The treatment of head and neck cancer has traditionally consisted of surgery with postoperative radiation therapy. Chemotherapy has been reserved for palliation.

Introduction

Head and neck cancer occurs at an incidence of approximately 40,000 cases annually in the United States.[1] Approximately one-third of patients present with early-stage disease, which is usually cured with single-modality surgery or radiation therapy.[2] The great majority of the remaining patients present with locoregionally advanced disease, ie, large primaries (T3, T4) and/or involvement of neck lymph nodes (N1 to N3). For many years, treatment for patients with locoregionally advanced disease has consisted of surgery with postoperative radiation therapy; patients with unresectable disease were treated with radiation alone. The majority of these patients developed recurrent disease (usually locoregionally) within the first 2 to 3 years following completion of therapy, resulting in poor long-term survival rates. As a result, investigational approaches have been pursued, including the integration of chemotherapy into combined-modality treatment plans.[3-5]

Chemotherapy in Recurrent Head and Neck Cancer

Most active agents in head and neck cancer have been defined in patients with recurrent or metastatic disease. Active single agents include cisplatin (Platinol), fluorouracil (5-FU), carboplatin (Paraplatin), the taxanes, and probably gemcitabine (Gemzar) and vinorelbine (Navelbine).[3] Additional agents with some reported activity include doxorubicin (Adriamycin), hydroxyurea, and mitomycin (Mutamycin). When administered to patients with recurrent disease, however, response rates to these single agents are low and overall median survival times rarely exceed six months. Combination chemotherapy, such as cisplatin/5-FU, has been shown to result in higher response rates of approximately 30%; however, there is no clear indication of prolonged survival when combination chemotherapy is used instead of single-agent chemotherapy.[6,7] Similarly, the biochemical modulation of 5-FU with interferon has failed to result in a further prolongation of life.[8] Investigation of new drugs or combinations is a current issue of interest. Also, the use of reirradiation with concomitant chemotherapy has resulted in encouraging early data.[9-14]

Combined-Modality Approaches for Head and Neck Cancer

Sequential Combined-Modality Therapy

Adjuvant and induction (neoadjuvant) chemotherapy approaches have been pursued with great interest over the past two decades. Initial pilot studies indicated much higher response rates when the combination of cisplatin and 5-FU was used for induction chemotherapy than had been reported in patients with recurrent disease.[15-19] Most pilot studies indicated overall response rates exceeding 80% and complete response rates of 50% and higher. Survival data, however, were frequently less optimistic. For example, of 51 patients treated at the University of Chicago with cisplatin/5-FU followed by surgery and radiation therapy and additional adjuvant cisplatin/5-FU, only 5 patients were alive with a follow-up exceeding 5 years.[19] Pilot studies also suggested that induction chemotherapy could be used with the intent of organ preservation.[20] Patients achieving biopsy-confirmed complete response to induction chemotherapy at the primary site were offered subsequent radiation therapy, with surgery reserved for patients with recurrent disease. The feasibility of this approach was confirmed in the pilot setting. Randomized studies testing sequential combined-modality therapy have also been conducted.[21-27] Based on the phase II data, any hypothetical impact of induction chemotherapy...
on survival rates would be postulated to be small. Since many published studies utilized suboptimal chemotherapy regimens (eg, single-agent chemotherapy, low dose intensity, inactive drugs) or entered too few patients to be able to detect small differences, they must be considered inconclusive.[28]

Several large studies involving active combinations and large patient cohorts have been published in recent years. None of these trials has demonstrated that induction chemotherapy (or adjuvant chemotherapy) significantly prolongs survival for the entire patient cohort. Subset analysis has suggested, however, that at least some patients may benefit from the addition of sequential combined-modality therapy.[22,23,26] For example, in the Intergroup study, there was a trend toward increased survival in patients with extracapsular lymph node spread or close surgical margins who received chemotherapy.[23]

Two randomized studies have investigated the role of induction chemotherapy in an organ preserving strategy. The first study was the Veterans Administration's larynx preservation study.[25] In this study, patients received either standard therapy with surgery and postoperative radiation or two to three cycles of induction chemotherapy followed by radiation therapy, with laryngectomy reserved as a planned salvage procedure.

Early data indicated no difference in survival between the two study arms. Of patients receiving chemotherapy, however, 64% did not undergo laryngectomy. Long-term survival data from this study have not been published.

A European study investigated a similar concept for patients with hypopharyngeal cancer.[27] Here too, induction chemotherapy resulted in similar survival data while allowing for organ preservation; 42% of patients in the chemotherapy arm were alive with a functional larynx at 3 years of follow-up and 35% at 5 years.

**Summary**
Sequential combined-modality therapy has not improved survival rates to date. This may be due to the presence of cross-resistant cancer cells when using cisplatin-based combination chemotherapy in sequence with radiation therapy.

Larynx preservation was shown to be feasible in two studies.[25,27] It is possible, however, that radiation therapy, by itself, would be as effective as chemotherapy followed by radiation therapy in allowing organ preservation. This hypothesis forms the basis of a large, current Intergroup study in the United States.

It must also be emphasized that induction chemotherapy remains an attractive setting in which to investigate new drugs or novel combinations in head and neck cancer. In particular, the taxanes and other recently identified agents with activity in solid tumors should be investigated as components of induction regimens.

**Concomitant Chemoradiotherapy**

Since failure to eradicate all tumor cells within the radiation field occurs in the majority of patients with locoregionally advanced head and neck cancer, it can be postulated that clinical radiation resistance is an important factor. One tool to overcome radiation resistance is the simultaneous administration of radiation and chemotherapy.[29,30] Preclinical experiments have indicated a variety of mechanisms of interaction by which concurrent chemotherapy can increase the cytotoxicity of radiation.

Clinical trials in patients with head and neck cancer have indicated that single agents, including 5-FU, bleomycin (Blenoxane), mitomycin, and methotrexate,[31-36] administered with concomitant radiation therapy can improve disease-free and/or overall survival rates. These findings have been confirmed by a recent meta-analysis, which found that concomitant chemoradiotherapy leads to a statistically significant improvement in the control of head and neck cancer.[37]

Combination chemotherapy also has been studied. A European study investigating the administration of cisplatin and daily IV bolus 5-FU in rapid alternation with radiation therapy vs radiation therapy alone has recently been updated.[38] Improved disease-free and overall survival rates were seen on the chemoradiation arm; however, survival rates on both study arms were poor, and the quality of radiation therapy administration on the control arm has been questioned.[39]

Phase II studies involving combination chemotherapy with split-course radiation therapy have frequently indicated very impressive locoregional control and survival data.[40-47] This is of great interest since protracted administration of radiation therapy by itself has been considered detrimental. It appears that, in the presence of chemoradiotherapy, at least limited protraction of radiation is feasible. Randomized clinical trials using these intensive regimens are awaited with great interest.

**Nasopharyngeal Cancer**

Nasopharyngeal cancer has historically been treated with radiation therapy alone since, due to its...
anatomic location, it is usually unresectable. The disease is known to have a higher propensity for regional and distant spread than other head and neck cancers. Nasopharyngeal cancer has a high incidence on a worldwide basis and has been associated with the Epstein-Barr virus and exposure to highly salted foods.[48] Histopathologically, it is most frequently a lymphoepithelioma; in the United States, however, up to one-third of cases are of squamous-cell histology and are linked to the classic head and neck cancer risk factors of tobacco and alcohol.

**Combined-Modality Therapy**

Phase II studies suggest that chemotherapy has greater activity in nasopharyngeal cancer than in other head and neck cancers.[48] A sequential combined-modality therapy approach has been tested. Preliminary data suggest that induction chemotherapy improves disease-free survival, although a positive effect on overall survival has not yet been demonstrated.[49] Recently, however, accrual for a randomized US study testing concomitant cisplatin and radiation therapy followed by adjuvant cisplatin and 5-FU was stopped prematurely when an interim analysis showed a large differential in disease-free and overall survival favoring the chemotherapy arm.[50] As a result, this approach is now considered standard therapy for patients with nasopharyngeal cancer. Whether these data are relevant to the endemic form of the disease in Asia remains to be established.[51,52]

**Summary and Future Directions**

The use of chemotherapy in head and neck cancer is becoming more established. Induction chemotherapy can be used with the intent of larynx preservation in patients with unresectable disease; concomitant chemoradiotherapy (eg, with 5-FU or mitomycin) can be justified in view of the otherwise poor prognosis of patients and the increasing body of evidence suggesting an improved outcome with this approach. Finally, for patients with nasopharyngeal cancer, concomitant cisplatin/radiation therapy followed by adjuvant cisplatin/5-FU should be considered an established standard approach. Current areas of interest include studies of new drugs, both in induction and concomitant therapy regimens, as well as the pursuit of novel treatment approaches in patients with recurrent disease. It is hoped that these studies will lead to improved therapeutic tools in the future. Finally, chemoprevention strategies remain important, given the high number of second malignancies in patients cured of their first head and neck cancer.

**References:**


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