



Lu Jian Jun. *Chinese Red*, 2000. Oil on canvas, 36" × 36". Courtesy of Weinstein Gallery, San Francisco, California.

*Significant advances  
have been made in  
the management of  
patients with head  
and neck cancers.*

# Treatment of Locally Advanced Head and Neck Cancer: Historical and Critical Review

*Muhyi Al-Sarraf, MD, FRCPC, FACP*

**Background:** *Advanced squamous cell cancers of the head and neck have traditionally been associated with high rates of morbidity and mortality. Advances in management have improved outcomes for most of these patients.*

**Methods:** *The author reviews the historical progress in management of these difficult tumors and adds his own wide experience to describe and evaluate newer approaches to management.*

**Results:** *Over the last 10 years, overall survival rates for patients with head and neck cancers have improved as has quality of life. New standards of care have been defined for patients with nasopharyngeal cancer and for those with advanced unresectable disease. Organ preservation is more commonly achieved.*

**Conclusions:** *Newer targeted therapies are likely to add to the progress that has already been achieved in the multimodality management of patients with head and neck cancers.*

## Introduction

The mode of treatment of patients with squamous cell carcinoma of the head and neck depends on the site and stage of the disease and on the overall health status of the patient. In most cases of stage I or II cancers, the single modality therapy of surgery or radiotherapy is the initial treatment of choice. Before 1980, the initial treatment of patients with locally advanced stage III or IV (M0) also would have been surgery and/or radiation therapy, a choice that also depended on the site of the disease, the resectability

---

*From the William Beaumont Hospital, Royal Oak, Michigan, and Wayne State University, Detroit, Michigan.*

*Submitted July 25, 2002; accepted August 30, 2002.*

*Address reprint requests to Muhyi Al-Sarraf, MD, William Beaumont Hospital, 3577 W 13 Mile Road, #404, Royal Oak, MI 48073. E-mail: mealsarraf@aol.com*

*No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.*

of the cancers, and the performance status and comorbidities of the patient. However, because of the poor results obtained with “traditional” therapy in this latter group, especially those with stage IV disease or unresectable cancers, systemic chemotherapy was introduced in the mid 1970s as part of combined modality treatment.<sup>1,2</sup> Later, chemotherapy was used in patients with earlier disease stages and with resectable disease for organ preservation and better cure rates. Systemic chemotherapy was usually administered with palliative intent to patients with advanced stage IV disease, M1 cancers, or recurrent disease beyond salvage local treatment.

The treatment of patients with locally advanced head and neck cancers has evolved since the introduction of combined modality treatment for these patients. Initially, a single chemotherapeutic agent such as methotrexate or cisplatin was prescribed before local definitive treatment. After that, the combination of cisplatin and bleomycin was introduced, administered as a single course before local therapy.<sup>1,2</sup> Later, two or three courses of cisplatin plus bleomycin were given as part of combined modality treatment. Methotrexate alone and/or vinca alkaloids (vincristine or vinblastine) were then added to the combination of cisplatin plus bleomycin.<sup>1,2</sup> In 1980, the combination of cisplatin and continuous infusion (96-120 hours) of 5-fluorouracil (5FU) was introduced,<sup>1,2</sup> which has become a widely used combination chemotherapy in patients with squamous cell carcinoma of the head and neck. Also, at approximately the same time, the concept of concurrent chemotherapy with radiation therapy was revisited, with the introduction of cisplatin given concurrent-

ly with radiation therapy as the primary treatment for patients with inoperable and/or unresectable head and neck cancers.<sup>2</sup>

During the last quarter of a century, clinical trials for patients with squamous cell carcinoma of the head and neck have demonstrated progress in treatment outcomes, including better local control, lower incidence of systemic recurrences, improved disease-free survival and, most importantly, improved overall survival. The quality of life has improved for many of these patients, especially when the larynx and voice function is preserved in cancers of the larynx or hypopharynx. The improvement in overall survival was demonstrated by prospective randomized phase III studies and meta-analyses and, more significantly, by population-wide statistics. The Surveillance, Epidemiology, and End Results (SEER) program at the National Cancer Institute evaluates change in cancer mortality rates in the United States. It is not generally recognized that the greatest decline in mortality rates in the period 1990 to 1997 has occurred in patients with head and neck cancers. This decline was noted for patients both above and below 65 years of age, for both men and women, and for both blacks and whites (Table 1).<sup>3</sup>

With the introduction of new active chemotherapeutic agents and combinations, new agents given with radiation therapy, targeted treatments, and better sequencing of treatment options, it is expected that further improvements in treatment outcomes will follow.

## Chemotherapy

The two major indications for administering chemotherapy are as a single modality or as concurrent chemotherapy-radiation therapy.

### Chemotherapy Alone

Chemotherapy as a single modality is used for patients with recurrent and/or metastatic tumor, but it is also used for patients with locally advanced cancers. The cisplatin-5FU combination is more effective than the single agents previously used — methotrexate, bleomycin, and cisplatin. Cisplatin-5FU is now the most commonly used chemotherapy combination,<sup>1,2,4</sup> with the most frequently used treatment regimen consisting of cisplatin 100 mg/m<sup>2</sup> given intravenously (IV) on day 1 and 5FU 1,000 mg/m<sup>2</sup> given by continuous infusion for 5 days every 3 to 4 weeks. For the last 20 years, efforts have been underway not only to improve on the results obtained with cisplatin-5FU by adding other agents, but also to search for more effective combinations to replace it.

Table 1. — Annual Change in Death Rates Between 1990-1997 for Selected Tumor Types and Patients

Sites	Mortality Rate (% Change)
All	-0.8
Melanoma	+0.1
Non-Hodgkin's lymphoma	+1.7
Urinary bladder	-0.3
Lung	-0.5
Colon/rectum	-1.8
Female breast	-2.1
Prostate	-2.2
Oral cavity/pharynx	-2.6
Men	-2.8
White	-2.6
Black	-3.8
Women	-2.3
White	-2.3
Black	-2.5

Data from Ries et al.<sup>3</sup>

Table 2. — Possible Mechanisms of Interaction Between Chemotherapy and Radiation Therapy

Modification of the slope of the dose-response curve.  
Decrease in accumulation or inhibition of repair of sublethal damage.  
Inhibition of repair of potentially lethal damage.  
Induction of tumor re-oxygenation.  
Selective cytotoxicity and/or radiosensitization of hypoxic cells.  
Increase in apoptosis.

Improvements in cancer therapy would include better antitumor efficacy, fewer side effects, and lower cost and hospitalization rates, thereby being more amenable to patients. Initially, many single agents, eg, bleomycin, methotrexate, and the vinca alkaloids, were added to the cisplatin-5FU regimen. This policy reduced the optimal doses of cisplatin or 5FU or both and increased side effects without increasing efficacy.<sup>2</sup> The addition of leucovorin or interferon or both to the cisplatin-5FU regimen provided similar results. Of the newer active single agents, the taxanes (docetaxel and paclitaxel) have shown the most promise.

The role of taxanes in head and neck cancers have been reviewed by Schrijvers and Vermorcken<sup>5</sup> and by Glisson.<sup>6</sup> As single agents, both demonstrate overall response rates that range from 20% to 42% in patients with recurrent and/or metastatic disease. It is noted that most of these patients treated with taxanes in these reports had no previous chemotherapy for recurrent cancers, and some patients with locally advanced head and neck cancers were included in these studies. This may explain the relatively high response rates reported by these investigators. Our experience indicates that the response rate to the taxanes alone after failure of a cisplatin combination is poor. This suggests that the taxanes should be used initially with cisplatin-5FU or as part of newer combination(s) of chemotherapy. Randomized trials comparing cisplatin-5FU to either cisplatin plus paclitaxel<sup>7</sup> or cisplatin plus docetaxel<sup>8</sup> reported no differences in response rates or complete responses (CRs) but some difference in side effects and the cost of each combination.

Efforts are underway to investigate the addition of one of the taxanes to the cisplatin-5FU regimen or to find newer combinations of two or three active agents in patients with recurrent and/or metastatic disease, as well as in patients with previously untreated locally advanced squamous cell carcinoma of the head and neck.<sup>4</sup> One such approach was reported by Posner et al<sup>9</sup> using docetaxel combined with cisplatin-5FU. Synergy has been reported between cisplatin and 5FU, between docetaxel and cisplatin, and between docetaxel and 5FU. In their initial trials, leucovorin was

added to docetaxel-cisplatin-5FU, which added to the incidence and severity of oral and oropharyngeal mucositis without appearing to add to the efficacy of this combination. The results from docetaxel-cisplatin-5FU alone suggest a high incidence of response but with appreciable toxicity.<sup>9</sup> Presently, two prospective, randomized phase III trials in patients with recurrent and/or metastatic disease or in patients with previously untreated locally advanced head and neck cancers are comparing three courses of cisplatin-5FU vs docetaxel-cisplatin-5FU in North America. Similar international trials are currently in progress.

Thus, docetaxel-cisplatin-5FU is a promising combination, but the phase III studies are not mature. Our experience indicates that docetaxel-cisplatin-5FU is more toxic than cisplatin-5FU, especially in regard to mucositis, diarrhea, and neutropenia. As a result, we have modified this promising combination in two ways. To reduce cisplatin-related side effects, including renal insufficiency, hearing loss, nausea and vomiting, peripheral neuropathy, and the diuresis associated with use of mannitol, we have substituted carboplatin for cisplatin. Because of the incidence and degree of mucositis, diarrhea, and right-sided abdominal pain, the continuous infusion of 5FU for 96 hours was changed to a schedule of 2,600 mg/m<sup>2</sup> as a 24-hour infusion given weekly with docetaxel (75 mg/m<sup>2</sup>) and carboplatin (300 mg/m<sup>2</sup> or an area under the curve [AUC] of 5, depending on creatinine clearance) given every 3 weeks for three courses. Our early experience suggests that this program may be the most effective and "patient friendly" combination we have used in patients with head and neck cancers (unpublished data, 2002).

### *Concurrent Chemoradiotherapy*

In the past, radiotherapy alone was the "traditional" single treatment for patients with unresectable and/or inoperable locally advanced head and neck cancers. Because of the poor results obtained with this approach in these patients, concurrent chemotherapy-radiation therapy has been investigated since the 1960s.<sup>1,2,4,10,11</sup> The rationale for such treatment is to increase local control by overcoming radioresistance and to eradicate systemic micrometastasis. The most significant potential mechanisms of interaction between chemotherapy and radiation therapy are summarized in Table 2.

Initially, agents like methotrexate, hydroxyurea, 5FU, or bleomycin were tested in combination with radiation therapy. Since each of these drugs produces mucositis and stomatitis, the local side effects of radiation therapy on the oral and oropharynx mucosa were

increased, which resulted in poor patient compliance, more interruptions of therapy, and no improvement in overall survival when compared to radiation therapy alone. Cisplatin does not induce mucositis and does not increase the local toxicity of radiation therapy in patients with head and neck cancers. It is probably the best currently available radiosensitizer, and it possesses all the mechanisms of interaction with radiation therapy that are summarized in Table 2. The clinical CR rate obtained with concurrent cisplatin and radiation therapy (single daily fraction) in patients with locally advanced head and neck cancers is in the range of 65% to 70%.<sup>2,4,10,11</sup> The majority of the patients in these studies had stage IV disease. Cisplatin has been administered in various schedules: weekly, daily, days 1-5 every 4 weeks, and every 3 weeks. One randomized ECOG-RTOG trial with weekly administration of cisplatin at 20 mg/m<sup>2</sup> during radiation therapy vs radiation therapy in locally advanced patients was negative. One positive randomized trial with the weekly schedule has been reported from Europe.<sup>12</sup> The addition of another agent or agents in combination with cisplatin (eg, 5FU or taxanes) concomitant with radiation therapy did not add to the clinical CR rate but increased local side effects, especially mucositis.<sup>4,6,10</sup> Thus, cisplatin alone appears to be the chemotherapeutic drug of choice for concurrent chemotherapy with radiation therapy in patients with head and neck cancers. At the present time, cisplatin alone given on a 3-week schedule is the most widely used in the United States.

Carboplatin, the second-generation platinum drug, possesses all of the radiopotential properties of cisplatin but has a different side effect profile. Carboplatin is used in a weekly schedule concurrent with radiation therapy in patients with head and neck cancers. The clinical CR rate reported in phase II studies with concomitant carboplatin and radiation therapy (single daily fraction) is in the range of 65% and 70%, which is similar to the clinical CR rate reported with cisplatin and radiation therapy.<sup>2,4</sup> For the last 7 years, our personal practice has been to use carboplatin rather than cisplatin in our concurrent chemotherapy-radiation treatment, using a weekly dose of 100 mg/m<sup>2</sup> or at an AUC of 1.5. In a comparison of radiation therapy alone or with either cisplatin or carboplatin in these patients, two randomized trials reported the superiority of either combination arm to the radiation therapy alone arm, with no statistical difference between the two combination arms.<sup>13,14</sup>

Mitomycin C also possesses most of the radiopotential mechanisms of interaction with radiation therapy (Table 2). Randomized trials comparing radiation therapy with or without mitomycin C showed improved local control but no differences in overall sur-

vival between the two groups.<sup>4</sup> More recently, gemcitabine and the taxanes have been tested for their radiosensitizing effects. The clinical CR rate for the combination of taxanes alone or with other agents given concurrently with radiation therapy is approximately 65%.<sup>4,6</sup> However, the local side effects, especially mucositis, are problematic.

Gemcitabine plus radiation therapy in phase I-II studies produced a high CR rate in the primary tumor site but had a high incidence of grade 3-4 local toxicities, especially pharyngeal scarring and stenosis.<sup>4</sup> The combination of 5FU and hydroxyurea concomitant with radiation therapy is effective, but again, the local side effects are severe.<sup>4</sup> The addition of cisplatin or paclitaxel increased the effectiveness of the combination of 5FU and hydroxyurea, but the clinical CR rate was similar to that reported with radiation therapy plus cisplatin or carboplatin.

## Locally Advanced Resectable Cancer

The “standard” treatment for patients with locally advanced tumor stages (stage III and IV) has been surgery followed by radiation therapy. The radiation was given as an adjuvant to reduce the incidence of local failure, but this approach has not been investigated in prospective, randomized studies to show improvement in overall survival. Despite adequate surgical resection with negative margins and the addition of adjuvant radiation therapy, the 5-year survival rate for these patients is usually less than 30%. Induction chemotherapy has not gained scientific support, since any reduction of the tumor bulk would not change tumor resection margins. Induction chemotherapy has been investigated in patients with resectable cancers where planned surgery was performed on all patients, and the results were negative. This resulted in a sense that induction chemotherapy is ineffective in patients with locally advanced disease regardless of their resectability or operability. However, this observation may not be correct.

Postoperative concurrent chemotherapy-radiation therapy with cisplatin given every 3 weeks for three courses was investigated by the RTOG in a phase II study.<sup>2</sup> Patients with positive surgical margins and/or stage IV disease were treated with cisplatin 100 mg/m<sup>2</sup> on days 1, 22, and 43 during radiation therapy. These patients were compared to an historically matched group with the same stage and site of cancers but with negative surgical margins. The local control rate was better in the patients treated with the combined chemotherapy-radiation therapy. Two randomized trials have also addressed this question.<sup>2,4,15</sup> Both were posi-

tive, thus supporting the addition of chemotherapy concomitantly with radiation therapy in locally advanced cancers. The most recent EORTC trial compared patients treated with postoperative radiation therapy alone vs postoperative chemotherapy-radiation therapy and reported a 3-year disease-free survival of 41% vs 59% ( $P=.0096$ ) and overall survival of 49% vs 65% ( $P=.0057$ ), respectively.

Postoperative chemotherapy followed by radiation therapy alone was investigated by the Detroit group<sup>2</sup> and found to be feasible. Three courses of cisplatin-5FU were administered without additional side effects or progression of the disease, and then radiation therapy was given. The sequence was tested by RTOG, and the feasibility of our local study was confirmed. Large prospective, randomized phase III trials were activated by RTOG and joined by other cooperative groups to compare surgery plus radiation therapy to surgery plus chemotherapy-radiation therapy. Local control and the incidence of systemic recurrences improved. However, the overall survival was not affected by the addition of chemotherapy, despite approximately a 2-year improvement in median survival and about a 9% difference in the actual 5-year survival rate in favor of the chemother-

apy group.<sup>5</sup> The lack of statistical significance of benefit reflect the relatively small number of patients included in these trials.

At least six meta-analyses have examined the addition of induction chemotherapy to local definitive therapy in patients with locally advanced cancer. The results differ depending on the type and the year of the studies included in these analyses. Study reports before the use of cisplatin-5FU in this population showed no benefit for induction chemotherapy. The meta-analyses that included studies after 1980s, especially those using cisplatin-5FU chemotherapy, showed superiority of chemotherapy followed by radiation therapy vs radiation therapy alone.<sup>16</sup> All of the meta-analyses reported the superiority of concurrent chemotherapy-radiation therapy over radiation therapy alone; however, Pignon et al<sup>16</sup> updated three meta-analyses from 63 randomized trials performed between 1965 and 1993 involving 10,741 patients. This meta-analysis confirmed the superiority of the overall use of chemotherapy, especially the concomitant use of chemotherapy-radiation therapy over radiation therapy only. The authors also reported the superiority of cisplatin-5FU administration as either induction or adjuvant therapy in these patients.

Table 3. — Meta-analysis of Concurrent Chemoradiotherapy vs Radiotherapy in Patients With Advanced Head and Neck Cancers: Mortality

Stratum and Treatment	Risk Difference (%)	P Value*
Overall results†	11	<.00001
Conventional RT both arms	9.2	.00041
RT same both arms, not conventional	16.6	.00008
Platinum-based CT‡	12.1	<.0001
Mitomycin-C based CT	14	.032
5-Fluorouracil-based CT	10.2	.11
Bleomycin-based CT	5	.36
Single agents only	10.7	.0004
Combination CT regimens	11.2	.0009
Combination cisplatin-5FU	15.3	<.0001

CT = chemotherapy  
 \* P values are two-tailed.  
 † Sensitivity analysis with removal of the trial by Haselow et al<sup>12</sup> from all other eligible trials yields the following: 17 trials (19 comparison) with 2,873 patients; OR, 0.60; 95% CI, 0.50 to 0.72,  $P<.00001$ ; risk difference, 12; 95% CI, 7.8 to 16.1,  $P<.0001$ .  
 ‡ Sensitivity analysis with removal of the estimates from the incompletely reported trial by Haselow et al<sup>12</sup> yields the following: 8 trials (9 comparisons) with 1,195 patients; OR, 0.53; 95% CI, 0.42 to 0.66,  $P<.00001$ ; risk difference, 15.4; 95% CI, 9.9 to 20.9,  $P<.00001$ .  
 Modified from Browman GP, Hodson DI, Mackenzie RJ, et al. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. *Head Neck*. 2001;23:579-589.

Recently, Browman et al<sup>17</sup> reported a meta-analysis including 18 trials with 3,192 patients, in which concurrent chemotherapy-radiation therapy was compared to radiation therapy alone (Table 3). Overall, the chemotherapy-radiation therapy arm was again superior to radiation therapy alone ( $P<.00001$ ). Single fraction, two fractions a day irradiation, single agents, combination chemotherapy, and especially cisplatin-5FU provided statistically significant results. Only platinum-based chemotherapy plus radiation therapy was highly significant ( $P<.0001$ ), while mitomycin C-based treatment was moderately significant ( $P=.032$ ). Thus, we believe that single-agent cisplatin or carboplatin with radiation therapy should be the current standard treatment approach in patients with locally advanced cancers.

For the last 10 years, our approach to treatment for patients with stage IV disease or for those with stage III disease (only T3 N1 M0) after their planned surgery who are not on study has been to prescribe chemotherapy using three courses of cisplatin-5FU followed by concurrent chemotherapy-radiation therapy. This treatment is tolerable and feasible, and it gives patients time to recover from their surgical resection before beginning the concomitant chemotherapy-radiation therapy treatment. The effectiveness of this specific approach needs to be confirmed by prospective, randomized trials.

## Unresectable Cancers

In the past, the treatment of choice for patients with unresectable or inoperable head and neck cancers was radiation therapy alone. Despite the initial response and high local control rates with radiation therapy, more than 80% of these patients recurred within 2 years, and the 5-year survival was poor. Thus, induction chemotherapy and later concurrent chemotherapy-radiation therapy were investigated.

One prospective, randomized study comparing induction chemotherapy with cisplatin-5FU followed by radiation therapy vs radiation therapy alone was positive, with significant improvement in local, regional, and distant control rates as well as in disease-free and overall survival in the combination arm.<sup>4</sup>

Concomitant chemotherapy-radiation therapy appears to be effective in phase II trials. At least seven prospective phase III trials comparing concurrent chemotherapy-radiation therapy vs radiation therapy have been reported (Table 4).<sup>18-24</sup> All were positive in favor of the combined-therapy arm. The majority of these randomized trials used hyperfractionated radiation therapy as the standard arm and in combination with chemotherapy, despite previous reports of no improvement in overall survival when daily irradiation was compared with twice-a-day radiation therapy.<sup>4</sup>

Also, the majority of these randomized studies used the combination of cisplatin-5FU with radiation therapy as the experimental arm, despite the previously reported phase II trials indicating a CR rate of approximately 65% to 70% using cisplatin-5FU concurrently with radiation therapy. This result was no different than administering cisplatin or carboplatin alone concurrently with radiation therapy. In the Intergroup study (SWOG and ECOG)<sup>23</sup> for locally advanced and unresectable head and neck cancers, patients were randomized into three arms: (1) single-agent cisplatin every 3 weeks during radiation therapy, (2) cisplatin-5FU with radiation therapy, or (3) radiation therapy alone. Standard daily fraction radiation therapy was given to all patient groups. The 3-year survival rates were 37%, 29%, and 20%, respectively. The difference was only statistically significant ( $P=.016$ ) between cisplatin plus radiation therapy and radiation therapy alone.

Thus, concurrent chemotherapy-radiation therapy is the “new” standard therapy for patients with locally advanced disease who are not undergoing a planned surgical resection. The main question remains as to whether two fractions per day of radiation therapy or once-daily radiation with chemotherapy is the preferred schedule. Another question is whether a single agent or a combination of agents should be given concomitantly with radiation therapy. Radiation alone is inadequate therapy.

Table 4. — Phase III Randomized Trials Comparing Concomitant Chemotherapy-Radiation Therapy vs Radiation Therapy Alone in Squamous Cell Head and Neck Cancers

Authors	Site	Treatment	Overall Survival (%)	Year	P Value
Merlano et al <sup>18</sup>	All	RT	10	5	<.05
		RT, PF	24		
Brizel et al <sup>19</sup>	All	RT bid	34	3	.07
		RT, PF	55		
Wendt et al <sup>20</sup>	All	RT bid, PF	24	3	<.05
		RT bid, PF	49		
Calais et al <sup>21</sup>	Oropharynx	RT bid	31	3	<.05
		RT bid, CF	51		
Jeremic et al <sup>22</sup>	All	RT bid	25	5	.0075
		RT bid, P daily	46		
Adelstein et al <sup>23</sup>	All	RT	20	3	.016
		RT, P	37		
		RT, PF ± S	29		
Staar et al <sup>24</sup>	Oropharynx/ hypopharynx	RT bid	39	2	.09
		RT bid, CF	44		

bid = twice a day  
 RT = radiotherapy  
 S = surgery  
 C = carboplatin  
 F = 5-fluorouracil  
 P = cisplatin

As previously mentioned, our practice for patients with locally advanced and resectable tumors is to provide induction chemotherapy first, followed by concomitant chemotherapy-radiation therapy. Other centers have reported the same practice.<sup>10</sup> Limited concurrent chemotherapy with radiation therapy is superior to induction chemotherapy followed by radiation therapy. By giving induction chemotherapy first, the cancer is downstaged in approximately 90% of patients, and up to 50% may achieve a clinical CR. Also, nutrition and nitrogen balance can be improved in these patients so they can better tolerate the chemotherapy-radiation therapy program, and they will have dental care without delay of therapy. After downstaging the disease, the concurrent chemotherapy-radiation therapy theoretically should be more effective in eradicating the remaining locoregional cancer. Also, giving effective chemotherapy first will reduce the incidence of systemic micrometastasis. These considerations contribute to improved disease-free survival and overall survival of patients treated with this "total chemotherapy-radiation therapy."

To achieve the maximal desired results from chemotherapy in patients who have locally advanced disease, a third course of chemotherapy is recommended if a response occurs after two courses of treatment. At the end of the third course, disease is re-staged, and the degree of response is documented. This may include re-biopsy of the primary disease. Response to induction chemotherapy is an important prognostic factor and may determine the sequence and timing of the next planned local definitive therapy. Patients with excellent response, high partial response, and especially clinical CR or histological CR (by biopsy) may avoid surgery and receive concurrent chemotherapy-radiation therapy. Patients with a lesser response will require surgical resection of all the disease or the remaining disease, followed by postoperative chemotherapy-radiation therapy. Computed tomography or magnetic resonance imaging may not be accurate in assessing CR in patients presenting with T3 or T4 cancer. Imaging abnormalities may persist, even in patients with histologically negative biopsies or in those who underwent surgical resection.

In patients with recurrent and metastatic cancers, chemotherapy should be administered to maximal response, followed by an assessment of salvage local therapy of surgery and/or re-radiation concomitant with chemotherapy. At the end of the salvage local therapy, an additional three to six courses of chemotherapy should be considered to try to increase the incidence and the durability of this salvage measure. If a clinical CR or stable partial response is achieved, a positron emission tomography scan, along with the usual re-stag-

ing evaluation, may be considered, with a repeat of the study after three to six courses of the same chemotherapy. For patients with locally recurrent disease beyond local treatment of surgery and/or radiation therapy, biopsy of the disease is recommended after achieving a clinical CR. An additional three courses of the same chemotherapy is recommended with two negative biopsies before treatment is stopped.

## Laryngeal Cancer

The conventional treatment of patients with locally advanced laryngeal cancers has consisted of surgery and/or radiation therapy. Many of these patients lose their larynx. In the early 1980s, we observed that patients who respond to cisplatin-based combination chemotherapy respond further with subsequent radiation therapy and, conversely, those who do not respond to initial chemotherapy, even after six courses, will not respond to radiation therapy.<sup>2</sup> This led us to offer chemotherapy first to patients with locally advanced laryngeal cancers. If a complete or partial response was achieved, they would then be given radiation therapy. The nonresponders would undergo surgery followed by radiation therapy.

At least two prospective, randomized phase III trials have been conducted, one in patients with cancers of the larynx<sup>15</sup> and the second in patients with cancers of the hypopharynx,<sup>25</sup> in which most of the patients previously had a laryngectomy. Both tested induction chemotherapy with cisplatin-5FU and selected the responding patients to receive either radiation therapy or the standard treatment of surgery followed by radiation therapy. The overall survival was the same between the two groups, and 50% to 60% of the surviving patients preserved their larynx on the investigational arm. These two studies demonstrated that laryngectomy (surgery) was equal to three courses of cisplatin-5FU chemotherapy, and surgery plus radiation therapy was equal to chemotherapy plus radiation therapy.

Following these results, the Intergroup Trial R91-11 conducted a study in patients with stage III-IV potentially resectable cancer of the larynx.<sup>26</sup> Patients were randomized to three arms: (1) chemotherapy followed by radiation therapy, (2) concurrent chemotherapy-radiation therapy, and (3) standard once-daily radiation therapy alone. The trial selected only concomitant chemotherapy-radiation therapy as the experimental arm., and once-daily radiation therapy was used in the third arm rather than twice-daily (hyperfractionated) irradiation, which may produce higher local control rates (organ preservation) than once-daily fraction

Table 5. — Survival in Nonrandomized Studies of Treatment of Previously Untreated Nasopharyngeal Cancer

Therapy	No. of Series	Patients Studied	Range	% Surviving (Average)
RT only	18	8,185	26-62	45
CT → RT	10	683	35-78	62
CT → RT	4	172	55-94	67
RT → CT	3	85	50-77	66
CT + RT → CT	3	162	70-80	77
CT → CT + RT	2	65	83-94	88

NPC = nasopharynx cancers  
 CT = chemotherapy  
 RT = radiotherapy

radiation therapy. Patients with T4 cancers were not included in the trial. Patients with N2 or N3 neck disease underwent neck dissection at the end of their treatment, regardless of their response to the initial treatment. No differences were reported in overall survival among the three groups, but patients who underwent concurrent chemotherapy-radiation therapy had significantly higher organ preservation rates. The laryngectomy-free survival improved with concurrent treatment vs radiation therapy alone ( $P=.02$ ). Also, time to laryngectomy for concurrent treatment vs induction ( $P=.0094$ ) and for concurrent treatment vs radiation therapy alone ( $P=.00035$ ) was superior.

Some investigators gave one course of chemotherapy to select patients for larynx preservation. Since the response rate to one course of chemotherapy is less than 50%, this led to a higher percentage of patients on that arm losing their larynx, thereby defeating the primary goal of such a study. The usual response rate to

three courses of chemotherapy is approximately 90%, leaving only 10% of these patients (the nonresponders) requiring surgery. Thus, the patients who were given just one course of chemotherapy and then concurrent chemotherapy-radiation therapy had an excellent survival, but more patients than expected lost their larynx.

Induction chemotherapy followed by concomitant chemotherapy-radiation therapy is the best nonsurgical treatment for laryngeal cancer we have used to date, and this approach has been confirmed by other investigators.<sup>2,4,11</sup> This total approach of chemotherapy-radiation therapy needs to be confirmed by prospective phase III trials vs concurrent chemotherapy plus radiation therapy.

## Nasopharyngeal Cancer

The results of treatments for patients with nasopharyngeal cancer are considered separately from other head and neck cancer patients due to differences in sex, age, nodal presentation, histopathology, response to radiation therapy and chemotherapy, incidence of systemic metastases, and overall survival.

Nasopharyngeal carcinomas are highly sensitive to radiation therapy (Table 5). Before 1980, radiotherapy was the treatment of choice for all stages of nasopharyngeal cancer. The results in patients with stages I and II disease are excellent, and radiation therapy has remained the initial therapy for these patients.<sup>27,28</sup> However, the majority of the patients with this disease present with locally advanced disease, especially stage IV cancers. Despite the excellent initial tumor clearance with radiation therapy in patients with locally advanced disease (stage III and IV), locoregional recur-

Table 6. — Response to Chemotherapy in Metastatic/Recurrent and Previously Untreated Nasopharyngeal Cancer

Agents	No. of Series	Total Patients	% Response Rate		% Complete Response	
			Range	Average	Range	Average
Metastatic/recurrent:						
No P	2	38	40-50	45	0-12	6
No PF	4	145	50-63	56	16-20	17
PF	7	221	38-86	65	4-25	16
PT	3	73	57-75	64	3-14	9
Previously untreated:						
No P	1	12		81		33
No PF	6	265	75-98	86	5-66	33
PF	9	428	62-100	87	10-50	30

F = 5-fluorouracil  
 P = platinum  
 T = paclitaxel

rence rates are high. Systemic involvement at presentation or later is common in these patients and may exceed 35%. These considerations limit survival, with estimated the 5-year survival rate using radiation therapy alone for patients with stage IV cancer being less than 30%.<sup>27,28</sup>

Nasopharyngeal cancer is also sensitive to chemotherapy (Table 6).<sup>4,27</sup> Compared with single agents, combination chemotherapy produces higher response rates and a longer duration of response, and cisplatin-5FU is the most widely used combination. Because of the poor results obtained with radiation therapy alone in patients with locally advanced disease, induction cisplatin-5FU before radiation therapy has been tested. The overall response rate to cisplatin-5FU is approximately 90%, and about 50% achieved CRs, with improved 5-year survival.<sup>27</sup> Concurrent cisplatin-radiation therapy, which has been investigated by us and later by other investigators, produced higher CR rates and better 5-year survival rates.<sup>2,27</sup> Since the introduction of effective chemotherapy as part of the salvage treatment after relapse in these patients with nasopharyngeal cancer, the 5-year survival rate in patients with stage IV disease who received radiation therapy as their initial treatment has risen to the 40% range.<sup>27</sup>

In phase II or III studies reported thus far with the use of limited chemotherapy with radiation therapy, induction only, concomitant only, or adjuvant only, the worldwide 5-year survival rate in patients with stage IV nasopharyngeal cancer has risen to approximately 50% to 55% (Table 5). This is pertinent to the randomized trials reported in this disease.

Nine prospective phase III randomized studies have compared radiation therapy alone to the same radiation therapy with chemotherapy (Table 7).<sup>29-39</sup> One negative adjuvant chemotherapy trial used a non-cisplatin combination and was carried on before the introduction of cisplatin-5FU in this disease. Of four induction chemotherapy trials, two used combinations without cisplatin-5FU, and the other two used cisplatin-5FU combinations. None of these four induction randomized studies reported a prolonged overall survival. The two cisplatin-5FU trials, however, reported a difference in overall survival rates of 7% and 12%. Some studies reported improved disease-free survival and/or freedom from local relapse. Several reasons may be cited to explain why these chemotherapy induction trials might not show improvement in overall survival. These include small patient numbers, inclusion of stage II patients, larger numbers of stage III patients, short dura-

Table 7. — Randomized Trials in Patients With Nasopharyngeal Cancers

	Authors	Agents	Overall Survival	P Value	Comments
Adjuvant	Rossi et al <sup>29</sup>	CAV	67% RT 59% RT-VCA	NS	
	Chi et al <sup>30</sup>	PF-L	61% RT-CT 55% RT	NS	
Induction	VUMCA <sup>32,33</sup>	PEB	40% CT-RT 45% RT	NS	
	Chau et al <sup>34</sup>	PE	70% CT-RT 56% RT	NS	
	Ma et al <sup>37</sup>	PFB	63% CT-RT 56% RT	NS	RFS P=.05, FLR P=.04
	Hareyamam et al <sup>38</sup>	PF	60% CT-RT 48% RT	NS	DFR 74% 56%
Concurrent	Chan et al <sup>39</sup>	P	76% CT-RT 69% RT	.1	T3* 68% P=.0075 46%
Induction/Adjuvant	Chan et al <sup>31</sup>	PF	80% CT-RT 81% RT	NS	
Concurrent/Adjuvant	Al-Sarraf et al <sup>35,36</sup>	P/PF	67% CT- RT 37% RT	<.001	DRS 74% 46%

\* according to the Ho staging system.  
A = doxorubicin      B = bleomycin  
C = cyclophosphamide      E = epirubicin  
F = 5-fluorouracil      P = cisplatin  
L = leucovorin      V = vincristine  
NS = not significant      DFS = disease-free survival  
DRS = disease-related survival      FLR = freedom local recurrence

Table 8. — Stage IV Nasopharyngeal Cancer:  
Change in Overall Survival, 1980-2000

Treatment	% 5-Year Survival
RT without salvage	<30
RT with salvage	±40
Concurrent CT + RT	50-55
Sequential CT → RT	50-55
RT → CT	50-55
CT + RT → CT	75
CT → CT + RT	>90
CT = chemotherapy	
RT = radiotherapy	

tions of follow-up, use of only two courses of chemotherapy, a high mortality rate (9%) in one study with non-PF chemotherapy, a low dosage of cisplatin and/or 5FU, and limited chemotherapy given (induction, concurrent, or adjuvant only). A recent phase III randomized study by Chan et al<sup>39</sup> comparing concurrent chemotherapy-radiation therapy to radiation therapy alone reported a 7% difference in progression-free survival, which was not statistically significant because of the small sample of patients included. However, in patients with T3 disease based on the Ho staging system,<sup>40</sup> the difference was 68% vs 46% ( $P=.0075$ ) favoring the combined treatment group.

We reported on the use of “total” chemotherapy-radiation therapy vs radiation therapy alone in patients with locally advanced nasopharyngeal cancer (90% stage IV).<sup>35,36</sup> The experimental arm consisted of concurrent cisplatin given for three courses with radiation therapy followed by three courses of cisplatin-5FU. This study demonstrated a significant difference in 5-year actual overall survival rate (67% vs 37%,  $P<.001$ ) and progression-free survival ( $P<.001$ ) in favor of the combined approach. The disease-related 5-year overall

survival rates were 76% and 46% ( $P<.001$ ), respectively. Total chemotherapy-radiation therapy produced significant improvement in the incidence of local and regional control and in the incidence of systemic recurrence.

A meta-analysis comparing combined chemotherapy-radiation therapy vs radiation therapy alone in locally advanced nasopharyngeal cancer included patients from six randomized studies (1,528 patients).<sup>41</sup> The addition of chemotherapy to radiation therapy increased disease-free/progression-free survival by 37% at 2 years, 40% at 3 years, and 34% at 4 years after treatment. Likewise, the overall survival increased by 20%, 19%, and 21%, respectively, with chemotherapy plus radiation therapy.

For the last 10 years in our practice, we have reversed the sequence of chemotherapy and have prescribed three courses of cisplatin-5FU induction followed by concurrent chemotherapy-radiation therapy, with cisplatin for three courses. In this unpublished trial, the 5-year actual overall survival was approximately 90%. Recent reports from other centers indicated approximately the same incidence of overall survival using the same sequence of total chemotherapy-radiation therapy.<sup>42</sup> Table 8 shows the change in actual 5-year survival of stage IV patients with nasopharyngeal cancer over the last 20 years.

## Targeted Therapy

Novel biologic agents have been developed to target multiple specific regions of the cancer cells. Protein tyrosine kinases are major components of cell signaling pathways. The various subfamilies of these kinases include receptors for epidermal growth factor receptors (EGFR), platelet-derived growth factor, vascular

Table 9. — Targeted Therapy With or Without Chemotherapy in Metastatic/Recurrent Head and Neck Cancers

Author	Agent	Chemotherapy	No. of Patients	Evaluable	Complete Response	Partial Response	% Response Rate
Hong et al <sup>43</sup>	C225	P	38	38	1	7	21
Baselga et al <sup>46</sup>	C225	P/C	96	96	2	12	15
Burtness et al <sup>47</sup>	C225	P	60	57	3	9	21
		P	63	58	2	3	9
Senzer et al <sup>49</sup>	SI-774		114	78		10	13
Cohen et al <sup>45</sup>	D-1839		52	47	1	4	11
Kies et al <sup>44</sup>	CH-66336		17	17		3	18
Zahalsky et al <sup>47</sup>	SU-5416		27	20		1	5
C = carboplatin							
P = cisplatin							

endothelial growth factor, fibroblast growth factor, and hepatocyte growth factor. EGFR is one of four receptors critical to cellular proliferation, differentiation, and survival, and it is widely expressed in malignant tissue, especially in squamous cell carcinoma of the head and neck. EGFR blockers, such as anti-EGFR monoclonal antibodies, tyrosine kinase inhibitors, ligand conjugates, and antisense oligonucleotides, have been investigated in patients with head and neck cancers.

Anti-EGFR antibodies target the extracellular domain. Small molecules, such as the tyrosine kinase inhibitors, target the intracellular tyrosine kinase signaling pathways and thus inhibit the EGFR pathways. EGFR expression was found to correlate with locoregional control and overall survival but not with the incidence of distant failure in patients with head and neck cancers. Table 9 summarizes recent reported results with these agents given alone or with platinum drugs.<sup>43-49</sup> Most of these patients were previously treated with first-line chemotherapy and even some with second-line chemotherapy for recurrent disease. These agents are not miracle drugs in patients with head and neck cancers. Used alone, response rates are approximately 10%; with single-agent chemotherapy, the response rates are about 20%. Some investigators have tried to inflate the rate of response rate by adding the group of patients with stable disease, and others have tried to correlate the response to the incidence and degrees of skin toxicities. Neither approach is correct or acceptable.

The ECOG study comparing single-dose cisplatin to cisplatin plus C225 (cetuximab) in patients with previously untreated recurrent or metastatic cancers reported an incidence rate of approximately 35% to 40% stable disease in both arms.<sup>47</sup> This randomized trial had design flaws. Neither ECOG nor other groups or centers give single-agent cisplatin as first-line treatment for these patients. Although the dose of cisplatin was adequate (100 mg/m<sup>2</sup>), neither ECOG nor other groups give this drug every 4 weeks in other situations. Giving cisplatin with C225 every 4 weeks may be acceptable because of the possibility of combination-induced toxicities.

Anti-EGFR antibodies were also found to exhibit radiosensitization properties in cell cultures and in animal systems experiments when given with radiation therapy. In a phase I study reported by Robert et al,<sup>50</sup> C225 and radiation therapy were given to 16 patients with locally advanced cancers (13 patients with stage IV). They reported a total clinical response rate of 100% and a CR rate of 87% (13 of 16 patients). A phase III randomized trial comparing radiation therapy alone vs radiation therapy plus C225 in patients with locally

advanced cancers recently finished accrual. As noted above, the standard treatment for these patients at the time of this study was concurrent chemotherapy-radiation therapy, and remains so today. Again, the results of this randomized trial may be meaningless because of the flawed trial design that used radiation therapy alone as the standard arm. Excellent reviews on targeted therapy in patients with head and neck cancers have been recently published.<sup>51,52</sup>

Properly designed protocols that combine these agents with chemotherapy, radiation therapy, and chemotherapy-radiation therapy should provide an additional positive impact on the results of treatment of this disease.

## Conclusions

Considerable progress has been made in the treatment results of patients with locally advanced head and neck cancers. This has resulted in a decrease in distant involvement and improvements in local control, quality of life (with organ preservation), disease-free survival, and overall survival. These endpoints have been demonstrated not only in carefully designed phase III trials and meta-analyses, but also — and more significantly — in the changes in the natural history of this disease as shown on the national level, especially in patients with advanced nasopharyngeal cancer. The use of “total” chemotherapy-radiation therapy treatment, the appropriate application of the newer chemotherapy active agents, and the inclusion of the biological and the specific targeted compounds as part of therapy in these patients should provide further improvement in treatment outcomes.

## References

1. Al-Sarraf M. Head and neck cancer: chemotherapy concepts. *Semin Oncol*. 1988;15:70-85.
2. Al-Sarraf M. Head and neck cancer: present status and future prospects of adjuvant chemotherapy. *Cancer Invest*. 1995;13:41-53.
3. Ries LAG, Wingo PA, Miller DS, et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. *Cancer*. 2000;88:2398-2424.
4. Manam R, Al-Sarraf M. Head and neck cancer. In: Giaccone G, Schilsky R, Sondel P, eds. *Cancer Chemotherapy and Biological Response Modifiers, Annual 20*. Amsterdam, Netherlands: Elsevier Science BV; 2002:1-16.
5. Schrijvers D, Vermorken JB. Role of taxoids in head and neck cancer. *Oncologist*. 2000;5:199-208.
6. Glisson BS. The role of docetaxel in the management of squamous cell cancer of the head and neck. *Oncology (Huntingt)*. 2002;16:83-87.
7. Murphy B, Li Y, Cella D, et al. Phase III study comparing cisplatin (C) and 5-fluorouracil (F) versus cisplatin and paclitaxel (T) in metastatic/recurrent head and neck cancer (MHNC). *Proc Annu Meet Am Soc Clin Oncol*. 2001;20:894. Abstract.
8. Cruz JJ, Fonesca E, Garcia-Gomez J, et al. Randomized phase II, multicenter trial of induction chemotherapy in patients with locally advanced head and neck carcinoma (LA-HNC). Docetaxel plus cis-

platin (DP) versus cisplatin and 5-FU (PF): interim results. *Proc Annu Meet Am Soc Clin Oncol*. 2002;21:920. Abstract.

9. Posner MR, Glisson B, Frenette G, et al. Multicenter phase I-II trial of docetaxel, cisplatin, and fluorouracil induction chemotherapy for patients with locally advanced squamous cell cancer of the head and neck. *J Clin Oncol*. 2001;19:1096-1104.

10. Vokes EE, Kies MS, Haraf DJ, et al. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. *J Clin Oncol*. 2000;18:1652-1661.

11. Argiris A. Update on chemoradiotherapy for head and neck cancer. *Curr Opin Oncol*. 2002;14:323-329.

12. Haselow RE, Warshaw MG, Oken MM, et al. Radiation alone versus radiation with weekly low dose cis-platinum in unresectable cancer of the head and neck. In: Fee WE, Goepfert H, Johns ME, et al, eds. *Head and Neck Cancer*. Toronto: BC Decker; 1990:279-281.

13. Jeremic B, Shibamoto Y, Stanisavljevic B, et al. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiother Oncol*. 1997;43:29-37.

14. Tsuchiya K, Nishioka T, Shirato H, et al. A randomized trial of concomitant chemoradiotherapy for head-and-neck cancers: cisplatin (CDDP) vs. carboplatin (CBDCA). *Int J Radiat Oncol Biol Phys*. 2001;51(suppl 1):337. Abstract 2215.

15. Bernier J, Dornge C, Eschwege F, et al. Chemo-radiotherapy, as compared to radiotherapy alone, significantly increases disease-free and overall survival in head and neck cancer patients after surgery: results of EORTC phase III trial 22931. *Int J Radiat Oncol Biol Phys*. 2001;51(suppl 1): plenary 1.

16. Pignon JP, Bourhis J, Dornge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lancet*. 2000;355:949-955.

17. Browman GP, Hodson DI, Mackenzie RJ, et al. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. *Head Neck*. 2001;23:579-589.

18. Merlano M, Benasso M, Corvo R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst*. 1996;88:583-589.

19. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 1998;338:1798-1804.

20. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. *J Clin Oncol*. 1998;16:1318-1324.

21. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. 1999;91:2081-2086.

22. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol*. 2000;18:1458-1464.

23. Adelstein DJ, Adams GL, Li Y, et al. A phase III comparison of standard radiation therapy (RT) versus split-course RT plus concurrent cisplatin (DDP) versus RT plus concurrent DDP and 5-fluorouracil in patients with unresectable squamous cell head and neck cancer (SCHNC): an intergroup study. *Proc Annu Meet Am Soc Clin Oncol*. 2000;19:1624. Abstract.

24. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy: results of a multicenter randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2001;50:1161-1171.

25. Induction chemotherapy plus radiation compared with surgery plus radiation with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. *N Engl J Med*. 1991;324:1685-1690.

26. Forastiere AA, Berkey B, Maor M, et al. Phase III trial to preserve the larynx: induction chemotherapy and radiotherapy versus con-

comitant chemoradiotherapy versus radiotherapy alone, Intergroup Trial R91-11. *Proc Annu Meet Am Soc Clin Oncol*. 2001;20:4. Abstract.

27. Al-Sarraf M, Reddy MS. Nasopharyngeal carcinoma. *Curr Treat Options Oncol*. 2002;3:21-32.

28. Mould RF, Tai TH. Nasopharyngeal carcinoma: treatments and outcomes in the 20th century. *Br J Radiol*. 2002;75:307-339.

29. Rossi A, Molinari R, Boracchi P, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol*. 1988;6:1401-1410.

30. Chi KH, Chang YC, Guo WY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys*. 2002;52:1238-1244.

31. Chan AT, Teo PM, Leung TW, et al. A prospective randomized study of chemotherapy adjunctive to definitive radiotherapy in advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*. 1995;33:560-577.

32. Cvitkovic E, Grange GRL, le Temple S, et al. Neoadjuvant chemotherapy (NACT) with epirubicin (EPI) cisplatin (CDDP) bleomycin (BLEO) (BEC) in undifferentiated nasopharyngeal cancer (UCNT): preliminary results of an international phase III trial. *Proc Annu Meet Am Soc Clin Oncol*. 1994;13:283.

33. International Nasopharynx Cancer Study Group. Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs radiotherapy alone in stage IV (> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progress-free survival. *Int J Radiat Oncol Biol Phys*. 1996;35:463-469.

34. Chau DT, Sham JS, Choy D, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and epirubicin followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. *Cancer*. 1998;83:2270-2283.

35. Al-Sarraf M, LeBlanc M, Giri PGS, et al. Superiority of five year survival with chemoradiotherapy (CT-RT) vs radiotherapy in patients (pts) with locally advanced nasopharyngeal cancer (NPC). Intergroup (0099) SWOG 8892, RTOG 8817, ECOG 2388) phase III study: final report. *Proc Annu Meet Am Soc Clin Oncol*. 2001;20:905. Abstract.

36. Al-Sarraf M, LeBlanc M, Giri PGS, et al. Chemo radiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*. 1998;16:1310-1317.

37. Ma J, Mai HQ, Hong MH, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol*. 2001;19:1350-1357.

38. Hareyamam M, Sakata, K Shirato H, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. *Cancer*. 2002;94:2217-2223.

39. Chan AT, Teo PML, Ngan RK, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol*. 2002;20:2038-2044.

40. Ho JH. Stage classification of nasopharyngeal carcinoma: a review. *IARC Sci Publ*. 1978;20:99-113.

41. Huncharek M, Kupelnick B. Combined chemoradiation versus radiation therapy alone in locally advanced nasopharyngeal carcinoma: results of a meta-analysis of 1,528 patients from six randomized trials. *Am J Clin Oncol*. 2002;25:219-223.

42. Rischin D, Peters L, Corry J, et al. Excellent disease control and survival in patients with advanced nasopharyngeal cancer treated with chemoradiation. *J Clin Oncol*. 2002;20:1845-1852.

43. Hong WK, Arquette M, Nabell L, et al. Efficacy and safety of the anti-epidermal growth factor antibody (EGFR) IMC-C225, in combination with cisplatin in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) refractory to cisplatin containing chemotherapy. *Proc Annu Meet Am Soc Clin Oncol*. 2001;20:895. Abstract.

44. Kies MS, Clayman GL, El-Naggar AK, et al. Induction therapy with SCH 66336, a farnesyltransferase inhibitor, in squamous cell carcinoma (SCC) of the head and neck. *Proc Annu Meet Am Soc Clin*

*Oncol.* 2001;20:225a.

45. Cohen EEW, Rosen F, Dekker A, et al. Phase II study of ZD1839 (Iressa) in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). *Proc Annu Meet Am Soc Clin Oncol.* 2002;21:899. Abstract.

46. Baselga S, Trigo JM, Bourhis J. Cetuximab (C225) plus cisplatin/carboplatin is active in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) progressing on a same dose and schedule platinum-based regimen. *Proc Annu Meet Am Soc Clin Oncol.* 2002;21:900. Abstract.

47. Burtneß BA, Li Y, Flood W, et al. Phase III trial comparing cisplatin (C) + placebo (P) to C + anti-epidermal growth factor antibody (EGF-R) C225 in patients (pts) with metastatic/recurrent head & neck cancer (HNC). *Proc Annu Meet Am Soc Clin Oncol.* 2002;21:901. Abstract.

48. Zahalsky AJ, Wong RJ, Lis E, et al. Phase II trial of SU5416 in patients with advanced incurable head and neck cancer. *Proc Annu Meet Am Soc Clin Oncol.* 2002;21:902. Abstract.

49. Senzer NN, Soulieres D, Siu L, et al. Phase 2 evaluation of OSI-774, a potent oral antagonist of the EGFR-TK in patients with advanced squamous cell carcinoma of the head and neck. *Proc Annu Meet Am Soc Clin Oncol.* 2001;20:6. Abstract.

50. Robert F, Ezekiel MP, Spencer SA, et al. Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. *J Clin Oncol.* 2001;19:3234-3243.

51. Kim ES, Kies M, Herbst RS. Novel therapeutics for head and neck cancer. *Curr Opin Oncol.* 2002;14:334-342.

52. Herbst RS, Langer CJ. Epidermal growth factor receptors as a target for cancer treatment: the emerging role of IMC-C225 in the treatment of lung and head and neck cancers. *Semin Oncol.* 2002;29(suppl 4):27-36.