Chemotherapy for squamous cell carcinoma of head and neck: The future is now

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Introduction

The management of squamous cell carcinoma of the head and neck (HNSCC) has been the focus of extensive clinical research during the last 20 years [1]. Traditionally, options for primary therapy have been limited to surgical resection and/or conventional radiotherapy; chemotherapy was reserved for patients with recurrent and/or metastatic disease. Nowadays, chemotherapy is under investigation in the neoadjuvant or adjuvant setting and as a replacement for routine radical surgery; concurrent chemoradiotherapy has led to increased survival rates for patients with unresectable disease and alternative radiotherapy fractionation schemes have been developed. In the near future, chemopreventive regimens may be administered routinely following the completion of multimodality chemoradiotherapy-based treatment programs.

A complex pattern of competing risks threatens the long-term survival of the head and neck cancer patient. Local and regional failure represent the main challenge to the majority of patients [1]. Distant failure is a less common event, predominantly seen in patients with advanced primary or nodal disease. Micrometastatic dissemination, however, has been suggested to be a much more common event [2, 3]. This is supported by some studies demonstrating improved local control with concomitant chemoradiotherapy in which distant metastases emerged as a significant cause of failure. Following effective locoregional and distant tumor control, second primary tumors are responsible for a considerable fraction of late 'failures'. Finally, patients die of cardiac, respiratory or other co-existing medical problems caused by the same risk factors leading to their primary malignancy.

In order to face the challenge of these competing risks, complex multimodality programs including combinations of chemotherapy, radiotherapy and surgery, sometimes followed by chemoprevention are being developed. Overall survival, pattern of failure, cause of death, and quality of life are the important study endpoints, while response rates and progression-free interval are intermediate endpoints of lesser significance.

This review will focus on recent developments in HNSCC and outline the scientific agenda for the remainder of the decade.

Molecular biology

Recent advances of molecular biology have greatly expanded our knowledge and understanding of carcinogenesis. Underlying genetic abnormalities have been described for colon cancer and a model of multistep carcinogenesis has been suggested [4]. Carcinogenesis in the head and neck is also understood as a multistep process, although a specific sequence of genetic events has not yet been described.

Specific genetic abnormalities can be identified with increased frequency; for example, the progression of oral premalignancies to invasive cancer has been associated with loss of RAR-α expression, which can be restored with retinoids [5]. Genetic alterations involving loss or amplification of a genetic message have been found with increased frequency in HNSCC [6–10]. Chromosomal deletions in 3p, 9p, 17p and 13q areas are the most frequent. Deletion of 9p is encountered in 2/3 of all HNSCC tumor specimens and is considered an early event of carcinogenesis [10]. The cell cycle gene p16 is located in this area; p16 protein is an inhibitor of the cyclin-CDK complex which regulates the transition to the synthetic or the mitotic phase of the cell cycle. The p16 gene is a putative tumor suppressor gene; inactivation of the p16 protein appears to be an early event of head and neck carcinogenesis and to make the cell more vulnerable to the acquisition of other mutations.

Loss of chromosome 17p has been observed in over 50% of HNSCC cases; it is associated with alteration of the p53 protein [11, 12]. The p53 gene codes for a 53
kD protein, which following DNA damage allows for an arrest in the cell cycle between the G1 and the synthetic phase until the repair of a genetic misprint is complete. In case of extensive DNA damage prolonged cell cycle arrest and apoptosis with cell death may occur [13]. This protective mechanism guards the genetic fidelity and prevents the propagation of occurring mutations.

Amplification of 11q13 is another frequent abnormality in HNSCC indicating the presence of a critical protooncogene in this location [14]. PRAD1 is coded in this location and is overexpressed in 1/3 of tumor specimens; moreover, PRAD1 gene amplification and the relevant mRNA overexpression have been correlated with tumor progression [15, 16].

Other putative protooncogenes have been incompletely studied. Epidermal Growth Factor Receptor (EGFR), a 140 kD protein is overexpressed in tumor specimens compared to normal tissue [17–20]. Overexpression of EGFR is more pronounced in poorly differentiated tissues [18] and in some studies correlates positively with tumor size and poor prognosis [20].

Analysis of the pattern of p53 inactivation in patients with HNSCC showed that the incidence of gene mutations is significantly higher in patients with history of tobacco and ethanol use [21, 22]. The occasional head and neck cancer patients without these exposures, exhibit endogenous site mutations which are not encountered in tobacco and ethanol users. Thus, there appears to be a genetic link between smoking and cancer.

PCR technique has been used to analyze histopathologically negative surgical margins of resected HNSCC with a known p53 mutation. In approximately half of the studied patients tumor specific p53 mutations could be identified in the phenotypically normal surgical margins [23]. Of interest, these 'upstaged' patients had a worse clinical outcome. Attempts have also been made for early diagnosis of cancer through the detection of abnormal p53 protein in the saliva or sputum [24, 25].

Genetic therapies have been applied against HNSCC in the laboratory. Cell cultures of HNSCC with dysfunctional p53 protein, showed dramatic regression after insertion of a wild type p53 gene, through a viral vector [26]. In addition, antibodies against the binding domain of the EGFR inhibited the growth of head and neck cancer cells in cell cultures [27].

A viral etiology for lymphoepithelioma is strongly supported by epidemiologic data and recent laboratory studies including the demonstration of viral genome in premalignant lesions [28–30]. The human papilloma virus (HPV) has also been implicated as a possible etiologic factor [22, 31].

It is hoped that innovative genetic therapies will evolve as major new therapeutics in the near future. In the meantime, molecular methods are increasingly applied as diagnostic and staging tools. It is conceivable that information derived from molecular studies will result in a more precise prognostic tools that may contribute to a better design of future clinical trials.

Management of recurrent and metastatic HNSCC

Chemotherapy

Single agent chemotherapy

According to many textbooks an acceptable standard of care for recurrent and metastatic HNSCC is single agent methotrexate [32, 33]. Treatment is administered at 40–50 mg/m²/week and the dose can be escalated as tolerated; mucositis and myelosuppression are dose-limiting. Response rates up to 30% have been claimed, but in a large multi-institutional trial only 10% of patients responded for a response duration of only two to three months [34].

Probably the most active single agent in HNSCC is cisplatin. Multiple phase II studies of cisplatin monotherapy claim response rates ranging between 14% and 41%, with a pooled average of 28% [32, 33]. Studies of dose escalation beyond the customary 100–120 mg/m² failed to improve the results, apparently because any possible benefit was balanced by the associated increased toxicity [35].

In 1985, Morton et al. reported a randomized study comparing three chemotherapy arms with a control arm of supportive care only in patients with end-stage HNSCC [36]. The median survival rates were 4.2 months for cisplatin monotherapy, 2.8 months for bleomycin monotherapy and 4.0 months for the cisplatin/bleomycin combination. These figures compared favorably to the median survival of 2.1 months for supportive care only. This study offered strong evidence that cisplatin-based chemotherapy prolongs survival in recurrent/metastatic HNSCC.

The hypothesis that cisplatin is more active than methotrexate was supported by the results of a trial by the Liverpool Head and Neck Oncology Group [37] (Table 1). In this four-arm randomized trial, 200 HNSCC patients were randomized to cisplatin alone, methotrexate alone, cisplatin and infusional 5-fluorouracil (5-FU) or cisplatin and methotrexate. There was no significant difference in the response rates, but the survival of the two cisplatin arms was significantly better than that of the methotrexate arm, at the cost of increased toxicity.

The single agent activity of cisplatin in HNSCC has been assessed in another randomized trial [38] (Table 1). Two hundred forty-five previously untreated patients with recurrent/metastatic disease were randomized to receive cisplatin monotherapy versus 5-FU monotherapy versus a combination of cisplatin with infusional 5-FU (PF). Response rates were 17% versus 13% versus 32%, respectively, and the response to PF was significantly higher compared to the monotherapy arms. The median survival, however, was 5.0
A wide range of doses. In a summary of five conducted cancer biomodulation studies with leucovorin, methotrexate, allopurinol, hydroxyurea and interferon have been reported [41].

From the biochemical pathways involving both DNA and RNA synthesis. These pathways can be exploited in efforts to modulate the activity of the drug. In head and neck cancer biomodulation studies with leucovorin, methotrexate, allopurinol, hydroxyurea and interferon have been reported [41].

Ifosfamide has also been studied in HNSCC in a wide range of doses. In a summary of five conducted phase II studies, 99 patients were evaluated with a cumulative response rate of 26% [42]. In previously untreated patients, however, a 43% response rate has been reported with a 24-hour infusion of 5 mg/m² repeated every three weeks [43].

Other established active agents include doxorubicin, cyclophosphamide, bleomycin and hydroxyurea, all yielding nondurable responses in 10%-30% of patients [33]. Single agent chemotherapy rarely results in clinical complete responses (CRs) and is used exclusively for palliation in patients with recurrent or metastatic HNSCC.

### Combination chemotherapy

The most extensively studied combination chemotherapy regimen is cisplatin in combination with 4–5 days of infusional 5-FU (PF). In single institution trials, response rates as high as 70% with CRs in 27% of patients with recurrent disease were reported [44]. Multi-center trials demonstrated responses of approximately 30% [34, 38]. The hypothesis that PF is the most active regimen in HNSCC was tested in at least four large randomized trials [34, 37, 38, 45]. As described in Table 1, response rates with PF were higher than with single agent chemotherapy and equal or superior to other combinations. The observed responses, however, were not durable and median survival rates were similar for all regimens.

Browman and Cronin reported an analysis of selected randomized trials comparing chemotherapy regimens in patients with recurrent or metastatic HNSCC [46]. Accepting tumor response as an endpoint they concluded that combination chemotherapy is superior to single agents; there was also a strong trend suggesting that PF is superior to other combinations. Survival differences were too small to be significant and quality of life parameters were not objectively measured in these trials. If one accepts the hypothesis that tumor response results in symptom control and improved quality of life, combination chemotherapy has a definite advantage. Indeed, PF is the accepted ‘standard’ regimen in most oncology practices. The combination of carboplatin/5-FU or the single agents cisplatin or methotrexate should be considered as possible alternatives. Since all of these therapies are limited by the poor survival rates, inclusion of patients in clinical trials of new agents or combinations is a much more useful longterm strategy and is strongly encouraged.

The hypothesis, that tumor response correlates with increased quality of life has not been tested in appropriately designed studies; only recently have quality of life parameters been incorporated into clinical studies. The expected results will offer a more comprehensive assessment of the efficacy of chemotherapy and will allow both patients and physicians to make a more informed treatment decision.

Biochemical modulation of the PF combination has also been pursued. Investigators from the University of Chicago introduced a combination of cisplatin, inhibitory.

### Table 1. Selected randomized trials of chemotherapy in recurrent/metastatic HNSCC.

<table>
<thead>
<tr>
<th>Study/chemotherapy [ref.]</th>
<th>Patients</th>
<th>CR + PR (%)</th>
<th>CR (%)</th>
<th>Median survival (M)</th>
</tr>
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<tbody>
<tr>
<td>Stanford [38]</td>
<td>249</td>
<td>32</td>
<td>5</td>
<td>5.5</td>
</tr>
<tr>
<td>PF</td>
<td>79</td>
<td>17</td>
<td>3</td>
<td>5.0</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>83</td>
<td>13</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>SWOG study [34]</td>
<td>277</td>
<td>32</td>
<td>6</td>
<td>6.6</td>
</tr>
<tr>
<td>PF</td>
<td>87</td>
<td>21</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Carboplatin/5-FU</td>
<td>86</td>
<td>10</td>
<td>2</td>
<td>5.6</td>
</tr>
<tr>
<td>EORTC study [45]</td>
<td>365</td>
<td>37</td>
<td>10</td>
<td>6.5</td>
</tr>
<tr>
<td>CABO</td>
<td>127</td>
<td>34</td>
<td>2</td>
<td>(All)</td>
</tr>
<tr>
<td>PF</td>
<td>116</td>
<td>13</td>
<td>3</td>
<td>(patients)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>122</td>
<td>11</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Cisplatin/methotrexate</td>
<td>50</td>
<td>12</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>50</td>
<td>14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>50</td>
<td>6</td>
<td>0</td>
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</tbody>
</table>

NA = not available.

The expected results will offer a more comprehensive assessment of the efficacy of chemotherapy and will allow both patients and physicians to make a more informed treatment decision.
sional 5-FU and the oral form of a racemic mixture of d- and l-leucovorin [47] (PFL). The oral administration of leucovorin resulted in reduced folate serum concentrations sufficient for 5-FU modulation in vitro. The response rate was 56% in previously treated patients. Dose-limiting toxicity was mucositis. The interferons are thought to be biochemical modulators of 5-FU and may also have single agent activity in HNSCC [48]. At least 4 phase II trials of a combination of cisplatin, infusional 5-FU and interferon-alpha have been reported [49–52]; however, response rates appear to be similar to those achieved with PF alone and toxicity, mostly mucositis and neutropenia, appears increased. The question of the potential contribution of IFN in a PF-IFN regimen, has been further tested in an international randomized trial and results are expected in the near future. Most other modulation trials of 5-FU have been conducted in previously untreated patients and will be discussed under ‘induction chemotherapy’ below.

**New agents**

Phase II studies of new agents have been conducted in recurrent or metastatic HNSCC and active agents with novel mechanism of action have been identified (Table 2).

When administered at 250 mg/m² as a 24° infusion, paclitaxel resulted in a 40% response rate in 30 chemotherapy-naïve patients, including five CRs [42]. Shorter infusion times have not yet been adequately tested in HNSCC. A study evaluating a possible dose-response relation for paclitaxel (135 mg/m² versus 200 mg/m² as a 24-hour infusion, both in combination with 75 mg/m² of cisplatin) was recently completed by ECOG and a preliminary report is expected in the near future. A combination of paclitaxel with ifosfamide is also under investigation [41].

An EORTC phase II study testing docetaxel at a dose of 100 mg/m² resulted in 2 CRs and 10 PRs in 40 eligible patients [53]. The median response duration was 6.5 months. An early report of an ongoing phase II study in the USA claims a response rate of 31%, including 2 CRs, in 16 eligible patients [54]. Combinations of docetaxel with other drugs and support with growth factors are currently under investigation.

Vinorelbine, a semisynthetic vinca-alkaloid, resulted in a 22% response rate, without CR’s, in chemotherapy-naïve patients with metastatic HNSCC [55]. When combined with cisplatin and 5-FU a response rate of 61% was reported in 18 patients [56]. An oral formulation of this drug has been shown to be active in patients with lung cancer [57] and exploration of this formulation may also be warranted in the palliative-care setting for HNSCC.

Gemcitabine, an analogue of deoxycytidine, was studied in 61 patients with advanced, unresectable or metastatic HNSCC [58]. Seven partial responses were seen among 54 evaluable patients (PR rate 13%) with no CR’s. Topotecan resulted in short-lived PRs in 4/18 chemotherapy-naïve patients [59].

**Salvage surgery for recurrent disease**

Locoregional recurrence of HNSCC after primary surgery and/or radiotherapy is an ominous sign. Although combination chemotherapy results in objective responses in 30% of these patients, CR’s are rare and cure is not achieved. A possible exception is nasopharyngeal carcinoma, where long-term disease free survival for an occasional patient with recurrent/metastatic disease treated with chemotherapy only has been reported [60]. Salvage surgical resection, therefore, needs to be considered as an option for patients with locoregionally recurrent HNSCC, if distant metastatic disease has been ruled out. An occasional patient may be cured with this approach, especially when the recurrence is located in a contralateral not previously operated neck or when radiation therapy was the only primary therapy.

There are few formal reports of salvage surgery in HNSCC. An Italian report on salvage neck resection indicated a 29.2% five-year survival rate for a series of 113 patients [61]. Salvage laryngectomy has been a standard approach for a previously irradiated larynx and a five-year survival as high as 39% has been reported [62, 63]. Salvage resection for recurrent oropharyngeal cancer has also resulted in significant long term survival rates [64].

Surgical resection of a solitary pulmonary metastasis in patients with lasting locoregional control, is also a reasonable option. It should be strongly recommended for patients with a long disease free interval, since a diagnosis of a new primary lung cancer cannot be ruled out. Even with documented metastatic disease long term disease free survival between 26% and 43% has been achieved with resection, in highly selected patients [63, 65].

**Salvage radiotherapy**

'Salvage' radiotherapy is usually offered to patients with recurrent disease after primary surgery. A second course of radiotherapy (re-irradiation) for palliation has also been attempted. Small tumors of the nasopharynx, larynx and oropharynx are more suitable than tumors in the floor of mouth or alveolar ridge. Re-irradiation for nasopharyngeal carcinoma, either in the form of external beam or interstitial irradiation,

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>CR + PR (%)</th>
</tr>
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<tbody>
<tr>
<td>Paclitaxel</td>
<td>40</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>31</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>26</td>
</tr>
<tr>
<td>Topotecan</td>
<td>22</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>22</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>13</td>
</tr>
</tbody>
</table>
is considered an option with high local control rates [66].

Stevens et al. reported their retrospective experience of high dose re-irradiation in HNSCC [67]. Of 85 patients with recurrent disease in a previously irradiated field, 27% achieved locoregional control and the five-year actuarial survival was 17%. Severe adverse normal tissue effects were encountered in 78 patients and limited surgical resection of necrotic tissue was required. With a follow up ranging between 13 and 84 months, 12 patients were alive without evidence of progressive disease. Therefore, a cautious and selective use of reirradiation may offer palliation and, possibly, long term tumor control for some patients. This approach, however, remains investigational due to the potentially serious complications [68].

Concomitant chemoradiotherapy for previously irradiated HNSCC has also been studied. Since cancer cells recurring in a previously irradiated field, by definition, exhibit radioresistance [69], the concomitant use of chemotherapy represents an attempt to overcome this radiation resistance [70, 71]. Several small clinical studies have been reported that confirm the feasibility of reirradiation with concomitant chemotherapy [72–78]. Most of these studies used a 5-FU-based regimen with either hydroxyurea or cisplatin; infusional paclitaxel has also been studied in this context [75]. Of interest, in most of these studies approximately 20% of patients are reported alive at follow-up periods of two to five years indicating the ability of concomitant chemoradiotherapy to control recurrent HNSCC, at least in some patients. Since response rates are much higher than observed with chemotherapy alone, an additional percentage of patients may achieve palliation of symptoms. Therefore, this approach may be more beneficial than chemotherapy alone, which at best benefits 30% of patients.

In conclusion re-irradiation with concomitant chemotherapy may be an option for selected patients and warrants further clinical investigation.

**Multi-modality therapy of locoregionally advanced HNSCC**

Surgery and/or radiation therapy have been the conventional treatment of choice for locoregional head and neck cancer. Either of these modalities is effective in the management of early lesions with long-term cancer control in 60%–80% of the patients [1]. The selection of the specific modality depends on the location of the primary site, other medical problems but also on local expertise, bias and geography. O'Sullivan et al. highlighted the discordance of the primary therapeutic approach in an international survey of 1,649 otolaryngologists and radiation oncologists [79]. They report striking examples of geographic and specialty-based treatment variations and they conclude that 'accidents of geography and pattern of referral' determine the selection of primary therapy to a great extent.

In patients with locoregionally advanced disease (stages III and IV, Mx) long-term cancer control is achieved in less than 30%. Surgery followed by radiation therapy is the accepted standard for tumors considered to be resectable; the remaining patients have traditionally been treated with radiotherapy alone. Surgery for these advanced lesions frequently results in a significant functional deficit with loss of speech and swallowing in many patients. Therefore, the integration of chemotherapy has been pursued with the goal of increasing survival rates and decreasing the need for aggressive use of surgery.

**Induction (neoadjuvant) and adjuvant chemotherapy**

The rationale for induction chemotherapy has been reviewed [1, 80, 81]. Initial results of phase II studies were very encouraging; response rates were much higher than in patients with recurrent or refractory disease [82–85]. Objective clinical CR rates were as high as 66% and total response rates exceeded 80%, approximately 30%–50% of the clinical CRs were confirmed histologically.

Subgroup analysis of the phase II studies suggested that survival rates were high among patients with nasopharyngeal carcinoma (NPC). Also patients who responded to chemotherapy survived longer than non-responders; this difference in itself did not prove the benefit of chemotherapy since it could simply reflect selection of a more favorable group of patients (chemotherapy response as a favorable prognostic factor). Another significant observation from these studies was that induction chemotherapy did not seem to increase the morbidity of the following surgical resection. Cisplatin and infusional 5-FU emerged as the most active combination, appropriate for definitive phase III investigations of neoadjuvant chemotherapy in head and neck cancer.

These initial positive results stimulated the design of large randomized studies of neoadjuvant (induction) chemotherapy designed to demonstrate improved survival rates, enhanced local control and eradication of latent distant micrometastatic disease. Many studies have been conducted and reported [86]. Only six conclusive randomized trials of neoadjuvant chemotherapy in HNSCC (excluding NPC) have been completed [87–93] (Table 3). All demonstrated a decreased incidence of distant metastases as site of first failure with chemotherapy. However, only one study showed enhanced local control by subset analysis [92]. Most significantly, the studies generally failed to show a significant survival benefit, since the failure to maintain local control is the dominant cause of death in HNSCC.

The National Cancer Institute Head and Neck Contracts Program accrued 462 patients with locally advanced HNSCC and randomized them to three arms [87, 88]. The standard arm was surgery and radiother-
The two experimental arms consisted of a single course of neoadjuvant cisplatin and bleomycin with or without cisplatin maintenance chemotherapy cisplatin. No survival benefit was achieved on either of the chemotherapy arms. It was intriguing, however, that the patients randomized to receive maintenance (adjuvant) cisplatin, despite poor compliance (only 9% of patients completed adjuvant chemotherapy as planned), had a significant decrease in distant metastases as a first manifestation of recurrent disease. This was the first study to suggest the systemic activity of 'adjuvant' chemotherapy in HNSCC even though only a small percentage of patients randomized to the adjuvant chemotherapy arm received all of the six planned cycles of cisplatin. The timid use of chemotherapy and poor quality control with poor compliance by patients and, possibly, physicians may be responsible for a lack of greater therapeutic benefit in this trial.

Between 1980 and 1985, SWOG conducted a randomized study involving 158 patients with resectable HNSCC [89]. Induction chemotherapy consisted of cisplatin, bleomycin, vincristine and methotrexate for three cycles, while the local therapy was standard surgery and radiotherapy for all patients. The response rate to induction chemotherapy was 70%; again, fewer distant failures were noted in the experimental arm (49% vs. 28% at four years; \( p = 0.07 \)). Median survival was 18 months in the experimental arm versus 30 months in the standard arm, but the difference did not meet statistical significance.

The Veterans Administration Cooperative Study Group accrued 332 patients with advanced laryngeal cancer who were randomly assigned to have either standard laryngectomy and post-operative radiotherapy or three cycles of PF followed by radiotherapy in responding patients [90]. On the experimental arm, laryngectomy was offered only if there was no response after two cycles of PF, or as salvage. The study exhibited a significant decrease of distant metastases as a first manifestation of failure with no difference in local control or survival. The most remarkable outcome of this study was the establishment of the principle of organ preservation, which will be described separately below.

Most recently, Paccagnella, and colleagues reported the results of an Italian Intergroup randomized study of 257 patients with stage III or IV HNSCC [92]. Induction chemotherapy for the experimental arm was four cycles of PF. Local therapy for the entire group was individualized. Patients considered to be unresectable by a multi-disciplinary panel were assigned to have radiotherapy. Surgical resection followed by radiotherapy was offered to resectable patients. There was no difference in overall survival, disease-free survival or local control for the entire group; a decrease in distant metastases was shown. Patients with inoperable disease benefitted from induction chemotherapy with improved local control and a small but statistically significant survival advantage by subgroup analysis (24% vs. 10% three-year overall survival; \( p = 0.04 \)).

Following a pilot study utilizing three cycles of PF after surgery (but before radiation), the Radiation Therapy Oncology Group (RTOG) initiated a randomized trial in order to test the concept of 'adjuvant' chemotherapy. Subsequently this study was adopted by the Head and Neck Cancer Intergroup and accrued 448 patients [91]. This study also, failed to show a significant difference in survival (44% vs. 48% at four years) and, again, the incidence of distant metastases as a first manifestation of failure was decreased (23% vs. 15%). A weakness of this study was the large number of patients, who were considered ineligible for randomization because of positive surgical margins; this highlights the difficulty in assessing resectability of HNSCC.

Induction chemotherapy has also been studied in NPC. Generally, NPC is thought to be more sensitive to radiation and/or chemotherapy [94]. A recent randomized study reported by Chan et al. [95] compared radiotherapy alone versus two cycles of PF followed by radiotherapy and four additional cycles of PF. Despite a high response rate of 87% to induction PF, there was no survival difference (two-year survival 80% on both arms). It has been pointed out that this study included a large percentage of patients with earlier stage disease and that radiotherapy alone was exceedingly successful in this study cohort. The theoretical advantage of PF (increased systemic control) is more likely to be observed in patients with advanced T or N stage, who are known to be at high risk of systemic microdissemination [96].

A second randomized study limited to patients with NPC has been reported in abstract form by Cvitkovic.

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### Table 3. Selected studies of neoadjuvant and/or adjuvant chemotherapy in HNSCC.

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Neoadjuvant chemotherapy</th>
<th>Adjuvant chemotherapy</th>
<th>Local therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNCP [87]</td>
<td>Cisplatin-Bleo × 1</td>
<td>Cisplatin × 6</td>
<td>S/XRT</td>
<td>Decreased distant metastases with adjuvant chemotherapy</td>
</tr>
<tr>
<td>Schuller [89]</td>
<td>CMBV × 3</td>
<td>-</td>
<td>S/XRT</td>
<td>Median survival 30 vs. 18 months with chemotherapy</td>
</tr>
<tr>
<td>VA study [90]</td>
<td>PF × 3</td>
<td>-</td>
<td>S/XRT vs. XRT</td>
<td>64% larynx preservation with chemotherapy</td>
</tr>
<tr>
<td>Paccagnella [92]</td>
<td>PF × 4</td>
<td>-</td>
<td>S/XRT or XRT</td>
<td>Survival prolongation with chemotherapy for unresectable disease, in subgroup analysis</td>
</tr>
<tr>
<td>Laramore [91]</td>
<td>-</td>
<td>PF × 3</td>
<td>S/XRT</td>
<td>Chemotherapy given after surgery but before XRT</td>
</tr>
<tr>
<td>Cvitkovic [97]</td>
<td>PEB × 3</td>
<td>-</td>
<td>XRT</td>
<td>Decreased distant metastases with chemotherapy Only for nasopharyngeal carcinoma</td>
</tr>
</tbody>
</table>

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Comments:
- Decreased distant metastases with adjuvant chemotherapy
- Median survival 30 vs. 18 months with chemotherapy
- 64% larynx preservation with chemotherapy
- Survival prolongation with chemotherapy for unresectable disease, in subgroup analysis
- Chemotherapy given after surgery but before XRT
- Decreased distant metastases with chemotherapy
- Only for nasopharyngeal carcinoma
et al. [97]. Neoadjuvant cisplatin, epirubicin and bleomycin followed by conventional radiotherapy was compared to radiotherapy alone. An early analysis demonstrated significant difference in disease-free survival favoring the neoadjuvant group, despite a higher rate of early deaths (9% vs. 1%) and noncompliance with radiotherapy (7% vs. 1%) among patients randomized to the experimental arm. A definitive survival analysis is still pending. A third randomized study by the RTOG has recently been closed early to accrual because of a statistical difference favoring the use of chemotherapy and data should be available in the near future.

Current investigation of induction chemotherapy
At the present time little information exists regarding the activity of paclitaxel or other new drugs in the induction setting. The biochemical modulation of 5-FU, however, has been studied extensively in the phase II setting.

Investigators from the University of Chicago studied the PFL combination of cisplatin, infusional 5-FU and the oral formulation of a racemic mixture of d- and l-leucovorin [47]. Applied in previously untreated patients, PFL resulted in a 81% objective response with 29% CR following only two cycles. When followed by concomitant chemoradiotherapy, the three-year survival rate exceeded 50% [98]. Dreyfus et al. studied PFL as a prolonged infusion of all three drugs and they reported CR of 65% with a total response of 80% following three cycles (CR rate was 26% after two cycles) in previously untreated patients [99]. No survival data have been reported. Other investigators have concluded that PFL is too toxic and not more active than PF alone [100]. The infusion of PFL has also been studied concurrently with radiotherapy [101].

The incorporation of IFN-α as a second modulator in the PFL regimen has also been pursued [102]. PFL-IFN proved to be quite toxic with myelosuppression and mucositis as dose limiting toxicities. In the neoadjuvant setting responses were observed in every one of the treated patients and the CR rate was 56%. When followed by concomitant chemoradiotherapy, the three-year survival exceeded 60% [103].

A potential obstacle to the optimal biomodulation of leucovorin is the presence of two stereoisomers. The l-stereoisomer is the pharmacologically active component, while the d-stereoisomer is inactive; it may also inhibit polyglutamation and the intracellular transport of the active l-leucovorin [104]. The pure l-stereoisomer has been combined with cisplatin and 5-FU in a French study of previously untreated stage III and IV HNSCC. A CR rate of 42.4% with total response of 81.8% was reported [105]. L-leucovorin has also been used with PF and IFN. The L-PFL-IFN regimen exhibited an impressive CR rate of 66% with 87% total response in previously untreated patients [106].

The pharmacology of 5-FU may also be of importance in HNSCC. Thymidylate synthase (TS) is the major intracellular target of 5-FU while dihydropyrimidine dehydrogenase (DPD) is largely responsible for the catabolism of the drug. Laboratory studies suggest that both are of prognostic importance in HNSCC [107]. Clinically, a significant variability of DPD activity has been associated with variability in systemic 5-FU exposure [108]. Variations with sex and age and a circadian variation in DPD activity and 5-FU levels have been described [109]. Milano et al. demonstrated an association of 5-FU area under the curve (AUC), with response and survival, in patients receiving PF induction chemotherapy [110]. The pharmacologic analysis of patients treated with L-PFL-IFN in Chicago confirmed the correlation of 5-FU concentration with response and toxicity [106]. Analysis of 59 eligible patients identified a significant association between 5-fluorouracil serum concentration and severity of neutropenia (p = 0.04) and mucositis (p = 0.02); also the maximum 5-fluorouracil concentration was higher in complete responders (p = 0.015). Etienne et al. also demonstrated that DPD activity in cancer cells correlated with response to 5-FU based chemotherapy [111]. Since the observed variation in 5-FU metabolism could result in subtherapeutic serum levels for some patients, and toxic exposure to 5-FU in others, prospective adjustment of 5-FU dose based on pharmacologic sampling has been attempted. This approach was reported to result in significant improvement of the response rate and reduction of toxicity [112].

Limited surgery and the principle of organ preservation
The principle of organ preservation has been established in breast cancer, rectal cancer and peripheral osteosarcomas. Similarly, preservation of the ability to phonaute and swallow without compromising a chance for cure is an essential goal for head and neck cancer patients.

The concept of using induction chemotherapy with the goal of organ preservation was introduced in 1987 by Jacobs et al. [113]. Twelve patients who achieved a complete pathologic response to induction chemotherapy, received primary radiotherapy as the only subsequent local therapy. A relapse-free survival of 60% and overall survival of 70% at two years suggested that it might be feasible to omit surgery and offer primary radiation alone for complete pathologic responders to induction chemotherapy.

Larynx preservation was further established by the VA Larynx Study [90]. Sixty-four percent of patients avoided laryngectomy without compromising survival compared to the control group of laryngectomy with postoperative radiotherapy. At a minimum follow-up of 34 months, the overall three-year survival of the chemotherapy group was 53% and not statistically different compared with the control group.

A second randomized study testing the feasibility of larynx preservation in patients with hypopharyngeal tumors has been completed by the EORTC. A preliminary report confirms the ability of induction chemo-
A time-dose relation for radiotherapy in HNSCC is supported by retrospective observations [117-119]. 'Split course' radiotherapy regimen. Both result in lower dose intensity and in higher locoregional failure rates. With prolongation of the radiotherapy course or with a biologic effect of radiation on tissues seems to decrease structures in the area of head and neck emphasizes the or regional disease. The presence of critical normal Complete tumor eradication is rarely achieved with Altered fractionation radiotherapy and concomitant chemotherapy. Intergroup study [91] indicate little benefit with adjuvant chemotherapy. However, they have not yet established the principle of organ preservation for sites other than the larynx.

Organ preservation and maintenance of the quality of life are very important objectives in our efforts to improve therapy of head and neck cancer. Revision of the surgical approach can minimize the sacrifice of normal tissue and the loss of function. Better design of the clinical trials could prove that elimination of surgery or limited surgery will not compromise cancer control, which is the ultimate objective. We also need to encourage innovative surgical approaches and to address the possibility that 'lumpectomy' or 'tumorectomy' might maintain cancer control in conjunction with chemoradiotherapy. In the future, definition of prognostic groups utilizing molecular analyses, may also allow for the design of studies of limited surgery for patients with favorable prognostic factors.

In conclusion, neoadjuvant chemotherapy as studied to date, does not appear to prolong survival in the typical patient with HNSCC but may do so in advanced NPC. It has a proven role in larynx preservation but it should not be considered standard therapy for other primary sites in the head and neck. The combination of cisplatin with infusional 5-FU has been extensively studied and should not be expected to prolong survival significantly. Neoadjuvant chemotherapy remains an excellent investigational tool to study new drugs or combinations or the biochemical modulation of old drugs. Further investigations are necessary to define more active regimens or to address further, in a randomized fashion, the principle of organ preservation at other sites. Adjuvant chemotherapy has been incompletely studied and presents more logistical difficulties than neoadjuvant chemotherapy. However, both the Head and Neck Contracts program [87, 88] and the Intergroup study [91] indicate little benefit with adjuvant chemotherapy.

**Altered fractionation radiotherapy and concomitant chemoradiotherapy**

Complete tumor eradication is rarely achieved with conventional radiotherapy in patients with bulky local or regional disease. The presence of critical normal structures in the area of head and neck emphasizes the need to minimize the toxicity to healthy tissues. The biologic effect of radiation on tissues seems to decrease with prolongation of the radiotherapy course or with a 'split course' radiotherapy regimen. Both result in lower dose intensity and in higher locoregional failure rates. A time-dose relation for radiotherapy in HNSCC is supported by retrospective observations [117-119]. Pretreatment cell cycle kinetics (potential doubling time) have also been shown to correlate with local control following radiotherapy.

Based on these data, accelerated and hyperfractionated schedules of radiotherapy are theoretically attractive. The EORTC randomized 356 patients with oropharyngeal carcinoma to a hyperfractionated regimen of 80.5 Gy in 70 fractions of 1.15 Gy delivered twice daily or the conventional 70 Gy in daily fractions of 2 Gy. Hyperfractionation was shown to improve local control (p = 0.02) with a trend toward increased overall survival (p = 0.08) [120]. A variety of other schedules of hyperfractionated radiotherapy have been developed and are currently being tested in multiinstitutional randomized studies. The RTOG 90–03 study compares three schedules of altered fractionation with a standard regimen of 70 Gy in daily fractions of 2 Gy. In Europe, the multiinstitutional Continuous Hyperfractionated Accelerated Radiotherapy Trial (CHART) compares a split course of 1.5 Gy thrice daily for 36 fractions, to standard radiotherapy.

Hypoxic cell sensitizers have also been investigated. Cells are known to be resistant to radiotherapy under hypoxic conditions [121, 122]. RTOG investigated the agent Etanidazole as a radiosensitizer in a phase III randomized trial; there was no benefit at a median follow up of three years [123]. Carbogen, nicotinamide and tirapazamine are other potential hypoxic radiosensitizers.

The concomitant administration of radiotherapy and chemotherapy has also been extensively studied [70, 71]. Randomized clinical trials have already established this approach to result in increased time to progression and, in some studies, overall survival.

The two modalities may be additive, since chemotherapy aims at disease out of the radiation field, a concept described as 'spatial cooperation'. More importantly, chemotherapy is aimed at overcoming 'in-field' radioresistance. Chemotherapeutic agents like cisplatin or carboplatin, the topoisomerase I or II inhibitors and the antimetabolites affect the cell's ability to repair radiation induced DNA damage [70, 71]. Other agents, like hydroxyurea, the fluoropyrimidines and the taxanes may also increase the fraction of cells in a more radiation sensitive phase of the cell cycle (cell cycle redistribution) [72, 124–126].

A radiation enhancing effect of fluoropyrimidines is well supported by laboratory and clinical experiments (Table 4). Lo et al. showed that bolus 5-FU in conjunction with conventional radiotherapy resulted in significantly superior local control and survival rates than conventional radiotherapy alone [127].

Building on laboratory observations of increased radiation enhancement with prolonged exposure to 5-FU, Byfield et al. conducted a phase I/II trial of infusional 5-FU combined with radiotherapy [128]. This study confirmed the feasibility of infusional 5-FU with concomitant radiotherapy and formed the basis for subsequent combination chemotherapy and phase III trials.
Recently, Browman et al. reported a randomized study comparing infusional 5-FU with concomitant 66 Gy of conventional radiotherapy, versus standard radiotherapy alone [129]. In 175 patients with stage III and IV unresectable HNSCC, the CR rate was significantly improved for the chemoradiotherapy arm (68% versus 56%, \( p = 0.04 \)); overall median survival was also prolonged (33 months vs. 25 months, \( p = 0.08 \)). Although the 5-FU arm was associated with greater toxicity, this did not compromise the delivery of radiotherapy.

Cisplatin is another well studied radiosensitizer with systemic antitumor activity. In a phase II study piloted by the RTOG three doses of cisplatin at 100 mg/m\(^2\) per day were administered on days 1, 22 and 42 of a standard radiotherapy course [130]. Surprisingly, only 61% of patients received the planned three doses of cisplatin because of toxicity, suggesting that within this Co-operative Group, three doses of cisplatin exceed ‘feasibility’ in a large percentage of patients. Nevertheless, the CR rate was 71%, and the four-year survival was 34%, results that compared favorably with historical controls of radiotherapy. This schedule is being compared to standard radiotherapy and to sequential chemoradiotherapy in several ongoing randomized RTOG studies.

Cisplatin was also combined with standard postoperative radiotherapy on a weekly schedule of 50 mg in patients with extracapsular extension of lymph node metastases [131]. When compared with radiotherapy alone, the survival was superior for the chemoradiotherapy arm (75% vs. 44%, \( p < 0.05 \) at two years); however, this survival analysis excluded patients dying as a result of ‘nonmalignant causes’. The incidence of distant metastases was not different in the two arms. Because of the small number of patients and the unorthodox survival analysis this study is not definitive; a final report and ‘orthodox’ analysis are still expected.

Cisplatin administered in two 96-hour infusions during a conventional 45 Gy course of radiotherapy was studied in a pilot trial of resectable stage III and IV HNSCC [132].

Carboplatin also enhances radiation cytotoxicity [133]. In phase I studies of carboplatin with conventional concurrent radiotherapy myelosuppression without major mucositis was dose-limiting. At a weekly dose of 100 mg/m\(^2\) for 6–8 weeks overall responses were similar to those achieved with cisplatin [134]. In a phase II study of 30 patients with stage IV HNSCC, progression free survival of 31 weeks and median overall survival of 49 weeks was achieved. Subsequent attempts to combine carboplatin with bleomycin were abandoned because of severe toxicity.

Methotrexate was tested in a small randomized trial [135]. The experimental arm consisted of two doses of methotrexate (100 mg/m\(^2\)) on days 1 and 14 of accelerated radiotherapy administered to a total dose of 45–55 Gy. Thus, the radiotherapy doses are suboptimal in both arms, at least by U.S. standards. Local control was significantly higher in the chemoradiotherapy arm and a trend toward improved survival was demonstrated (43% vs. 35% at 4 years; \( p = 0.075 \)).

The radiosensitizing effect of bleomycin was studied by several groups. The Northern California Oncology Group conducted a randomized study in patients with inoperable HNSCC [136]. The experimental arm consisted of two weekly doses of bleomycin during a conventional course of radiotherapy followed by adjuvant bleomycin and methotrexate. This regimen resulted in higher CR rates than radiotherapy alone (67% vs. 45%; \( p = 0.06 \)), superior locoregional control at two years (64% vs. 26%; \( p = 0.01 \)) and marginally improved survival (75% vs. 44% at two years, not statistically significant). A similar study conducted by the EORTC failed to reproduce these results, possibly because of low radiotherapy doses and poor compliance [137].

Investigators at Yale University studied the incorporation of one or two doses of mitomycin-C at 15 mg/m\(^2\) to a conventional radiotherapy schedule. In two successive studies, superior locoregional control was achieved, but overall survival was not significantly different [138, 139].

Paclitaxel, another agent with systemic activity in HNSCC, has also been investigated as a radiosensitizer. Several investigators have reported potentiation of the effect of radiation by paclitaxel in preclinical settings. The magnitude of the effect seems to depend on exposure time and drug concentration and may be mediated by cell cycle arrest at the radiation response G\(_2\)/M junction. Phase I and II studies of paclitaxel with concurrent radiotherapy are currently in progress [140]. Other agents, like docetaxel, vinorelbine, topotecan, and gemcitabine and also appear to have radiation enhancing activity. These agents are candidates for further clinical trials of chemotherapy with radiotherapy.

**Table 4. Positive randomized trials of radiosensitizing 5-FU.**

<table>
<thead>
<tr>
<th>Author [ref]</th>
<th>Drug</th>
<th>Standard radiation</th>
<th>Patients</th>
<th>Overall survival</th>
<th>Progression free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo [127]</td>
<td>5-FU bolus</td>
<td>Gy</td>
<td>136</td>
<td>32% vs. 14% at 5 yrs (( p = 0.8 ))</td>
<td>40% vs. 18% at 2 yrs (( p = 0.05 ))</td>
</tr>
<tr>
<td>Browman [129]</td>
<td>5-FU infusional</td>
<td>Gy</td>
<td>175</td>
<td>Median 33 mos vs. 25 mos (( p = 0.057 ))</td>
<td>Not reported (( p = 0.08 ))</td>
</tr>
<tr>
<td>Merlano [149]</td>
<td>cisplatin, bolus</td>
<td>Gy</td>
<td>157</td>
<td>41% vs. 23% at 3 yrs (( p = 0.05 ))</td>
<td>25% vs. 7% at 3 yrs (( p = 0.01 ))</td>
</tr>
</tbody>
</table>
ruption of the radiotherapy schedule, which has been shown to result in suboptimal tumor control for radiotherapy as single treatment modality [117-119]. In one reported study from Australia, PF was administered in low doses resulting in potentially suboptimal systemic control [141]. In addition, no benefit in local control and survival was demonstrated. Cisplatin at 50 mg/m², and 5-FU at 350 mg/m²/day infused over 5 days were repeated twice during the first and fourth week of a standard 60-64 Gy radiotherapy course. Even at these doses the course was compromised by severe mucosal toxicity.

In order to maintain systemic activity and allow for recovery of normal tissues from toxicity, multiagent chemotherapy has more frequently been integrated with split course radiotherapy. In a Canadian multicenter randomized trial standard radiotherapy was compared to infusional 5-FU and mitomycin-C concomitantly with two 14-day radiotherapy courses separated by a four-week rest period [142]. Response and survival rates were similar in both arms; thus, chemotherapy was able to compensate for the suboptimal irradiation in the experimental arm, but not to further improve on survival or locoregional control parameters.

Several phase II studies combined 5-FU with other drugs including cisplatin or hydroxyurea, building on the initial experience by Byfield et al. [128]. Taylor et al. used cisplatin 60 mg/m² plus five days of infusional 5-FU concurrently with radiation in a single daily fraction, in cycles repeated every other week [143]. This schedule was complicated by severe mucositis, but resulted in satisfactory local control. Only 27% of patients recurred locally and the median survival was 37 months.

Adelstein et al. combined PF with two-three-week courses of radiotherapy separated by several weeks of rest. PF was administered concomitantly with each course of radiotherapy and during the first week after radiotherapy (total of 4 courses). Phase II data from 54 patients with locally advanced HNSCC were very encouraging [144]. These promising results were subsequently confirmed at the Cooperative Group level [145] and the regimen is currently undergoing phase III testing.

Based on laboratory observations by Looney et al. [146], Merlano et al. developed a schedule of rapidly alternating chemoradiotherapy. In a randomized trial, it was shown that an alternating chemoradiotherapy schedule utilizing vinblastine, bleomycin, methotrexate and leucovorin rescue was better than using that same chemotherapy regimen in the induction setting followed by conventional radiotherapy; both the CR rate (p < 0.03) and overall survival (p < 0.02) were significantly improved in the alternating chemoradiotherapy arm [147]. These investigators also devised a regimen consisting of cisplatin 20 mg/m²/day and bolus 5-FU at 200 mg/m²/day for 5 consecutive days, alternating with radiotherapy in three two-week courses [148]. In a subsequent randomized study of 157 patients, this chemoradiotherapy was superior compared with standard radiotherapy of 70 Gy. The CR rate was almost double in the experimental arm (42% vs. 22%; p = 0.037). Median survival (17 months vs. 12 months; p < 0.05) and 3 year survival (41% vs. 22%) were also superior [149]. This study has been criticized for suboptimal delivery of radiotherapy in the standard arm, since the median delivered dose was only 62 Gy. An additional pilot study confirming the activity and feasibility of alternating chemoradiotherapy has been published [150]. A German group investigated biomodified 5-FU in the form of PFL as a radiosensitizer, with simultaneous accelerated hyperfractionated radiotherapy [101]. The total radiation dose of 70 Gy was administered in eight weeks with scheduled interruptions on weeks 3 and 6. Mucositis and neutropenia were the dose limiting toxicities. This regimen has been subjected to randomized testing with no final data available at present.

At the University of Chicago, we developed a regimen consisting of infusional 5-FU (800 mg/m²/day for five days) and oral hydroxyurea (1000 mg every 12 hours twice daily for 11 doses) administered concomitantly with radiotherapy (2 Gy daily for five days) followed by eight days of rest [72]. In addition to the individual antineoplastic and radiosensitizing properties of the two drugs, hydroxyurea, a ribonucleotide reductase inhibitor, depletes cellular pools of deoxyuridine monophosphate, and enhances binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase. FHX achieved a response rate approaching 90% even in previously treated patients, and responses appeared to be durable in previously untreated patients [72].

In subsequent phase II studies FHX was administered with curative intent in patients with locally advanced disease after induction therapy with 2-3 cycles of PFL or PFL-IFN and optional organ preserving surgery. In three consecutive studies testing this approach, three-year survival rates have exceeded 50% suggesting a high curative potential for this approach in patients with advanced disease [98, 103, 111]. In addition, early stage patients appear to be cured in a high percentage without surgery when using the FHX regimen [151]. These early results are very encouraging and support the possibility that in the presence of chemotherapy, protraction of radiotherapy is not detrimental.

A shorter course of 10 weeks of hyperfractionated split course radiotherapy, administered concomitantly with cisplatin, 5-FU and hydroxyurea (C-FHX) was recently developed [74]. Dose limiting toxicities of myelosuppression and mucositis are attenuated by adding granulocyte colony stimulating factor (G-CSF). C-FHX is currently being studied in previously untreated patients with advanced HNSCC; a preliminary analysis suggests superb local control [152].

In order to maintain the intended dose intensity and manage the frequently severe toxicities of these inten-
sive regimens, tight patient supervision and optimal supportive care are necessary. The high toxicities, especially in a multi-institutional setting, can result in inappropriate dose reductions or treatment cycle delays which influence negatively the ultimate chance of successful cancer control. These therapies require a commitment by physicians and patients to comply with the protocol and should be pursued by experienced and dedicated teams.

In summary, the use of concomitant chemoradiotherapy has led to a number of encouraging observations. Using single agent chemotherapy with concomitant radiation therapy, randomized studies have frequently resulted in improved disease-free survival and/or overall survival. In particular, regimens including 5-FU have led to increased survival. This is true for bolus administration of 5-FU, its administration as a continuous intravenous infusion and its administration with cisplatin in a schedule of rapidly alternating chemoradiotherapy. All of these studies have involved patients with unresectable head and neck cancer who otherwise are known to have an exceedingly poor prognosis. While all of these regimens have resulted in increased toxicity, and no single study has been replicated by a second confirmatory trial, it would seem appropriate to offer patients who cannot be entered on a current clinical protocol one of these regimens as 'standard therapy'. Phase II studies of concomitant chemoradiotherapy utilizing combination chemotherapy regimens have also led to highly encouraging results. Only one of these regimens is currently being studied in a randomized phase III setting. Given the encouraging phase II data outlined above, it would seem appropriate to investigate this approach further, despite theoretical objections of administering protracted radiation therapy. Current clinical data indicate that, in the presence of chemotherapy, protraction of radiation therapy may not be detrimental.

Conclusion

In 1996, there is an established role for chemotherapy in head and neck cancer. Patients with recurrent disease will be offered combination chemotherapy. In this setting, investigations of new drugs or combinations and the pursuit of concomitant chemo-reirradiation are of interest. In patients with locoregionally advanced disease, induction chemotherapy can be used with the goal of larynx preservation. In addition, a role for chemotherapy in nasopharyngeal cancer appears to be emerging with increased survival as therapeutic goal. The combination of cisplatin and 5-FU does not need to be tested further, however, a more definitive evaluation of a biochemically modulated PF regimen might be of interest. Furthermore, induction chemotherapy represents an ideal investigational tool in which to further evaluate the activity of several new drugs in head and neck cancer patients. Finally, concomitant chemoradiotherapy has resulted in increased survival in several randomized clinical studies. Given the poor outcome of standard radiotherapy in patients with unresectable disease, we favor the administration of concomitant chemoradiotherapy in this group of patients as a standard therapy. In our opinion, the use of radiation therapy alone in this group of patients should be restricted to patients with poor performance status or other high medical risks that render the administration of chemotherapy unadvisable. Finally, given the high incidence of second malignancies and general medical complications in cured head and neck cancer patients, studies of chemoprevention and good preventive medical care by a medical oncologist should be made available to all patients.

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