Combined Modality Treatment of Squamous Cell Cancer of the Head and Neck

John Devlin, MD, and Eric Sherman, MD

Dr. Devlin is a Medical Oncology/Hematology Fellow and Dr. Sherman is an Associate Member and Attending Physician in the Department of Medical Oncology at the Fox Chase Cancer Center in Philadelphia, Pa.

Address correspondence to:
Eric Sherman, MD, Fox Chase Cancer Center, Department of Medical Oncology, 333 Cottman Avenue, Philadelphia, PA 19111; E-mail: eric.sherman@fccc.edu.

Keywords
Squamous cell cancer of the head and neck (SCCHN), combined modality treatment, sequential, concurrent, organ preservation, EGFR inhibitors

Abstract: Squamous cell cancer of the head and neck is a debilitating disease. Combined modality treatments with surgery, chemotherapy, and radiation have been evaluated in multiple settings over the past 30 years. While surgery and radiation remain the potentially curative modalities, the addition of chemotherapy can in some cases decrease the rate of distant metastasis. When concurrent chemoradiation is employed, overall survival is improved, although toxicity can be higher. Studies have also shown a role for concurrent treatment in an effort to avoid total laryngectomy and preserve organ function. Multidisciplinary evaluation should be a routine part of care in this patient population. Future areas of research include the epidermal growth factor inhibitors, which have shown promise in early studies.

The term "head and neck cancer" generally refers to a heterogeneous group of epithelial neoplasms arising in the upper aerodigestive tract, 90% of which are squamous cell in origin. The remaining 10%, not reviewed here, include thyroid cancer and salivary gland adenocarcinomas. Nasopharyngeal carcinoma also differs in etiology and prognosis and will not be reviewed. Head and neck cancer represents 3% of all human cancers and 2% of all cancer deaths in the United States, with an annual incidence of approximately 45,000 cases. It is more prevalent in men and patients of African descent.[1] Traditional risk factors for this disease are alcohol and tobacco use,[2] although more recently exposure to human papilloma virus has been implicated in disease pathogenesis.[3] Multiple molecular and genetic mutations have been found in premalignant and malignant tissues, thought to occur as a consequence of direct exposure to these risk factors in a "multihit" model of pathogenesis, which have been well described elsewhere.[4] Clinical presentations vary, as tumors arising in different anatomic locations can create unique symptomatology, depending on which structure they involve. Staging generally uses the TNM system for each site of origin.[5]

Treatment of advanced squamous cell cancer of the head and neck (SCCHN) most often involves some combination of radiation, surgery, and chemotherapy, with a potentially expanding role for targeted therapy. Radiation and surgery are generally felt to be the potentially curative modalities in this disease, although chemotherapy and targeted therapy may improve outcomes when combined with one or both of these approaches in advanced disease. In cases of early-stage malignancy (stage I or II), surgery or radiation is often employed as the initial treatment modality with curative intent, with cure rates approaching 90%. In stark contrast, incurable diffuse metastatic disease would generally warrant palliative chemotherapy alone. Patients with locoregionally advanced or recurrent disease without a surgical or radiation option share a similarly poor prognosis, and although not curable, would also benefit from palliative chemotherapy alone in most cases.

Some patients fall between these extremes, presenting with potentially curable but locally advanced disease (stage III or IV), where consideration of combined modality treatment may be justified. It is not infrequent in this patient population, however, for a patient to be deemed medically inoperable, owing mostly to comorbidity related to tobacco and alcohol use.

Rationale for Combined Modality Treatment

Cure rates are lower, ranging from 10% to 65%, in patients with stage III or IV disease who are treated with surgery and/or radiation in the same manner as patients with stage I or II cancers. This finding implies the inability of radiation therapy and/or surgery to achieve the same degree of effective tumor killing and/or removal, and is probably multifactorial in etiology.

The first factors to consider are tumor-related, and may explain why radiation is unable to completely sterilize the surgical bed or control the disease in some of these patients. Tumors possess certain characteristics that make them difficult to treat. For example, innate hyperpermeability of vascular structures within the tumor microenvironment precludes effective oxygen delivery to some areas within the tumor, and thus large amounts of hypoxic tissue can persist. Formation of oxygen-derived free radicals by radiation is more difficult if not impossible to achieve in the relative absence of oxygen. Second, cancer cells are well known to repopulate tumor mass, sometimes at an accelerated rate, making long-lasting effects of radiation less significant. Third, some tumors are inherently radioresistant, as a result of cell-cycle stage. Finally, tumor size at this stage disease is usually significant, and overall burden may be simply too much to overcome with random radiation-related killing. The efficacy of radiation is therefore limited in these later-stage patients.

The second major factor is an unfortunate reality in this patient population: only a small percentage of patients can actually have effective curative surgery without significant loss of vital organ function or serious cosmetic morbidity. Because of the sensitive locations of these tumors, often in close proximity to vital structures, surgery for cure is technically demanding, and should ideally be performed by an experienced head and neck surgeon. The surgeon must paradoxically minimize resection to preserve function and cosmesis while still resecting enough tissue to provide negative margins and thus optimize the chance for cure. Multidisciplinary evaluation should also be performed, as speech and swallow therapists, physical therapists, audiologists, plastic and reconstructive surgeons, psychologists and psychiatrists, nutritionists, substance abuse counselors, and pulmonologists may all contribute to care for these patients at some point. However, despite these efforts, and for a variety of social, practical, and medical reasons, few patients at this stage of disease can undergo curative surgery without enduring significant procedure-related morbidity.

The theoretical rationale for considering adding chemotherapy to locoregional treatment in some fashion, assuming the above factors, is 2-fold and logical. First, chemotherapy-induced radiosensitization of cancer cells within a given radiation field will theoretically enhance local control. Second, decreasing the rates of distant micrometastases, which are not directly treated by local radiation and/or surgery, can theoretically improve distant control. The rationale is that the combination of improved local and distant control will in turn decrease the chance of recurrence, and improve the chances of cure and survival. A third theoretical reason to use induction chemotherapy is as a predictor of the radiosensitivity of the malignant cells when radiation therapy is being considered to preserve organ function instead of surgery.

The extensive literature investigating the realities of combined modality therapy is complicated. Power of studies is often limited by the heterogeneity of tumor primary sites, which all have different behaviors. Compliance and accrual are sometimes poor, and often times there are multiple variables adjusted in each study, making data difficult to reliably interpret. Initial studies in the 1970s and 1980s focused on the sequential administration of chemotherapy and radiation, in either the adjuvant or neoadjuvant setting (or both), in patients with locally advanced yet resectable disease, in an effort to improve survival in this stage of disease.

While these trials did not show improvement in overall survival, it was noted that patients who responded to chemotherapy also had better responses to radiation therapy, and rates of long-term survival and local control were respectable. From these observations, studies developed that focused on organ (ie, larynx) preservation as a primary goal, which is justifiable as most patients consider a total laryngectomy to be perhaps the most feared procedure available.[6] Only 26–40% of patients are able to acquire esophageal speech,[7] and although approximately 60–80% are candidates for a tracheal-esophageal puncture, daily maintenance of the prosthesis can be cumbersome.[8] McNeil et al[9] questioned a group of 35 firefighters and executives, and found that they would be willing to sacrifice on average 14% of their life expectancy in order to avoid total laryngectomy. Although not at the expense of local control, preserving laryngeal function therefore stands out as an important goal. Examination of quality of life in patients with laryngeal cancer treated with total laryngectomy, near-total laryngectomy, or partial laryngectomy found that a permanent tracheostomy had a major influence, and not solely the loss of lung-powered speech.[10] In the 1980s, several groups evaluated sequential chemotherapy and radiation therapy (with surgery reserved for the salvage setting) as a method of preserving organ function. The use of neoadjuvant chemotherapy was partially a predictor for tumor sensitivity to radiation therapy.

Later studies evaluated the combination of concurrent chemotherapy and radiation therapy, with the specific goal of further improving rates of organ preservation and perhaps survival. This approach has also been evaluated in patients with unresectable or marginally resectable disease. Each of the 3 above groups is reviewed in detail below.

Sequential Chemotherapy and Locoregional Treatment

Phase II study data are available for multiple active chemotherapeutic agents in SCCHN, either alone or in combination (Table 1). Response rates tend to be higher, sometimes even doubled, in chemotherapy-naive patients compared to those with recurrent disease. The consistently high response rates of platinum-based therapy, particularly when used in combination with 5-fluorouracil (5-FU), led investigators to include this regimen most often in subsequent studies in the curative setting.

Despite some encouraging response rates, chemotherapy alone has not yet been shown capable of curing SCCHN. (There are, however, some very interesting early studies from the M. D. Anderson Cancer Center that may prove otherwise in the future.[11]) Combination of this treatment modality (neoadjuvant, adjuvant, or both) with either radiation, surgery, or both, has been evaluated in early studies. Studies in the 1970s and 1980s established the standard of care for resectable head and neck cancers to be surgical resection followed by adjuvant radiation. As a result, this was usually the control group in randomized studies comparing addition of chemotherapy to this regimen. Table 2 summarizes these studies, with selected reviews following.

In a 1987 landmark study from the Head and Neck Contracts Program, 462 patients with resectable yet locally advanced disease of 6 different primary sites were randomized preoperatively to 1 of 3 arms, namely a control arm of standard surgical resection followed by adjuvant radiation alone, a second arm of induction therapy with a single preoperative cycle of cisplatin and bleomycin (followed by surgery and radiation), or a third arm with the same preoperative cisplatin and bleomycin, surgery and radiation, plus a maintenance regimen of monthly cisplatin for 6 cycles (which only 9% of patients were able to complete). No significant difference in disease-free or overall survival was detected between the 3 arms, although, interestingly, the time to distant failure was longer, and the chance of distant failure lower, in the maintenance arm.[12] Additionally, patients with N2 disease appeared to derive the most clinical benefit per subsequent subset analysis.[13] One limitation in this study is the relative paucity of induction chemotherapy administered, with 1 cycle clearly inadequate by today's standards.

Table 1. Chemotherapy Agents Evaluated in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Drug	Patients, N	Response Rate, % (range)
Methotrexate	988	31 (10–45)
Bleomycin	347	21 (6–45)
Cisplatin	288	28 (14–41)
5-Fluorouracil	118	15 (0–33)
Paclitaxel	65	38 (30–40)
Docetaxel	58	38 (30–40)
Carboplatin	169	22 (10–30)
Ifosfamide	99	26

The Intergroup Adjuvant Study 0034 by Laramore and colleagues[14] randomized patients with optimally resected locally advanced SCCHN of various primary sites to receive either standard adjuvant radiation or 3 cycles of adjuvant cisplatin and 5-FU followed by standard radiation. A significantly decreased rate of distant metastases was observed in the chemotherapy group, but no effect on rate of local recurrence or 4-year survival was detected (44% vs 46%). It is worth noting that despite its sequence before radiation, only 62% of patients randomized to the chemotherapy arm successfully received it with minor or no protocol violation.

A 1994 multicenter phase III Italian study by Paccagnella and associates[15] randomized 237 patients with stage III-IV SCCHN of 4 primary sites to either a control arm of standard treatment (surgery and/or radiation therapy and neck dissection) or an experimental arm using 4 cycles of neoadjuvant cisplatin and 5-FU followed by

Table 2. Phase III Randomized Trials Evaluating the Addition of Sequential Chemotherapy to Surgery ± Radiotherapy

Author	Patients, N	Chemotherapy Regimen	Control	Survival Benefit (*P*≤.05)
Head and Neck Contracts Program[12]	462	Cisplatin/bleomycin (neoadjuvant ± adjuvant)	Surgery followed by adjuvant RT (3-arm study)	None
Ervin et al[16]	114	Cisplatin/bleomycin/ methotrexate/leucovorin (neoadjuvant, then either adjuvant or observation for responders)	Surgery + RT	3-year failure-free survival superior in responders with adjuvant therapy (88% vs 57%, *P*=.03)
Domenge et al[17]	287	Cisplatin/bleomycin/ methotrexate (adjuvant)	Surgery + RT	None
Richard et al[18]	222	Bleomycin/vincristine (neoadjuvant)	Surgery ± RT	None
Intergroup 0034[14]	448	Cisplatin/5-FU (adjuvant, pre-RT)	Surgery + RT	None
Depondt et al[19]	324	Carboplatin/5-FU (neoadjuvant)	Surgery ± RT or RT alone	None
Paccagnella et al[15]	237	Cisplatin/5-FU (neoadjuvant)	Surgery and RT, or RT if not resectable	None
Dalley et al[20]	280	Cisplatin/5-FU (neoadjuvant)	Surgery/RT	None
Horiuchi et al[21]	424	Oral tegafur/uracil (adjuvant)	Surgery alone	None

5-FU = 5-fluorouracil; RT = radiation therapy.

the same standard treatment. No significant difference in overall or disease-free survival was found between the groups. Subsequent subset analysis did find a statistically significant difference in 3-year survival in patients with unresectable disease (10% vs 24%). Incidence of distant metastases in this subset of patients was also significantly lower with chemotherapy (32% vs 9%).[19]

A landmark meta-analysis by Pignon et al[22] of over 10,000 patients in 63 randomized trials evaluated whether or not the addition of chemotherapy to local surgical and radiation treatment would add any clinical benefit. Combined analysis of all trials found a small but real absolute survival advantage of 4% at 2 and 5 years posttreatment favoring chemotherapy. There was no significant improvement in overall survival with the use of adjuvant chemotherapy, and a nonsignificant trend in improved survival was elucidated for neoadjuvant chemotherapy. Subset analysis of neoadjuvant cisplatin and 5-FU, however, showed a significant but modest survival benefit.

Concurrent chemoradiation has been evaluated in the adjuvant setting for high-risk patients. Table 3 summarizes these studies. Hazard ratios are included. The European Organization for Research and Treatment of Cancer (EORTC) study[23] and Radiation Therapy Oncology Group (RTOG) study[24] were the 2 largest studies and showed conflicting results in overall survival. Although the RTOG study did not show an overall survival benefit, there was a benefit in both local-regional control and disease-free survival. There were some important differences in the inclusion criteria of all 3 studies. All of this must be taken into account when discussing the benefits and risks of adding chemotherapy to postoperative radiation therapy in selected high-risk patients.

Currently, the literature does not support sequential chemotherapy and locoregional treatment as the standard of care, although there may be select populations of patients who would benefit from such an approach, as suggested by the neoadjuvant data outlined herein. There is currently a multicenter phase III randomized study (principal investigators: Ezra Cohen and Everett Vokes) examining the benefit of the addition of neoadjuvant therapy to concurrent chemotherapy and radiation therapy in patients with N2 or N3 locally advanced head and neck cancer.

Table 3. Trials Evaluating Concurrent Chemoradiation Therapy for High-Risk Patients in the Adjuvant Setting

Author	Pts, N	Comparison	Local-Regional Control	Progression-free Survival HR (95% CI)	Overall Survival HR (95% CI)
Bachaud et al[25]	83	RT vs RT + weekly cisplatin	No (*P*=.08)	HR NR *P*<.02	HR NR *P*<.01
Bernier et al[23] (EORTC)	167	RT vs RT + cisplatin × 3 every 3 wk	Yes (*P*=.007)	0.75 (0.56–0.99) *P*=.04	0.70 (0.52–0.95) *P*=.02
Cooper et al[24] (RTOG)	459	RT vs RT + cisplatin × 3 every 3 wk	Yes (*P*=.01)	0.78 (0.61–0.99) *P*=.04	0.84 (0.65–1.09) *P*=.19

CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; HR = hazard ratio; NR = not reported; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group.

Table 4. Selected Organ Preservation Studies

Group	Patients, N	Chemotherapy Regimen	Rate of Organ Preservation	Survival Advantage
VALCSG[26,27]	332	Cisplatin/5-FU	66%	Comparable to surgery + RT
EORTC[28]	202	Cisplatin/5-FU	42% at 3 years (functional larynx)	Comparable to surgery + RT
GETTEC[29]	68	Cisplatin/5-FU	20% at 3 years	Inferior to surgery + RT

EORTC = European Organization for Research and Treatment of Cancer; 5-FU = 5-fluorouracil; GETTEC = Groupe d'Etudes des Tumeurs de la Tete et du Cou; RT = radiation therapy; VALCSG = Veterans Affairs Laryngeal Cancer Study Group.

Some physicians believe that neoadjuvant chemotherapy will have the greatest advantage in patients with significant nodal involvement. There is also a phase III study being sponsored by the Dana-Farber Cancer Institute investigating this same question in stage III and IV, M0 SCCHN. Further studies may be warranted to investigate its impact in larger numbers of patients and using more modern regimens.

Chemotherapy and Radiation for Organ Preservation

Laryngeal cancers are technically curable by surgery, albeit with high levels of postoperative morbidity. A number of studies evaluating cure rates and locoregional control with combined modality treatment in lieu of surgical intervention as upfront treatment. The control group typically consisted of the standard upfront surgery plus adjuvant radiation; some of these studies are listed above in Table 4.

The Veterans Affairs Laryngeal Cancer Study Group (VALCSG) conducted a seminal study,[26] randomizing patients with locally advanced yet resectable laryngeal carcinoma to either standard laryngectomy with adjuvant standard radiation, or to 3 cycles of cisplatin and 5-FU, followed by radiation for partial or complete responders to chemotherapy (total dose, 65–75 Gy). In the experimental arm, total laryngectomy was reserved for patients with tumors that did not have a major response to induction chemotherapy or as salvage treatment for residual or relapsed disease after radiation therapy. Of note, there was no radiation-alone control arm. Roughly 66% of long-term survivors in the intervention arm successfully avoided total laryngectomy, and quality of life assessments favored the chemoradiation arm, with less chance of pain and depression.[30] Furthermore, overall survival rates in both arms were equivalent, with an 8-year median follow-up, even in patients with resistant disease who required salvage surgery, suggesting that the delay in receiving surgery did not adversely affect survival.[27]

In the EORTC study, patients with squamous cell cancer of the hypopharynx were randomized to either total laryngectomy with partial pharyngectomy and neck dissection followed by adjuvant radiation, or to 3 cycles of cisplatin and infusional 5-FU, followed by radiation, with surgery reserved for the salvage setting. If a complete response of the primary tumor site did not occur after 3 cycles of induction chemotherapy, the cancer was treated

Table 5. Randomized Studies of Concurrent Chemoradiation vs Radiation Alone

Author	Patients, N	Radiation Schedule	Chemotherapy Regimen	Survival Benefit (*P*≤.05)
GORTEC[31,32]	226	Standard	Carboplatin/5-FU	Yes (*P*=.02)
Adelstein et al[33,34]	100	Standard	Cisplatin/5-FU	No (but relapse-free survival *P*=.03)
Wendt et al[35]	270	Hyperfractionated	Cisplatin/5-FU	Yes
Keane et al[36]	212	Standard	Mitomycin/5-FU	No
Brizel et al[37]	122	Hyperfractionated	Cisplatin/5-FU	No (*P*=.07)
Jaremic et al[38]	130	Hyperfractionated	Cisplatin	Yes

5-FU = 5-fluorouracil; GORTEC = Groupe d'Oncologie Radiotherapie Tete et Cou.

with surgery. There were no significant differences in 5-year disease-free or overall survival between the 2 arms, after median follow-up of just over 4 years. Roughly 42% of patients at 3 years, and 35% at 5 years had achieved laryngeal preservation without need for laryngectomy, feeding gastrostomy, or tracheotomy. Delaying surgery while attempting organ preservation did not adversely impact survival.[28]

The Groupe d'Etudes des Tumeurs de la Tete et du Cou (GETTEC) study[29] randomized 68 patients (of a planned 300) with resectable, locally advanced laryngeal squamous cell cancer to either surgery and radiation or to cisplatin and infusional 5-FU followed by radiation for responders with at least 80% tumor regression (nonresponders received salvage surgery). Rates of locoregional control, as well as 3-year disease-free and overall survival, were higher in the standard control arm; however, the study was fraught with limitations. Accrual was poor and the study was underpowered. The 2 arms were not well balanced with respect to stage, with more stage IV patients in the intervention arm. There was little uniformity in radiographic staging. Roughly 17% of patients in the intervention arm had a major protocol violation. Surgical management of the neck was not extensively delineated. Data remain difficult to interpret.

A meta-analysis of these 3 studies did find a nonsignificant (*P*=.10) 6% survival advantage favoring surgery, followed by radiation.[39]

Preserving organ function appears to be a realistic goal, and the use of sequential chemotherapy and radiation (with surgery reserved for the salvage setting) in an effort to avoid certain total laryngectomy seems reasonable in a selected group of patients. However, there are many questions as to whether sequential chemotherapy and radiation therapy is better than radiation therapy alone and whether concurrent chemotherapy could improve rates of organ preservation (eg, RTOG 91-11, see discussion below).

Concurrent Chemotherapy and Radiation

The rationale for concurrent chemoradiation is to combine the local and systemic benefits of radiosensitizing chemotherapy, while decreasing rates of distant metastasis, with the efficacy of radiation in decreasing tumor bulk. Significant overall survival advantages from using this approach have been reported in the literature. Although treatment duration is attenuated, short-term toxicity is also higher, necessitating careful weighing of the risk-benefit ratio for individual cases.

One major limitation in interpreting these data is the myriad ways of administering treatment. Since dosing of each modality is attenuated when given concurrently with the other, optimal dosing and fractionation schedules have been consistently elusive variables. Perhaps more frustrating is that direct comparison between schedules is rare, and as such it is difficult to define the current standard. Table 5 summarizes studies comparing radiation alone to combined treatment.

The GORTEC study (Groupe d'Oncologie Radiotherapie Tete et Cou) randomized patients with unresectable stage III-IV oropharyngeal squamous cell cancer to either definitive standard radiation therapy or radiation therapy concurrent with carboplatin and 5-FU (weeks 1, 3, and 7 of radiation). Locoregional control (42% vs 66%, *P*=.03) and 3-year disease-free survival (20% vs 42%, *P*=.04) favored the combined-modality arm, as did 3-year overall survival (31% vs 51%, *P*=.02). Hematologic toxicity, need for gastrostomy tube, and mucositis were significantly higher in the chemoradiation group, however.[31,32]

Other schedules have been evaluated. Merlano et al[40] randomized 157 patients with unresectable SCCHN to either standard radiation or an alternating (not concurrent) cisplatin/5-FU and radiation treatment. The chemotherapy arm found a higher rate of complete responses as well as overall survival (41% chemora-

Table 6. Randomized Studies Comparing Sequential and Concurrent Chemoradiation Therapy

Author	Patients, N	Chemotherapy Regimen	Survival Benefit (*P*<.05)	Method Favored
SECOG[41]	267	Bleomycin/methotrex-ate/Vincristine ± 5-FU	None (*P*=.04 for disease-free survival)	Concurrent
Adelstein et al[42]	54	Cisplatin/5-FU	None (*P*=.03 for relapse-free survival)	Concurrent
Merlano et al[43]	116	Bleomycin/methotrex-ate/vinorelbine/leucovorin	Yes	Concurrent
Taylor et al[44]	214	Cisplatin/5-FU	None (*P*=.01 for disease-free survival)	Concurrent
RTOG 91-11 (3-arm study)[45]	547	Sequential cisplatin/5-FU then RT vs concurrent cisplatin/RT vs RT alone	"Laryngectomy-free survival" 88% at 2 yrs (concurrent); 75% at 2 yrs (sequential); 70% at 2 yr (RT alone)	Concurrent

5-FU = 5-fluorouracil; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SECOG = South-East Cooperative Oncology Group.

diation vs 23% radiation alone), a benefit lasting after extended follow-up.

One intriguing phase III study by Adelstein et al[46] evaluating the optimal method to deliver concurrent chemoradiation randomized 295 patients with unresectable SCCHN to conventional radiation alone (Arm A), to concurrent radiation with cisplatin (Arm B), or to a split course of single daily fractionated radiation with concurrent cisplatin and 5-FU (Arm C). Concurrent cisplatin and standard fractionated radiation therapy (Arm B) offered a statistically significant improvement in 3-year survival compared to conventional radiation alone (37% vs 23%), although with a higher rate of serious toxicity.

Brizel et al[37] randomized 122 patients (116 analyzed) with locally advanced disease (53% of whom were considered unresectable) to either hyperfractionated radiation (total dose, 7,500 cGy) or hyperfractionated radiation (total dose, 7,000 cGy) with concurrent daily 5-FU and cisplatin during weeks 1 and 6, followed by 2 additional cycles of chemotherapy alone (56% of patients actually completed this treatment). Although the duration of mucositis (4 vs 6 weeks) and rates of gastrostomy tube placement (29% vs 44%) were higher in the chemoradiation group, many endpoints favored this arm. The rates of local control (44% vs 70%, *P*=.01), 3-year progression-free survival (41% vs 61%, *P*=.08) and overall survival (34% vs 55%, *P*=.07) were all higher in the chemoradiation arm.

Meta-analyses have generally confirmed a survival advantage using concurrent therapy. Munro[47] found a roughly 12% increase in overall survival with the use of concurrent single-agent chemotherapy and radiation, when compared to radiation alone. El-Sayed and Nelson[48] found a 22% mortality reduction with combined therapy versus radiation alone.

There are at least 4 studies directly comparing sequential and concurrent chemoradiation packages in patients with unresectable disease, and 1 notable study evaluating organ preservation (Table 6).

The meta-analysis by Pignon et al[22] also found a possible small survival advantage with concurrent chemoradiation compared to sequential administration, but this was not significant. Overall, when compared to radiation treatment alone, a significant absolute 8% overall survival advantage at 5 years was reported with concurrent therapy.

Perhaps the most intriguing organ-preservation study comparing sequential and concurrent chemoradiation is the RTOG 91-11 trial, which randomized patients with locally advanced, potentially resectable laryngeal squamous cell cancer to radiation alone, to cisplatin on days 1, 22, and 43 concurrent with radiation, or to sequential cisplatin and infusional 5-FU followed by radiation for responders (as in the VALCSG study). Salvage surgery was available for persistent residual or relapsed disease. Two-year laryngectomy-free survival was highest in the concurrent arm (88%), which also had the highest rates of locoregional control (78%) and 2-year disease-free survival (61%), and the lowest rate of distant metastases at 2 years (8%). It is worth noting that the sequential arm, although inferior to the concurrent arm in the above measures, had higher rates than the radiation-alone arm of 2-year laryngectomy-free survival (75% vs 70%), locoregional control (61% vs 56%), and 2-year disease-free survival (52% vs 44%). Rates of distant metastases were also lower (9% vs 16%). It is also interesting that overall survival did not differ significantly between the 3 arms. Serious toxicity was higher in the combined treatment arms; however, no significant difference in rates of treatment-related deaths was found.[45]

Concurrent chemotherapy and radiation has consistently displayed an overall survival advantage, is currently the standard of care in most cases of locally advanced, unresectable SCCHN, and appears to benefit patients hoping for organ preservation in the resectable setting. Treatment planning is complex and toxicity is significant. Multidisciplinary evaluation and follow-up should be a part of routine care in these patients.

Targeted Therapy

Overexpression of the epidermal growth factor receptor (EGFR) is frequent in SCCHN, and is associated with more aggressive tumor behavior and poor outcomes.[49] Agents have been recently developed that effectively block this receptor. Both intravenous antibody (cetuximab [Erbitux, ImClone/Bristol-Myers Squibb]) and oral small-molecule (gefitinib [Iressa, AstraZeneca], erlotinib [Tarceva, Genentech/OSI]) formulations are clinically available. Convenience of oral therapy and potentially less systemic toxicity make this an attractive option assuming efficacy is preserved. The most common toxicities, acneiform rash and diarrhea, generally do not lead to discontinuation of therapy in most patients evaluated thus far. There are a few relevant trials to review in this regard.[50-55]

However, there were intriguing preclinical data suggesting synergy between monoclonal antibodies to EGFR and radiation therapy.[56] This observation led to a phase III multicenter trial by Bonner and colleagues,[57] randomizing 424 patients to receive either radiation alone or radiation with weekly cetuximab. Patients were stratified by nodal status, performance status, T stage, and radiation fractionation schedule. Investigators were allowed to choose their own radiation schedule (ie, once-daily vs twice-daily vs concomitant boost). Treatment arms were well balanced and follow-up extended for 2–3 years. The addition of cetuximab to radiation therapy resulted in a statistically significant benefit in overall survival versus radiation alone (62% vs 55% at 2 years and 57% vs 44% at 3 years; log-rank P=.02). Locoregional control (the primary outcome) was also significantly better at 3 years for the cetuximab arm (56% vs 48%, log-rank P=.02). More mature survival data are not yet available. Incidence of serious mucositis was similar in the 2 groups; skin rash and infusion reactions were more common in the combined therapy group.

An intriguing phase II study by Pfister et al[58] evaluated the combination of cisplatin, cetuximab, and concomitant boost radiation therapy in 21 patients with stage III/IV SCCHN. The study was stopped early because of 2 deaths; however, 2-year overall survival was impressive at 76%, warranting further study of this combination.

Summary

SCCHN is a cause of substantial morbidity and mortality, with tobacco and alcohol serving as the predominant risk factors. Combined modality treatment has been clearly shown to benefit patients in selected settings, but the morbidity of this approach must be balanced with its benefit. A coordinated team approach (including surgeons, medical oncologists, radiation oncologists, speech therapists, social workers, nutritionists, radiologists, etc) is essential in order to optimize the quality and safety of this approach. Future research directions include the feasibility and risk/benefit ratio of delivering chemotherapy and radiation therapy in previously radiated sites, the addition of induction chemotherapy to combined chemoradiation, the addition of targeted agents with combined modality treatment, and many others.

References

1. Lee K, Strauss M. Head and neck cancer in blacks. *J Natl Med Assoc*. 1994;86:530-534.

2. Spitz M. Epidemiology and risk factors for head and neck cancer. *Semin Oncol*. 1994;21:281.

3. Gillison M, Koch W, Capone R, et al. Evidence for a causal association between human papilloma virus and a subset of head and neck cancers. *J Natl Cancer Inst*. 2000;92:709-720.

4. Forastiere A, Koch W, Trotti A, et al. Head and neck cancer. *N Engl J Med*. 2001;345:1890-1900.

5. Greene F, Page D, Fleming I, et al. AJCC (American Joint Committee on Cancer) *Manual for Staging of Cancer*, 6th ed., 2002. New York, NY: Springer-Verlag; 2002.

6. Dropkin M, Malgady RG, Scott DW, Oberst M, Strong EW. Scaling of disfigurement and dysfunction in postoperative head and neck patients. *Head Neck Surg*. 1983;8:559-570.

7. Pfister D, Harrison LB, Strong EW, Bosl GJ. Current status of larynx preservation with multimodality therapy. *Oncology*. 1992;6:33-43.

8. Miller S. The role of the speech-language pathologist in voice-restoration after total laryngectomy. *CA Cancer J Clin*. 1990;40:174-182.

9. McNeil B, Weichselbaum R, Pauker SG. Speech and survival. *N Engl J Med*. 1981;305:982-987.

10. Desanto L, Olsen K, et al. Quality of life after surgical treatment of cancer of the larynx. *Ann Otol Rhinol Laryngol*. 1995;104:763-769.

11. Kies M, Lewin J, Diaz E, et al. Definitive treatment of intermediate stage laryngeal squamous cell cancer (SCC/L) with chemotherapy (CT). *Proc Am Soc Clin Oncol (post-meeting edition)*. 2004;22 (14S):5533.

12. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the Head and Neck Contracts Program. *Cancer*. 1987;60:301-311.

13. Jacobs C, Makuch R, Efficacy of adjuvant chemotherapy for patients with resectable head and neck cancer: a subset analysis of the Head and Neck Contracts Program. *J Clin Oncol*. 1990;8:838-847.

14. Laramore G, Scott C, al-Sarraf M, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *Int J Rad Oncol Biol Phys*. 1992;23:705-713.

15. Paccagnella A, Orlando A, Marchiori, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancer: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst*. 1994;86:265-272.

16. Ervin T, Clark J, Weichselbaum R, et al. An analysis of induction and adjuvant chemotherapy in the multidisciplinary treatment of squamous-cell carcinoma of the head and neck. *J Clin Oncol*. 1987;5:10-20.

17. Domenge C, Marandas P, Vignoud J, et al. Post-surgical adjuvant chemotherapy in extra-capsular spread invaded node (N+R+) of epidermoid carcinoma of the

head and neck. A randomized multicentric trial. Second International Conference in Head and Neck, Boston, 1988. *Am Soc Head Neck Surg*. 1988;74.
18. Richard J, Kramar A, Molinari R, et al. Randomised EORTC head and neck cooperative group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharynx carcinoma. *Eur J Cancer*. 1991;27:821-827.
19. Depondt J, Gehanno P, Martin M, et al. Neoadjuvant chemotherapy with carboplatin/5-FU in head and neck cancer. *Oncology*. 1993;50(suppl 2):23-27.
20. Dalley D, Beller E, Aroney R, et al. The value of chemotherapy (CT) prior to definitive local therapy (DLT) in patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (HN). *Proc Am Soc Clin Oncol*. 1995;14:297.
21. Horiuchi M, Inuyama Y, Miyake H, and the Head and Neck UFT Study Group. Efficacy of surgical adjuvant with tegafur and uracil (UFT) in resectable head and neck cancer: a prospective randomized study. *Proc Am Soc Clin Oncol*. 1994;13:284.
22. Pignon J, Bourhis J, Domenge C, et al. Chemotherapy added to local-regional treatment for head and neck squamous cell carcinoma: three meta-analyses of updated individual data. *Lancet*. 2000;355:949-955.
23. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 2004;350:1945-1952.
24. Cooper J, Pajak T, Forastiere A, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous cell carcinoma of the head and neck. *N Engl J Med*. 2004;350:1937-1944.
25. Bachaud J, Cohen-Jonathan E, Alzieu C, et al. Combined post-operative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *Int J Rad Oncol Biol Phys*. 1996;36:999-1004.
26. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med*. 1991;324:1685-1690.
27. Wolf G, Hong W, Fisher S, et al. Larynx preservation with induction chemotherapy and radiation in advanced laryngeal cancer: final results of the VA laryngeal cancer study group cooperative trial. *Proc Am Soc Clin Oncol.* 1993;12:277. Abstract 892.
28. Lefebvre J, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. *J Natl Cancer Inst.* 996;88:890-899.
29. Richard J, Sancho-Garnier H, Pessey J, et al. Randomized trial of induction chemotherapy in larynx carcinoma. *Oral Oncology*. 1998;34:224-228.
30. Terrell J, Fisher S, Wolf G, et al. Long-term quality of life after treatment of laryngeal cancer. The Veterans Affairs Laryngeal Cancer Study Group. *Arch Otolaryngol Head Neck Surg*. 1998;124:964-971.
31. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst*. 1999;91:2081-2086.
32. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J Rad Biol Phys*. 2003;55:93-98.
33. Adelstein D, Saxton J, Lavertu P, et al. A phase III trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. *Head Neck*. 1997;19:567-575.
34. Adelstein D, Lavertu P, Saxton J, et al. Long-term results of a phase III randomized trial comparing concurrent chemoradiotherapy and radiation therapy (RT) alone in squamous cell head and neck cancer (SCHNC). *Proc Am Soc Clin Oncol*. 1999;18:394.
35. Wendt T, Grabenbauer G, Rodel C, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized study. *J Clin Oncol*. 1998;16:1318-1324.
36. Keane T, Cummings B, O'Sullivan B, et al. A randomized trial of radiation therapy compared to split course radiation therapy combined with mitomycin-C and 5-fluorouracil as initial treatment for advanced laryngeal and hypopharyngeal squamous carcinoma. *Int J Rad Oncol Biol Phys*. 1993;25:613-618.
37. Brizel D, Albers M, Fisher S, et al. Hyperfractionated irradiation with or without chemotherapy for locally advanced head and neck cancer. *N Engl J Med*. 1997;338:1798-1804.
38. 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;18:3320-3321.
39. Lefebvre J, Wolf G, Luboinski B, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): (2) Larynx preservation using neoadjuvant chemotherapy (CT) in laryngeal and hypopharyngeal carcinoma. *Proc Am Soc Clin Oncol*. 1998;17:382
40. Merlano M, Benasso M, Corvo R. 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.
41. A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. An interim report from the SECOG participants. South-East Co-operative Oncology Group. *Eur J Surg Oncol*. 1986;12:289-295.
42. Adelstein D, Sharan V, Earle A, et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. *Cancer*. 1990;65:1685-1691.
43. Merlano M, Rosso R, Sertoli M, et al. Randomized comparison of two chemotherapy, radiotherapy schemes for stage III and IV unresectable squamous cell carcinoma of the head and neck. *Laryngoscope*. 1990;100:531-535.
44. Taylor I, Murthy A, Vannetzel J, et al. Randomized comparison of neoadjuvant cisplatin and FU infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *JCO*. 1994;12:385-395.
45. Forastiere A, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med*. 2003;349:2091-2098.
46. Adelstein D, Li Y, Adams G, et al. An Intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 2003;21:92-98.
47. Munro A. An overview of randomised controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer.* 1995;71:83-91.
48. El-Sayed S, Nelson N. Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region: a meta-analysis of prospective randomized trials. *J Clin Oncol*. 1996;14:838-847.
49. Dassonville O, Formento J, Francoual M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. *J Clin Oncol.* 1993;11:1873-1878.
50. Cohen E, Rosen F, Stadler W, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2003;10:1980-1987.
51. Kane M, Cohen E, List M, et al. Phase II study of 250mg gefitinib in advanced squamous cell carcinoma of the head and neck (SCCHN). *Proc Am Soc Clin Oncol (post-meeting edition)*. 2004;22(14S):5586.
52. Soulieres D, Senzer N, Vokes E, et al. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol.* 2004;1:77-85.
53. Trigo J, Hitt R, Koralewski P, et al. Cetuximab monotherapy is active in patients (pts) with platinum refractory recurrent/ metastatic squamous cell carcinoma of the head and neck (SCCHN) : results of a phase II study. *Proc Am Soc Clin Oncol (post-meeting edition).* 2004;22(14S):5502.
54. Humblet Y, Vega-Villegas E, Mesia R, et al. Phase I study of cetuximab in combination with cisplatin or carboplatin and 5-FU (5-FU) in patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). *Proc Am Soc Clin Oncol (post-meeting edition).* 2004;22(14S):5513.
55. Robert F, Ezekiel M, Spencer S, 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;13:3234-3243.
56. Milas L, Mason K, Hunter N, et al. In vivo enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. *Clin Cancer Res.* 2000;5:701-708.
57. Bonner J, Harari P, Giralt J, et al. Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck : a phase III study of high dose radiation therapy with or without cetuximab. *Proc Am Soc Clin Oncol (post-meeting edition).* 2004;22(14S):5507.
58. Pfister D, Aliff T, Kraus D, et al. Concurrent cetuximab, cisplatin, and concomitant boost radiation therapy (RT) for locoregionally advanced, squamous cell head and neck cancer (SCCHN): preliminary evaluation of a new combined-modality paradigm. *Proc Am Soc Clin Oncol.* 2003;22:495. Abstract 1993.

(continued from page 352) is more common among people of Middle Eastern descent, though it can also occur among other ethnicities as well. Also, of the 2 genes that code for the 5-HT_3 receptors, 5HTA and 5HTB, with 5HTB it appears that individuals with a single nucleotide polymorphism for the type B receptor are at significantly more risk for emesis.

Thus, there may be genetic predispositions for the occurrence of emesis and/or the efficacy of antiemetic agents. Understanding these aspects better will help us achieve better control of emesis in patients undergoing chemotherapy.

It is important for us to maintain a focus in terms of the concept we are pursuing in our research. For antiemetics, we have to remember that we don't want a good result to be substituted for a potentially excellent result. Right now, we have good control. However, we want to be able to achieve better control. We should not stop trying to improve antiemetic therapy.

H&O Could patients be profiled for these genetic predispositions?

RG I do not think we would ever conduct gene array profiles for the primary purpose of assessing emetic risk. However, these profiles will be done increasingly in order to evaluate cancer susceptibility and in tumors to evaluate treatment options. If we were looking at a thousand or more genes, including an emesis-related gene would be useful.

H&O Has the public's perception of cancer-related emesis kept up with advances in antiemetic therapy?

RG There are so many concerns for patients about to undergo treatment for cancer. However, the public and healthcare professionals should understand that nausea and vomiting might not be as big of a problem as many people perceive. The media has done a poor job of informing people about the true state of antiemetics. Most lay people associate emesis with chemotherapy and do not know about the improvements that have been made over the past 20 years. Medicinal marijuana is given attention by people hoping to stem the nausea and vomiting experienced by cancer patients, but this strategy is actually a weak approach compared to the other agents that are now available. It would be unfortunate if someone were treated with an agent that is less effective than others that are already available.

Suggested Reading

Viale PH. Integrating aprepitant and palonosetron into clinical practice: a role for the new antiemetics. *Clin J Oncol Nurs.* 2005;9(1):77-84.

Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol.* 2005;23(12):2822-2830.

Aapro M. Granisetron: an update on its clinical use in the management of nausea and vomiting. *Oncologist.* 2004;9(6):673-686.

Hesketh PJ. New treatment options for chemotherapy-induced nausea and vomiting. *Support Care Cancer*. 2004;12(8):550-554.

Rittenberg CN. The next generation of chemotherapy-induced nausea and vomiting prevention and control: a new 5-HT3 antagonist arrives. *Clin J Oncol Nurs.* 2004;8(3):307-308, 310.