy in the treatment of SCCHN has yet to be confirmed [14]. Theoretically, in responders, this approach should decrease the tumour burden (improving the chances of cure following resection and/or organ preservation), reduce the likelihood of the formation of distant metastases, and, thereby, prolong survival. Despite indications that this approach may improve response rate, prolongation of survival has not been achieved. A randomized trial in 195 patients with resectable oral cavity squamous cell carcinoma, conducted over a 10-year period, showed no survival advantage of preoperative cisplatin/5-FU [15]. Strong evidence for the lack of survival efficacy of neoadjuvant therapy was provided by a meta-analysis on nearly 11,000 patients [8]. While the effects of neoadjuvant chemotherapy on survival need further investigation, an area in which this approach has been shown to be of value is in organ preservation [16, 17]. In an American randomized study of 332 patients with stage III/IV laryngeal carcinoma, comparing the use of chemotherapy followed by radiotherapy with conventional laryngectomy followed by radiotherapy, the former strategy enabled laryngeal preservation in 64% of patients in this group [16]. Importantly, organ preservation was achieved without an adverse effect on survival. After a median follow-up of 33 months, there was no difference in overall survival between the two groups. Interestingly, however, there was a significant increase in local recurrence with chemotherapy/radiotherapy but a significant reduction in the development of distant metastases compared with the surgery/radiotherapy group. In a European trial, 202 patients with hypopharyngeal SCC were included in a similar randomized comparison [17, 18]. With a 10-year follow-up, there was no deleterious impact on overall disease control and survival, and more than half of the survivors were able to retain a functional larynx [18]. The preservation of organ function can have an important impact on a patient’s quality of life. A small study compared swallowing outcome (assessed using emotional and functional measures) in patients who received chemoradiotherapy or who underwent resection followed by post-surgical radiotherapy for stage III/IV oropharyngeal primaries, and who were disease-free after at least 12 months [19]. This study showed that patients receiving chemoradiotherapy had a significantly better swallowing outcome than those receiving surgery and subsequent radiotherapy. Interestingly, however, there were no significant differences between treatment groups for laryngeal and hypopharyngeal primary tumours. Finally, the Radiation Therapy Oncology Group (RTOG) published preliminary results of a 3-arm randomized trial for organ preservation in 547 patients with laryngeal SCC [20]. Patients were randomly assigned to receive either neoadjuvant chemotherapy (as in the American trial discussed previously), chemoradiotherapy (70 Gy with cisplatin 100 mg/m\(^2\) on days 1, 22 and 43) or irradiation alone. The preliminary results revealed a significantly improved larynx preservation rate in the chemoradiotherapy arm but with a significantly increased incidence of acute toxicity. There was no difference in survival between the three arms.

For unresectable disease, radiotherapy was for many years the treatment of choice. In our experience, this approach to therapy can be expected to be associated with a 5-year survival rate of 15–25%. The use of radiotherapy alone has now largely been superseded by chemoradiotherapy, whenever compatible with the patient’s performance status. The benefits of chemoradiotherapy were shown in the meta-analyses reported by Browman [6] and Bourhis [7], and, more specifically, in a number of recently published studies in unresectable disease. In a French randomized study in 163 evaluable patients with unresectable oro- and hypo-pharyngeal carcinomas, the addition of 3 cycles of cisplatin (100 mg/m\(^2\)) and 5-FU (750 mg/m\(^2\) for cycle 1 and 430 mg/m\(^2\) for cycles 2 and 3) to radiotherapy significantly improved the overall survival rate (48% vs 36%, \(P = 0.05\)) [21]. The benefits were generally confined to the 123 patients with oropharyngeal carcinoma: in these patients the median survival time was prolonged to 17 months compared with 10 months \((P < 0.05)\). For the 40 patients with hypopharyngeal carcinoma, however, there was no significant difference between the two treatment arms. Maguire et al. reported that the use of hyperfractionated radiotherapy in combination with cisplatin and 5-FU gave a longer survival than that seen in a historical control group of patients receiving radiotherapy alone [22]. At a median follow-up of 23 months, the overall survival rates were 80% and 43% \((P < 0.01)\), respectively. Although the efficacy was encouraging, grade 3 mucosal toxicity was universal and there was a relatively high incidence of grade 3/4 late toxicities. Following on from this, a German randomized study compared hyperfractionated accelerated radiotherapy (HART) alone and with chemotherapy (C-HART) in patients with inoperable SCCHN, mainly oro- (60%) and hypo-pharyngeal (32%) malignancies [23]. Adding a combination of 5-FU and mitomycin C to HART significantly improved locoregional control and progression-free and overall survival rates at 5 years. There was no significant difference between treatment arms in acute and late reactions. Another German study is now comparing C-HART using 5-FU in combination with either mitomycin C or cisplatin in patients with stage IV disease. A recently reported study highlighted the problem of chemoradiotherapy-associated dysphagia, which is common and can be life-threatening if mismanaged [24].

Although neoadjuvant chemotherapy has shown some benefit in resectable disease, albeit for organ preservation rather than survival, the use of this approach followed by radiotherapy alone or by surgery, should the primary tumour become resectable, has not shown any survival benefit in unresectable disease, and is not a recommended standard approach [25]. However, a recent randomized trial in unresectable disease showed that the addition of docetaxel to four cycles of cisplatin-5-FU significantly improved overall survival, suggesting that neoadjuvant chemotherapy should be revisited [26].

**Metastatic and recurrent disease**

In recurrent and metastatic disease, chemotherapy is the standard management option and is generally used with palliative intent. Chemotherapy using single-agent cisplatin has been shown to prolong survival compared with best supportive care [27], and a response rate of between 15 and 30% can be expected [28–30]. The combination of cisplatin with other active agents,
such as 5-FU and methotrexate, has increased response rates to
around 35% [28, 29], but this has not been accompanied by
significant improvements in overall survival (median 6–9
months). Despite the absence of obvious survival benefit, many
clinicians consider combination regimens as a standard treatment
approach today and generally comprise cisplatin/carboplatin in
combination with either 5-FU or a taxane.

Reirradiation has shown some success in recurrent disease or
in patients presenting with a second primary [31, 32]. While this
appears to be a feasible approach, at least for some patient sub-
groups, its utility needs to be confirmed in randomized trials.

Patients with advanced SCCHN have limited therapeutic
options once they progress on platinum-based chemotherapy,
and there is no standard treatment approach [33]. The median
survival of such patients is only around four months. Those
treated with commonly used salvage chemotherapy regimens
generally have a poor response rate, in the region of 3%.

Conclusions and goals for future treatment strategies
Progress has been, and continues to be, made in the treatment of
head and neck cancers. However, current outcomes particularly
for the advanced stages of the disease are poor and necessitate
new and innovative approaches to disease management. In mapp-
ing out the aims for future treatment plans, which are necessarily
different at the various stages of the disease and which are
dictated by our experience to date, it is important that we temper
our idealism with realism (Figure 2). In early stage disease,
progress in surgical and pre-surgical techniques (imaging) has
enabled more accurate resection. The goal now is to maintain
a favourable efficacy/toxicity ratio for treatment and to reduce
the incidence of second primary tumours, the major cause of
relapse. One of the milestones in treatment in recent years has
been the confirmation, from randomized studies and meta-
analyses, that the addition of chemotherapy to radiotherapy
improves survival in patients with both resectable and non-
resectable, advanced disease. Likewise, altered fractionation ra-
diation schedules have enabled the delivery of intensified doses
of radiotherapy with improved locoregional disease control. As
expected, both of these approaches are generally associated with
an increase in the incidence of acute grade 3/4 side effects. This
toxicity limits the use of such intensified therapies in patients
that present with co-morbidities. The immediate aim of treat-
ment at this stage should be to increase survival, locoregional
control and organ preservation and to reduce both the formation
of distant metastases and the incidence of severe acute treatment-
related toxicities, particularly mucositis. In addition, the use of
neoadjuvant chemotherapy, which has so far failed to fulfil
expectations, merits further investigation in well defined, con-
trolled trials. The outlook for patients with recurrent/metastatic
disease remains poor, particularly for those whose disease pro-
gresses on platinum-based therapies. For these patients, our goal
is to improve response rates to chemotherapy and, wherever pos-
able, to prolong survival without compromising quality of life.

In the search for treatments to improve outcome in various
cancers, molecular targeted therapies are at the forefront of in-
vestigational strategies. In head and neck cancers, much of the
data generated with such therapies to date is with the EGFR
inhibitors, particularly the IgG1 monoclonal antibody (MAb)
cetuximab (Erbitux®) which enhances the effects of conventional
chemotherapy and acts as a radiosensitiser. Clinical experience
with cetuximab in combination with radiotherapy in locally
advanced disease and chemotherapy in recurrent/metastatic
disease is promising [34, 35]. Particularly encouraging are the
findings in cisplatin-resistant disease showing the activity of
cetuximab both in combination with cisplatin [36, 37] and as a
single agent. The ability of targeted therapies to increase the
therapeutic index of current conventional therapies without in-
creasing their toxicities means that these agents undoubtedly
have a valuable role to play in clinical practice and one that must
be evaluated further.

Disclosure

The author is a member of advisory boards for Sanofi-Aventis,
Merck Liphra Sante and Merck KGaA.

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