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# Expanding Role of the Medical Oncologist in the Management of Head and Neck Cancer

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**ABSTRACT** The multidisciplinary approach to treating squamous cell carcinoma of the head and neck is complex and evolving. This article aims to review some recent developments in squamous cell carcinoma of the head and neck, in particular the expanding role of chemotherapy in its management. Surgery and radiotherapy have remained the mainstay of therapy. Chemotherapy is increasingly being incorporated into the treatment of squamous cell carcinoma of the head and neck. Previously, radiotherapy following surgery was the standard approach to the treatment of locoregionally advanced resectable disease. Data from randomized trials have confirmed the benefits of concurrent chemoradiotherapy in the adjuvant setting. Chemoradiotherapy is also the recommended approach for unresectable disease. Induction chemotherapy has been useful in resectable disease where organ preservation is desirable, but this approach was inferior for the goal of larynx preservation, while leading to similar survival when compared with concomitant chemoradiotherapy. There is recent evidence that taxanes added to induction chemotherapy with cisplatin and fluorouracil result in improved survival outcomes. Novel targeted agents, such as epidermal growth factor receptor antagonists, are showing promise in the treatment of patients with both locoregionally advanced and recurrent/metastatic squamous cell carcinoma of the head and neck. (*CA Cancer J Clin* 2008;58:32–53.) © American Cancer Society, Inc., 2008.

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## INTRODUCTION

Head and neck cancer is the eighth most common cause of cancer death worldwide. Its incidence varies widely among different regions.<sup>1,2</sup> In North America and the European Union, head and neck cancer accounts for 3% to 4% of all cancer diagnoses.<sup>3,4</sup> Conversely, in Southeast Asia and Africa, head and neck cancer accounts for approximately 8% to 10% of all cancers.<sup>2</sup> Although the incidence of head and neck cancers has decreased slightly from 1975 to 2002 in the United States,<sup>5</sup> approximately 46,000 new cases are still expected in 2007 alone.<sup>4</sup>

Squamous cell carcinomas arise from organs lined by squamous epithelium. Squamous cell carcinoma of the head and neck (SCCHN), regardless of site within the head and neck, tends to share similar etiologies, pathogenesis, natural history, and response to therapy. In addition, there are lymphoid tissues, neuroendocrine cells, melanocytes, and minor salivary glands within the mucosal lining of these organs where neoplasms may arise. Such tumors are biologically distinct from SCCHN and have different natural histories. Similarly, tumors arising from the thyroid and major salivary glands behave differently than SCCHN. For the purposes of this review, we will limit our discussion to squamous cell carcinoma arising from aerodigestive organs within the head and neck.

Historically, the treatment of SCCHN has been in the realm of surgeons and radiation oncologists. Over the last 2 decades, there have been major developments in the field of surgery, radiation therapy, and chemotherapy. In radiation therapy, intensity-modulated radiation therapy and the development of various fractionation schemes have allowed improved delivery and tolerability of radiation. Advances in conservation surgical techniques with procedures such as hemilaryngectomy, laryngeal prosthesis, and laser surgery have allowed better preservation of organ function.

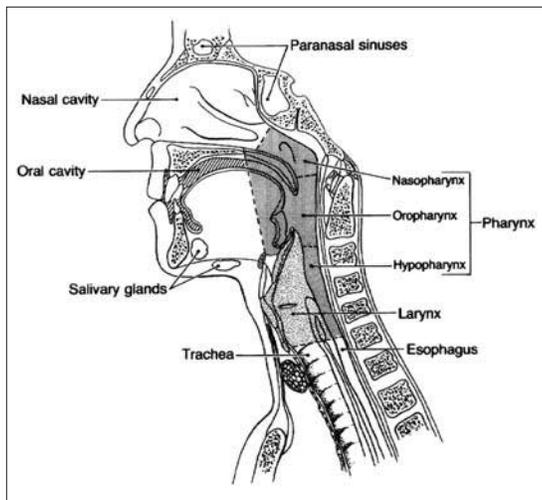


FIGURE 1 Head and Neck Anatomy. Reprinted from Vokes EE, Weichselbaum RR, Lippman SM, Hong WK<sup>6</sup> with permission from *The New England Journal of Medicine*.

As more chemotherapeutic agents are identified and the activity of chemotherapy is improved, the treatment of SCCHN has evolved to incorporate chemotherapy as a key component in the multimodality treatment approach of advanced SCCHN. This increases the complexity of SCCHN therapy. Compounding this is the management of associated comorbidities from local effect of the tumor resulting in aspiration, dysphagia, malnutrition, and chronic illnesses such as alcoholism, nicotine dependence, liver cirrhosis, and chronic obstructive pulmonary disease. This review aims to highlight the increasing role of chemotherapy in the management of SCCHN.

#### ANATOMY, CLINICAL FEATURES, AND STAGING

##### Anatomy

The head and neck are divided into several anatomically defined regions, namely the nasal cavity and paranasal sinuses, oral cavity, pharynx, and larynx (Figure 1). The pharynx comprises the nasopharynx, oropharynx, and hypopharynx, while the larynx is divided into the supraglottic, glottic, and subglottic regions.

##### Clinical Features

Presenting signs and symptoms vary with the location of the primary tumor.<sup>6</sup> Patients with

early-stage cancer frequently have vague symptoms with minimal physical findings. Nasal cavity and paranasal sinuses tumors present with unilateral epistaxis or nasal obstruction. Nasopharyngeal cancer frequently presents late with nodal neck metastasis. Local symptoms may be attributable to eustachian tube obstruction (serous otitis) or cranial nerve invasion. Oral cavity cancers present as nonhealing ulcers, pain, or poorly fitting dentures. Laryngeal tumors are often manifested by persistent hoarseness. Later symptoms include dysphagia, chronic cough, hemoptysis, stridor, and respiratory distress. Tumors of the oropharynx and supraglottic larynx usually present late with cervical adenopathy, pain, otalgia, dysphagia, or dysphonia.

##### Staging

The American Joint Committee on Cancer (AJCC) 2002 tumor-node-metastasis staging system<sup>7</sup> divides tumors arising from the head and neck into several specific regions, namely lip-oral cavity, pharynx (nasopharynx, oropharynx, and hypopharynx), larynx, and nasal cavity-paranasal sinuses. The definitions for regional lymph node (N) involvement and spread to distant sites (M) are uniform for all regions. The N definition is based on the size and laterality of the involved nodes. One exception is the N definition in nasopharyngeal carcinoma (see section on nasopharyngeal carcinoma). The lifetime incidence of distant metastasis<sup>8,9</sup> correlates with nodal stage: N1 10%, N2 15%, and N3 approximately 30% risk.<sup>8,9</sup>

The staging for the primary tumor (T) differs among tumor sites. For tumors in the lip-oral cavity and oropharynx, the T definition is based on size. In contrast, the T definition is based on subsite involvement and is specific to each subsite for the glottic larynx, supraglottic larynx, hypopharynx, and nasopharynx.

Staging evaluation is specific for each tumor site and involves physical examination, endoscopic examination, and radiologic imaging. Risk factors such as cigarette smoke and alcohol expose and precondition the mucosa of the aerodigestive tract to cancerous change-field cancerization and result in the occurrence of second metachronous and synchronous tumors.<sup>10</sup>

Therefore, imaging of the thorax is often included in the staging of SCCHN because of the potential of these tumors to metastasize to the lungs and to evaluate the presence of second primary tumors. Endoscopy, such as laryngopharyngoscopy, is often employed to enhance the evaluation of the primary tumor. Directed endoscopy of the lung and esophagus is performed if there are signs or symptoms relating to these organs. Positron emission tomography (PET) scans may be used to determine the benign or malignant nature of noncalcified lung nodules or to identify occult neck metastases.

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#### ETIOLOGY OF HEAD AND NECK CANCER

##### **Tobacco and Alcohol Are Major Risk Factors**

SCCHN is strongly associated with cigarette smoking<sup>11</sup> and alcohol consumption.<sup>12,13</sup> The risk of developing SCCHN is proportional to the number of cigarettes smoked and duration of smoking.<sup>14,15</sup> Smoking cessation reduces the risk of developing SCCHN over time.<sup>14</sup> Pipe and cigar smokers are at higher risk for developing oral cavity cancers compared with cigarette smokers.<sup>14</sup> Other forms of tobacco products, such as betel quid, are associated with SCCHN in certain geographic regions.<sup>16,17</sup> The risk of developing SCCHN increases with the frequency, duration, and concentration of alcohol consumed.<sup>18,19</sup> The combined risk of alcohol and smoking in causing SCCHN is multiplicative rather than additive.<sup>13,14,17,20–23</sup>

##### **The Role of Human Papillomavirus**

A proportion of patients with SCCHN do not have the traditional risk factors for developing such malignancies.<sup>24</sup> The nonsmoker, nondrinker SCCHN patients tend to be younger and have the primary tumor located within the lingual or palatine tonsils.<sup>25–27</sup> Human papillomavirus (HPV) has been identified in the pathogenesis of SCCHN in this group.<sup>24,28,29</sup> The proposed mechanism of disease is that HPV oncoproteins E6 and E7 inactivate the tumor suppressor genes *p53*<sup>30–33</sup> and *pRb*<sup>32,34</sup> in the host cell, respectively, thereby increasing cell-cycle regulation and inhibiting apoptosis.

HPV DNA has been found in approximately 25% of SCCHN.<sup>35</sup> HPV-associated tumors tend to arise in the oral cavity and pharynx,<sup>25,35,36</sup> but not in the larynx.<sup>37</sup> HPV-16 is found within 85% to 90% of HPV-positive SCCHN.<sup>35</sup> It is unclear if there is an interaction between HPV and alcohol or tobacco.<sup>29,38–40</sup> HPV-positive SCCHN has been positively associated with sexual behavior parameters, such as multiple sexual partners, sexually transmitted diseases, oral sex, oral-anal contact, and human immunodeficiency virus infection.<sup>29,41–45</sup> Patients with Fanconi anemia have a 500-fold risk of developing SCCHN.<sup>46</sup> Abnormal DNA repair and chromosomal instability characteristic of this disorder result in increased alteration of genes already implicated in the development of SCCHN and potentiate HPV-mediated tumorigenesis.<sup>47</sup>

The prognosis of HPV-positive SCCHN appears to be better than HPV-negative SCCHN.<sup>31,48–51</sup> There is evidence to suggest that HPV-positive tumors are more radiosensitive.<sup>52,53</sup> Other hypotheses to account for the improved outcome are the absence of field cancerization<sup>50</sup> and the absence of comorbid conditions such as cirrhosis or chronic obstructive pulmonary disease that impact on overall prognosis of individual patients.

There are epidemiologic and therapeutic implications with the identification of HPV in SCCHN. Since patients with HPV-positive tumors are more radiosensitive, this parameter may be used in the selection of patients for organ-preservation strategies. The increasing use of the HPV vaccine for cervical cancer may also play a role in primary prevention of HPV-positive SCCHN.<sup>54</sup>

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#### GENERAL PRINCIPLES OF TREATMENT

Once staging is completed, for treatment considerations, SCCHN can be divided into several general stages (Figure 2): early-stage disease (Stages I and II); nonmetastatic locoregionally advanced disease (LA-SCCHN) (Stages III and IVA/B [M0]); and metastatic (Stage IVC). Approximately 15% to 30% of patients present with early-stage disease, and 60% to 80% present with locoregionally advanced disease.<sup>4</sup> Distant metastasis at the time of presentation is less common (2% to 17%),<sup>55–58</sup> but a small percentage

of patients may have a second primary tumor within the aerodigestive tract or lungs.

**Treatment Modalities for SCCHN**

Surgery and radiotherapy are the curative treatment modalities for SCCHN. Surgery has several advantages over radiotherapy: (1) limited amount of tissue is exposed to treatment; (2) treatment time is shorter; (3) acute and chronic radiation toxicities are avoided; and (4) tumor and nodal disease are assessed accurately. The advantages of radiotherapy include the following: (1) surgical complications are avoided; (2) appearance and, potentially, function of treated organ can be preserved; (3) irradiation of lymph nodes can be included with little added morbidity compared with the added morbidity of extensive neck dissection; and (4) medically unfit patients may tolerate radiotherapy better than surgery.

Chemotherapy itself is not a curative treatment modality. To this end, chemotherapy is used by itself as palliative therapy for patients with metastatic disease. When chemotherapy is administered at somewhat decreased doses simultaneously with radiotherapy, radiosensitization of the tumor occurs, resulting in increased tumor cell death. Chemotherapy at full doses can also be delivered together with radiotherapy to harness the radiosensitization and systemic cytotoxic properties of chemotherapy. In SCCHN, chemotherapy may be administered before definitive treatment (induction or neoadjuvant), simultaneously with radiotherapy (concomitant or concurrent), or after surgery (adjuvant) (Figure 3). The first 2 approaches are supported by results of randomized clinical trials (RCTs).

The choice of treatment modality for an individual patient needs to be carefully considered. It is good clinical practice that this decision-making process be deliberated at a multidisciplinary tumor board. Particular attention must be placed on choosing the most effective treatment approach while aiming to preserve organs and organ function and managing associated comorbid conditions. Functional outcomes such as speech and swallowing factor heavily in choosing the appropriate treatment modality. Several performance measures for good functional preservation include the ability to eat in public, under-

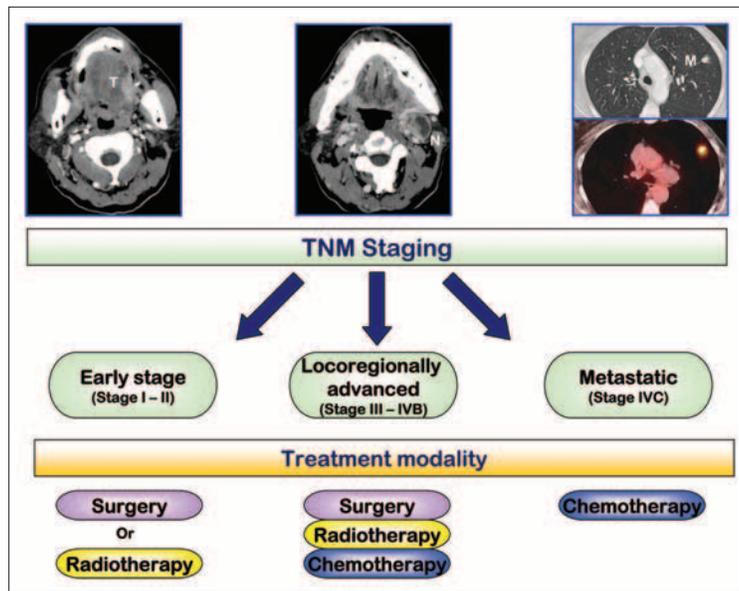


FIGURE 2 Staging of Squamous Cell Carcinoma of the Head and Neck and General Treatment Schema.

Induction chemotherapy	Chemotherapy → Radiotherapy or Surgery
Definitive concurrent chemoradiotherapy	Chemotherapy Radiotherapy
Adjuvant chemoradiotherapy	Surgery → Chemotherapy Radiotherapy
Induction chemotherapy Definitive concurrent chemoradiotherapy	Chemotherapy → Chemotherapy Radiotherapy

FIGURE 3 Treatment Schema for Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck.

standability of speech, and normalcy of diet.<sup>59,60</sup> Appropriate and expert use of modern surgical and radiation techniques can meet these goals, but the therapy must be carefully individualized.

**Treatment for Early-stage SCCHN**

For early-stage disease, curative therapy can be achieved with single-modality surgery or radiotherapy (Figure 2). The choice of modality depends on the specific site, stage, resectability, and functional outcome after therapy. Chemotherapy is not used in early-stage SCCHN. The 5-year overall survival rate for Stage I cancer is 80% to 90%, and Stage II is 65% to 80%.<sup>61-64</sup>

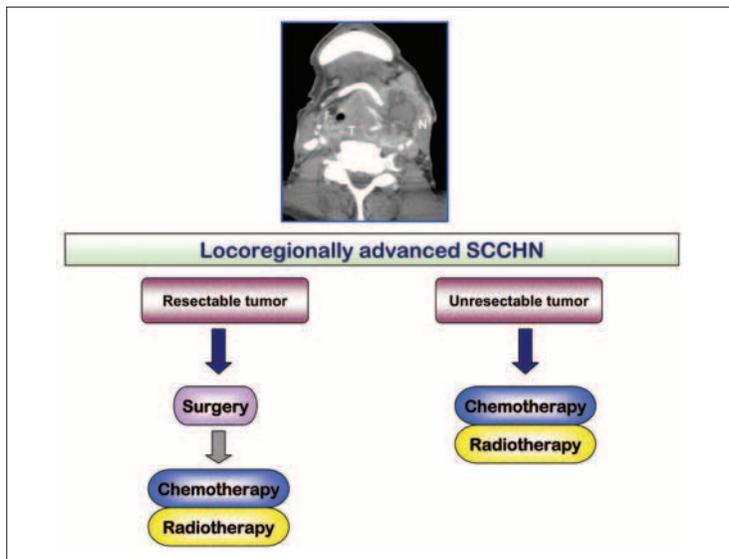


FIGURE 4 Various Treatment Schema Utilized in Squamous Cell Carcinoma of the Head and Neck Therapy.

#### Treatment for LA-SCCHN

LA-SCCHN implies advanced T stage where tumor invasion into other structures has occurred or lymph node metastases without evidence of distant metastases. LA-SCCHN poses one of the most complex management challenges. This stage of disease is still potentially curable, but requires combined-modality therapy.

Implicit in choosing the primary treatment modality (radiotherapy and surgery) for LA-SCCHN is to determine resectability (Figure 4). There is no formal definition of “resectable,” and it varies significantly between disease site, disease extent, surgeons, and institutions. Ideally, the determination of resectability should be made for each individual patient during a multidisciplinary tumor board, taking into account the potential functional compromise and survival benefit conferred by each treatment modality. Of note, for some patients with resectable disease, an “organ-preserving” approach may be desired. These patients will usually be treated with concomitant chemoradiotherapy, with surgery reserved for patients with residual disease or recurrence after completion of chemoradiotherapy.

Unresectable tumors should be treated with definitive concurrent chemoradiotherapy.<sup>65</sup> This approach results in a 5-year overall survival of 30% to 50% in recent studies.<sup>66–68</sup> Patients with resectable tumors should undergo surgery. The locoregional recurrence rate is approximately

40% after successful surgical resection.<sup>69,70</sup> Adjuvant radiotherapy for this stage of SCCHN has been effective in reducing the locoregional recurrence rates to approximately 30%.<sup>69,70</sup> When adjuvant radiotherapy is combined concurrently with chemotherapy, the locoregional recurrence rates drop to approximately 20%.<sup>71,72</sup>

#### Pattern of Failure

An important aspect of SCCHN management is to understand the pattern of treatment failure. After definitive therapy, SCCHN patients may recur at the primary tumor site or regional lymph nodes (termed locoregional relapse) or at distant sites such as the lungs or liver (termed distant relapse). In general, LA-SCCHN patients treated with single-modality therapy (surgery or radiotherapy) tend to relapse locoregionally (50% to 60% at 2-year) rather than at distant sites (15% to 20% at 2-year).<sup>66–68,73,74</sup> The addition of chemotherapy impacts both locoregional and distant control rates. Paccagnella et al showed that induction chemotherapy reduced the 3-year distant relapse rate from 38% to 14%.<sup>75</sup> This observation held true in a retrospective review of University of Chicago trials.<sup>76</sup> Concurrent chemoradiotherapy, on the other hand, has been shown to improve locoregional relapse rates, but its impact on distant failure is inconsistent.<sup>67,68,77,78</sup>

#### Treatment for Recurrent and/or Metastatic SCCHN

Local recurrences without evidence of distant metastases may be salvaged surgically if the primary therapy was radiotherapy or with radiotherapy if the primary therapy was surgery. However, for unresectable recurrent and/or metastatic disease, the therapy is aimed at palliation since the cure rates at such an advanced stage are extremely low. Palliation is achieved with the use of chemotherapy and supportive care. The response rates to chemotherapy in this setting range from 10% to 40% depending on the agent(s) used.

#### ADVANCES IN THERAPY

##### Definitive Chemoradiotherapy for LA-SCCHN

Conventional, once-daily, fractionation radiotherapy in 2 Gy fractions up to a total of 66 to 70 Gy over 7 weeks has been used as definitive

therapy in unresectable SCCHN and sometimes in resectable tumors instead of surgery.<sup>79</sup> This results in high locoregional relapse rates (50% to 60% at 2-year) and overall survival of approximately 40% at 3-year.<sup>66-68,73,74</sup> Efforts to improve the locoregional control of SCCHN by altering the fractionation of radiotherapy have only been marginally successful. Hyperfractionation<sup>79,80</sup> (multiple smaller fractions per day over the same time period) and accelerated fractionation<sup>79,81</sup> (delivery of the total dose over a shorter time period) have been compared with conventional fractionation; altered fractionation regimens have led to a 10% to 20% improvement in local control rates, but effects on survival are less clear.<sup>79</sup> Altered fractionation regimens consistently induce more severe acute mucositis than standard 7-week radiotherapy, but late toxicities are not appreciably increased.

In an attempt to improve local control and survival, chemotherapy has been investigated as an adjunct to locoregional treatment. Various schedules of chemotherapy and radiotherapy have been investigated: induction chemotherapy (chemotherapy given before radiotherapy), adjuvant or sequential chemotherapy (chemotherapy given after radiotherapy), and concurrent or concomitant chemotherapy (chemotherapy given at the same time as radiotherapy) (Figure 3). Theoretical benefits of delivering concurrent chemoradiotherapy are twofold: (1) local antitumor activity of radiotherapy is enhanced by the simultaneous use of chemotherapy as radiosensitizers and (2) the systemic activity of chemotherapy may eradicate possible micrometastases outside the irradiated field and improve survival.

Meta-analyses have shown that concurrent chemoradiotherapy is superior to other sequences of chemotherapy and radiotherapy.<sup>82,83</sup> A systematic review by Browman et al pooled analyses of 18 RCTs and detected a reduction in mortality for concomitant chemoradiotherapy compared with radiotherapy alone (relative risk = 0.83).<sup>83</sup> The MACH-NC group reviewed 63 randomized trials conducted between 1965 and 1993 comparing combinations of locoregional treatment and chemotherapy versus locoregional treatment alone.<sup>82,84</sup> The magnitude of the survival benefit associated with the addition of concomitant chemoradiotherapy was 8% at 5 years.

This survival benefit was mainly due to an improvement in the locoregional control and only had a marginal effect on distant metastases.

The use of concomitant chemoradiotherapy for locoregionally advanced unresectable SCCHN is further supported by several recent RCTs (Table 1). Adelstein et al, Olmi et al, and Calais et al reported randomized trials comparing conventional doses of radiotherapy with or without concomitant chemotherapy.<sup>74,85,86</sup> Regardless of the specific chemotherapy regimens used, the trials demonstrated a significant and consistent benefit in local control rates, translating into improvement in disease-free survival by a magnitude of 15% to 20%. When hyperfractionated radiotherapy was tested with or without concomitant chemotherapy, investigators were able to show a further improvement in disease-free survival as a result of improved local control from hyperfractionated radiotherapy alone, but this was further improved with concomitant chemotherapy.<sup>68,87,88</sup> To further support the role of concomitant chemotherapy, the trials by Brizel et al, Budach et al, and Dobrowsky et al are noteworthy.<sup>66,67,89</sup> The radiotherapy dose delivered in the chemoradiotherapy arms was intentionally lower than in the radiotherapy-alone arms. Despite this apparent disadvantage, the chemoradiotherapy arms were still superior. These trials reinforce the concept that concurrent chemotherapy provides a synergistic enhancement of efficacy.

#### Toxicities Associated with Chemoradiotherapy

Radiotherapy to the head and neck is commonly associated with acute and late toxicities. Commonly observed acute toxicities are mucositis, stomatitis, and dermatitis, while depending on the site of irradiation, late toxic effects may include chronic xerostomia, dysgeusia, dysphagia, skin fibrosis, trismus, feeding-tube dependence, aspiration, and thyroid dysfunction. In general, the acute toxicities of radiotherapy are increased with the addition of concurrent chemotherapy. Interobserver variability, differing toxicity assessment scales, and less-rigorous toxicity data collection during clinical trials may account for different rates of nonhematologic acute toxicities.<sup>90</sup> For example, in the clinical trial by Calais et al, 35% of

TABLE 1 Randomized Trials of Concomitant Chemoradiotherapy for Locoregionally Advanced Head and Neck Cancer

Study	RT	CRT	Chemo-therapy	Platinum Dose	Local Control	Disease-free Survival	Overall Survival
Adelstein DJ, Li Y, Adams GL, et al, <sup>85</sup> 2003*	70 Gy, QD, 7 wks	70 Gy, QD, 7 wks	Cis	100 mg/m <sup>2</sup> wks 1, 3, and 6	—	3-y, 33% versus 51%†	3-y, 23% versus 37%†
Olmi P, Crispino S, Fallai C, et al, <sup>86</sup> 2003*	70 Gy, QD, 7 wks	70 Gy, QD, 7 wks	Carbo, 5-FU	75 mg/m <sup>2</sup> x 4d wks 1, 4, and 8	—	2-y, 23% versus 42%†	2-y, 40% versus 51%
Calais G, Alfonsi M, Bardet E, et al, <sup>74</sup> 1999	70 Gy, QD, 7 wks	70 Gy, QD, 7 wks	Carbo, 5-FU	70 mg/m <sup>2</sup> x 4d wks 1, 3, and 6	3-y, 42% versus 66%†	3-y, 20% versus 42%†	3-y, 31% versus 51%†
Jeremic B, Shibamoto Y, Milicic B, et al, <sup>68</sup> 2000	77 Gy, BID, 7 wks	77 Gy, BID, 7 wks	Cis	6 mg/m <sup>2</sup> /d	5-y, 50% versus 36%†	5-y, 25% versus 46%†	5-y, 25% versus 46%†
Huguenin P, Beer KT, Allal A, et al, <sup>87</sup> 2004	74 Gy, BID, 7 wks	74 Gy, BID, 7 wks	Cis	20 mg/m <sup>2</sup> /d x 5d wks 1 and 5	5-y, 27% versus 59%†	5-y, 24% versus 27%	5-y, 32% versus 46%
Bensadoun RJ, Dassonville O, Ramaoli A, et al, <sup>88</sup> 2006	80 Gy, BID, 7 wks	80 Gy, BID, 7 wks	Cis, 5-FU	100 mg/m <sup>2</sup> wks 1, 3, and 6	—	2-y, 25% versus 48%†	2-y, 20% versus 38%†
Brizel DM, Albers ME, Fisher SR, et al, <sup>66</sup> 1998	75 Gy, BID, 6 wks	70 Gy, BID, 7 wks	Cis, 5-FU	12 mg/m <sup>2</sup> /d x 5d wks 1 and 5	3-y, 44% versus 70%†	3-y, 41% versus 61%†	3-y, 34% versus 55%†
Budach V, Stuschke M, Budach W, et al, <sup>67</sup> 2005	78 Gy, BID, 6 wks	70 Gy, BID, 6 wks	Mito, 5-FU	—	5-y, 37% versus 50%†	5-y, 27% versus 29%†	5-y, 24% versus 29%†
Dobrowsky W, Naude J, <sup>89</sup> 2000*	70 Gy, QD, 7 wks	55 Gy, BID, 17 d	Mito	—	2-y, 31% versus 48%†	—	2-y, 24% versus 41%†

\*Three-arm study.

†Statistically significant difference.

Abbreviations: RT, radiation therapy; CRT, concurrent chemoradiotherapy; QD, daily; BID, twice daily; Cis, cisplatin; Carbo, carboplatin; 5-FU, 5-Fluorouracil; Mito, mitomycin-C; —, not reported.

patients in the radiotherapy-alone arm experienced Grade 3/4 mucositis compared with 65% of patients in the chemoradiotherapy arm.<sup>74</sup> On the other hand, Bensadoun et al reported that 69% of patients in the radiotherapy-alone arm experienced Grade 3/4 mucositis compared with 82% of patients in the chemoradiotherapy arm.<sup>88</sup> Patients receiving chemoradiotherapy tend to experience more weight loss and more frequently require a feeding tube during therapy. Such rates could be double that of radiotherapy alone.<sup>74</sup> The duration of acute toxicities also tends to be longer in patients receiving chemoradiotherapy.<sup>66</sup> Furthermore, chemotherapy-specific toxicities such as nausea, vomiting, neuropathy, nephropathy, and ototoxicity occur with the use of systemic doses of chemotherapy.

Hematologic toxicities are seldom observed with radiotherapy alone. However, the addition of chemotherapy can cause significant anemia, leucopenia, and neutropenia in a proportion of patients. The rates of hematologic toxicities generally depend on the chemotherapy regimens

used. In one study, single-agent cisplatin at 100 mg/m<sup>2</sup> given every 3 weeks with radiotherapy was associated with Grade 3/4 anemia and leucopenia in 18% and 42% of patients, respectively, while the radiotherapy-alone arm had only a 1% leucopenia rate.<sup>85</sup> Other regimens have rates of severe leucopenia varying between 9% and 40% with chemoradiotherapy.<sup>66,88</sup>

Acute hematologic and nonhematologic toxicity rates are consistently higher in the chemoradiotherapy arm across the clinical trials. Hospitalizations for toxicity related to concurrent chemoradiotherapy are increased, and dose reductions in chemotherapy are commonly needed.<sup>68</sup> Toxic death rates are numerically higher with chemoradiotherapy.<sup>66,68,74,85,88</sup> Forastiere et al reported a toxic death rate that is almost double in patients receiving concurrent chemoradiotherapy (4%) compared with radiotherapy alone (2%), but this difference was not statistically significant.<sup>65</sup> Similarly, the toxic death rate reported by Calais et al was 1% in the concurrent chemoradiotherapy arm and

none in the radiotherapy-alone arm.<sup>74</sup> In a review of 324 patients with LA-SCCHN who were enrolled in 5 consecutive chemoradiotherapy trials at the University of Chicago, the toxic death rate was 9.3%.<sup>91</sup> The most common causes of early- and late-treatment-related deaths were sepsis and surgical complications, respectively.

Patient selection for chemoradiotherapy and adequate supportive care during therapy are crucial. Comorbidities play an important role in determination of therapy. Comorbidities in younger patients may not impact on overall survival, but complication rates are increased with more advanced intercurrent conditions.<sup>92</sup> In elderly patients, the presence of comorbidities has a definite impact on survival.<sup>93</sup> In line with this observation, the benefit of concomitant chemoradiotherapy decreases with increasing age.<sup>94</sup> The increasing risk of death with increasing age may result from a combination of death from therapy-related complications or existing intercurrent illnesses. The medical oncologist must weigh the risk of chemoradiotherapy with its potential benefit while taking into account the patient's comorbidities, performance status, and function of involved organ.

Since approximately 50% of patients with LA-SCCHN receiving concurrent chemoradiotherapy are expected to be alive at 3 years or longer, particular attention must be paid to possible long-term chronic toxicities of chemoradiotherapy. Most clinical trials have reported equivalent rates of long-term toxicities between radiotherapy alone and concurrent chemoradiotherapy. Rates of osteoradionecrosis are not increased with concurrent chemoradiotherapy.<sup>67,74,88</sup> One important long-term quality-of-life outcome after chemoradiotherapy to the head and neck is swallowing function. The reader is referred to a detailed review on this topic.<sup>95</sup>

#### Biologic Agents in Frontline Therapy

An important step forward in the field of concomitant chemoradiotherapy was made with the advent of molecularly targeted therapies. It has been observed that the epidermal growth factor receptor (EGFR) is overexpressed in almost all SCCHN tumors, and overexpression of EGFR is associated with higher disease stage,

lymph node metastasis, and poorer survival.<sup>96,97</sup> EGFR expression increases progressively with increasing degrees of dysplasia and becomes markedly elevated in carcinomas, suggesting that EGFR upregulation is an early event in SCCHN oncogenesis.<sup>98</sup> Since EGFR plays a significant role in SCCHN, a randomized trial comparing radiotherapy with or without cetuximab (anti-EGFR monoclonal antibody) was performed in patients with LA-SCCHN.<sup>73,99</sup> The 2-year locoregional control rates increased from 48% to 56% with concurrent cetuximab-radiotherapy (Table 2). Major toxicities were dermatitis, mucositis, dysphagia, and acneiform rash (in the cetuximab arm). The toxicity rates in both arms were similar, except for rash in the cetuximab arm. This trial provides an important proof of principle that modulating the biology of SCCHN in combination with a physically targeted agent can impact on therapeutic outcome. This increases the armamentarium of drugs that are active with radiotherapy. The favorable toxicity profile of cetuximab allows this drug to be combined with existing chemoradiotherapy regimens in future trials.

It is important to note the trial described above did not compare cetuximab-radiotherapy with concurrent chemoradiotherapy, which is the standard of care today for LA-SCCHN. Therefore, concurrent chemoradiotherapy must not be equated with cetuximab-radiotherapy. Secondly, since the toxicities associated with standard chemoradiotherapy may be poorly tolerated in elderly or frail patients, cetuximab-radiotherapy has often been considered in this setting. However, the median age in the trial was 56 years (34 to 81 years), and the trial did not specifically evaluate elderly patients or patients with poor performance status.

#### Current Questions and Future Challenges

There remain many unanswered questions. First, the importance of radiotherapy dose fractionation during concomitant chemoradiotherapy is unknown. Meta-analysis evidence points toward improved locoregional control and survival with altered fractionation radiotherapy.<sup>111</sup> This needs to be addressed in chemoradiotherapy trials comparing conventional radiotherapy with

TABLE 2 Selected Novel Targeted Therapeutics Trials in Squamous Cell Carcinoma of the Head and Neck

	Drug	Phase	Primary Endpoints and Results
Recurrent and/or metastatic SCCHN			
Cohen EE, Rosen F, Stadler WM, et al, <sup>100</sup> 2003	Gefitinib 500 mg	II	RR 11%, med surv 8 mo
Wheeler RH, Jones D, Sharma P, et al, <sup>101</sup> 2005	Gefitinib 500 mg	II	1st line RR 15%, 2nd line RR 0%
Kirby AM, A'Hern RP, D'Ambrosio C, et al, <sup>102</sup> 2006	Gefitinib 500 mg	II	RR 8%, med surv 4 mo
Cohen EE, Kane MA, List MA, et al, <sup>103</sup> 2005	Gefitinib 250 mg	II	RR 1%, med surv 6 mo
Soulieres D, Senzer NN, Vokes EE, et al, <sup>104</sup> 2004	Erlotinib 150 mg	II	RR 4%, med surv 6 mo
Williamson SK, Moon J, Huang CH, et al, <sup>105</sup> 2006	Sorafenib 400 mg BID	II	RR 3%, med surv 7 mo
Belón J, Irigoyen A, Rodríguez I, et al, <sup>106</sup> 2005	Gefitinib 250 mg, cisplatin and docetaxel	II	RR 62%, med surv NR
Kim ES, Kies MS, Glisson BS, et al, <sup>107</sup> 2006	Erlotinib 150 mg, cisplatin and docetaxel	II	RR 88%, med surv NR
Vokes EE, Cohen EE, Mauer AM, et al, <sup>108</sup> 2005	Erlotinib and bevacizumab	I/II	RR 15%, med surv 7 mo
Burtneess B, Goldwasser MA, Flood W, et al, <sup>109</sup> 2005	A: Cetuximab + cisplatin B: Cetuximab	III	A: RR 26%*, med surv 9 mo B: RR 10%, med surv 8 mo
Chan AT, Hsu MM, Goh BC, et al, <sup>110</sup> 2005	Cetuximab and carboplatin in NPC	II	RR 12%, med surv 8 mo
Locoregionally advanced SCCHN			
Bonner JA, Harari PM, Giralt J, et al, <sup>73</sup> 2006	A: RT + cetuximab B: RT	III	Med dur local control A: 24 mo* B: 15 mo Med surv A: 49 mo* B: 29 mo

\*Statistically significant difference.

Abbreviations: SCCHN, squamous cell carcinoma of the head and neck; RR, response rate; med surv, median survival; BID, twice daily; NR, not reported; med dur local control, median duration of local control; NPC, nasopharyngeal carcinoma; RT, radiation therapy.

altered fractionation regimens (RTOG 0129). Second, there has been much variability in the delivery and choice of chemotherapy. Most investigators have used platinum-based regimens, frequently with 5-Fluorouracil (5-FU). However, numerous other chemoradiotherapy regimens have been studied. For example, the TFHX regimen pioneered at the University of Chicago utilizing paclitaxel, 5-FU, and hydroxyurea with concurrent radiotherapy has demonstrated high local control and survival rates.<sup>112,113</sup> Many different schedules of cisplatin administration have been used, ranging from daily cisplatin at 6 mg/m<sup>2</sup>/day continuously<sup>68</sup> to boluses of cisplatin at 100 mg/m<sup>2</sup> every 3 weeks.<sup>85</sup> To add to this complexity, investigators have combined other chemotherapies to cisplatin, such as 5-FU or mitomycin. With the multitude of possible permutations, we may never

come to a definitive dose or schedule for the chemotherapy. It is sufficient to state that concurrent chemoradiotherapy with a platinum agent is the current standard of care when a chemoradiation regimen is selected for therapy of LA-SCCHN; however, this remains a moving target as more effective chemotherapies and biologics are investigated.

As the use of concurrent chemoradiotherapy increases in SCCHN, patient selection for primary surgery or definitive concurrent chemoradiotherapy becomes more complex. There has been no prospective randomized trial comparing outcomes of primary surgery versus definitive concurrent chemoradiotherapy to guide us. Therefore, a multidisciplinary approach coupled with close communication among the medical oncologist, radiation oncologist, radiologist,

**TABLE 3** Randomized Trials of Adjuvant Concomitant Chemoradiotherapy for Locoregionally Advanced Nonmetastatic Head and Neck Cancer

	RTOG 9501 <sup>*72</sup>	EORTC 22931 <sup>†71</sup>	German ARO 96–3 <sup>†124</sup>
Number of patients	459	334	440
Chemotherapy	Cisplatin 100mg/m <sup>2</sup> , d 1, 22, and 43	Cisplatin 100mg/m <sup>2</sup> , d 1, 22, and 43	Cisplatin 20mg/m <sup>2</sup> , 5-FU 600mg/m <sup>2</sup> , d 1 to 5 and 29 to 33
Radiotherapy	60 to 66 Gy/6 wks	66 Gy/6.5 wks	Negative LN—50 Gy, positive LN—56 Gy, ECS—64 Gy/6.6 wks
Endpoints (CRT versus RT)			
Locoregional failure rate	19% versus 30%	18% versus 31%	17% versus 38%
Distant failure rate	21% versus 25%	20% versus 23%	30% versus 32%
Disease-free survival	47% versus 36% <sup>‡</sup>	47% versus 36% <sup>‡</sup>	62% versus 50% <sup>‡</sup>
Overall survival	56% versus 47% <sup>‡</sup>	53% versus 40%	58% versus 49%

\*Three-year endpoint.

†Five-year endpoint.

‡Statistically significant difference.

Abbreviations: CRT, concurrent chemoradiotherapy; RT, radiation therapy; 5-FU, 5-Fluorouracil; ECS, extracapsular spread; LN, lymph node.

and surgeon is crucial to develop the best treatment plan for a particular patient.

#### Postoperative Chemoradiotherapy for LA-SCCHN

Although surgery alone may be adequate treatment for early-stage SCCHN, additional therapy is required to prevent disease recurrence, even after an apparently complete resection for LA-SCCHN. A number of pathologic poor-risk factors have been associated with higher recurrence rates after surgery, including positive margins of resection,<sup>114–116</sup> extracapsular extension of disease from a lymph node,<sup>115–120</sup> oral cavity primary,<sup>118</sup> involvement of lymph nodes at levels 4 or 5 from carcinomas arising in the oral cavity or oropharynx,<sup>121</sup> perineural extension,<sup>118,121</sup> and vascular tumor emboli.<sup>121</sup> Data from 2 large randomized trials have substantiated that microscopically involved resection margins and/or extracapsular spread of tumor from lymph nodes are the most significant adverse prognostic factors.<sup>121</sup>

Retrospective studies have shown that adjuvant radiotherapy significantly reduces the recurrence rate of LA-SCCHN, especially for poor-risk patients.<sup>122,123</sup> Despite adjuvant radiotherapy achieving good local control rates, distant metastasis occurred in almost one-third of patients with poor-risk factors.<sup>117</sup> Therefore, investigators have combined radiotherapy with radiosensitizing doses of chemotherapy. This strategy

utilizing cisplatin weekly with radiotherapy resulted in improvement in overall and disease-free survivals over radiotherapy alone (5-year overall survival 36% versus 13%).<sup>119</sup> However, distant disease control rates were similar. This implies that although good local control is achievable with radiosensitizing chemoradiotherapy, distant micrometastases are not obliterated with low doses of chemotherapy.

To further improve local failure, distant failure, and overall survival rates, full-dose chemotherapy has been utilized with radiotherapy. This strategy harnesses the radiosensitizing and systemic cytotoxic properties of chemotherapy. Furthermore, this strategy has been proven superior to radiotherapy alone for definitive therapy of LA-SCCHN, as described above. Three such trials have been reported to date (Table 3): the European Organization for Research and Treatment of Cancer (EORTC) 22931,<sup>71</sup> the Radiation Therapy Oncology Group (RTOG) 9501,<sup>72</sup> and the German ARO 96–3 trial.<sup>124</sup>

Both the EORTC<sup>71</sup> and RTOG<sup>72</sup> trials had similar designs and administered adjuvant cisplatin at high doses (100 mg/m<sup>2</sup>) on days 1, 22, and 43 of radiotherapy to patients with completely resected SCCHN. The EORTC trial reported a beneficial effect on overall survival and local control with adjuvant chemoradiotherapy. In the RTOG trial, despite having an improvement in disease-free survival in the adjuvant chemoradiotherapy arm, there was only a

trend toward improved local control and overall survival rates. Combined analysis of the 2 trials showed an advantage in locoregional control and survival for patients receiving adjuvant chemoradiotherapy in the setting of poor-risk features, ie, extracapsular invasion and/or positive resection margins.<sup>121</sup> The German ARO 96-3 trial<sup>124</sup> differed from the above trials in that patients were given different doses of radiotherapy based on their risk factors and used a doublet chemotherapy regimen of cisplatin and 5-FU. The locoregional control rate and disease-free survival in the adjuvant chemoradiotherapy arm were significantly better than radiation alone. Taken together, these trials provide new evidence that adjuvant chemoradiotherapy with a cisplatin-based regimen improves locoregional control rates and disease-free survival, and improvement in overall survival appears very likely.

Adjuvant concurrent chemoradiotherapy is associated with higher incidences of severe acute toxicities. For example, in the EORTC and RTOG trials, the rates of severe mucositis in the concurrent chemoradiotherapy arms were approximately double that in the radiotherapy-alone arms. Late toxicities were similar between both arms.<sup>71,72</sup> Chemotherapy completion rates were only 49%, 61%, and 73% in the EORTC, RTOG, and ARO 96-3 studies, respectively. Careful patient selection for chemoradiotherapy and intensive supportive care during therapy is crucial to ensure successful completion of the treatment regimen. Certain subgroups, such as elderly patients, patients with advanced T stage, and patients with larynx/hypopharynx primaries, tend to experience more severe late toxicities, feeding-tube dependence, and laryngopharyngeal dysfunction after adjuvant chemoradiotherapy.<sup>94,125</sup> Moreover, the benefit of chemoradiotherapy is less clear in the elderly.<sup>94</sup> Alternative strategies utilizing biological agents<sup>126</sup> or cytotoxic agents with more tolerable toxicity profiles<sup>127</sup> should be investigated for adjuvant therapy in the elderly or the medically unfit.

In order to improve overall survival, the gain in locoregional control from the radiosensitizing effect of the chemotherapy needs to be integrated with therapy that decreases the risk of distant metastases. Adequate control of distant failure still has not been achieved, with

approximately 20% to 30% of patients failing as a result of metastatic disease.<sup>71,72,124</sup> One possible hypothesis is the chemotherapy used in these trials is ineffective in eradicating micrometastasis. Therefore, the incorporation of additional effective drugs should be investigated in the adjuvant setting.<sup>128</sup> One such trial is the RTOG 0234 trial, which is a randomized Phase II trial combining postoperative radiation with cetuximab and either docetaxel or cisplatin.

#### Revisiting Induction Chemotherapy

Chemotherapy results in remarkably high response rates in treatment-naïve LA-SCCHN patients. The response rates to induction chemotherapy approach 50% to 70%, including a 10% to 15% complete response rate. Despite achieving complete responses, the response to chemotherapy is transient, and definitive therapy with surgery and/or radiotherapy is required. However, the sensitivity of SCCHN to induction chemotherapy can be capitalized on to improve locoregional and distant control.

Organ preservation with induction chemotherapy followed by radiotherapy was first reported by Jacobs et al to be a feasible approach to eliminate the need for surgery without compromising survival.<sup>129</sup> This led to the Veterans Affairs Cooperative Study demonstrating equivalent survival rates between patients who received induction chemotherapy followed by radiotherapy and those who had laryngectomy.<sup>130</sup> Lefebvre et al reported similar results several years later.<sup>131</sup> With the use of induction chemotherapy followed by radiotherapy, patients were able to retain a functional larynx and only require a laryngectomy as salvage therapy (Table 4).

Developing in parallel with the induction chemotherapy approach was concomitant chemoradiotherapy, which in itself is able to achieve high locoregional control rates. The 2 approaches were compared in the InterGroup 91-11 trial.<sup>65,132</sup> The trial had 3 arms: (1) induction chemotherapy followed by radiation therapy (RT), (2) concurrent chemoradiotherapy, and (3) daily single-fraction RT (Table 4). The concurrent chemoradiotherapy arm showed the best laryngectomy-free survival and local control rate. Acute toxicities were higher in both chemotherapy arms, but late toxicities and swallowing

**TABLE 4** Selected Induction Chemoradiotherapy Trials for Locoregionally Advanced Nonmetastatic Head and Neck Cancer with Organ Preservation and Survival Endpoints

Study	Regimen/Treatment Arm	Primary Endpoint	Comments
Endpoint: laryngeal preservation VA Study Group, <sup>130</sup> 1991	A: RT B: Cis, 5-FU x 3 → RT +/- Sx	Larynx preservation 2 y 64%	2-y survival A: 68% B: 68% P = NS
Lefebvre JL, Chevalier D, Luboinski B, et al, <sup>131</sup> 1996	A: RT B: Cis, 5-FU x 3 → RT +/- Sx	Larynx preservation 5 y 35%	3-y survival A: 43% B: 57% P = NS
Forastiere AA, Maor M, Weber RS, et al, <sup>132</sup> Intergroup 91-11, 2003	A: RT B: Cis, 5-FU x 4 → RT +/- Sx C: Cis + RT	Larynx preservation 2 y A: 70% B: 75%* C: 88%*	5-y survival A: 56% B: 55% C: 54% P = NS
Endpoint: survival Paccagnella A, Orlando A, Marchiori C, et al, <sup>75</sup> GSTTC, 1994, 2004	A: RT +/- Sx B: Cis, 5-FU x 4 → RT +/- Sx	10-y survival A: 9% B: 19% P = NS	Patients with unresectable tumors 10-y survival A: 6% B: 8%*
Domenge C, Hill C, Lefebvre JL, et al, <sup>133</sup> GETTEC, 2000	A: RT +/- Sx B: Cis, 5-FU x 3 → RT +/- Sx	Median survival A: 3.3 y B: 5.1 y*	CR after chemotherapy: 20%
Remenar E, Van Herpen C, Germa Lluch J, et al, <sup>134</sup> EORTC 24971, 2006	A: Cis, 5-FU x 4 → RT +/- Sx B: Doc, Cis, 5-FU x 4 → RT +/- Sx	Median PFS A: 8 mo B: 13 mo*	Median survival A: 15 mo B: 19 mo*
Hitt R, López-Pousa A, Martínez-Trufero J, et al, <sup>135</sup> Madrid, 2005	A: Cis, 5-FU x 3 → Cis + RT B: Pac, Cis, 5-FU x 3 → Cis + RT	CR after induction A: 14% B: 33%	Median time to treatment failure A: 12 mo B: 20 mo*
Posner MR, Herchock D, Le Lann L, et al, <sup>136</sup> TAX324, 2006	A: Cis, 5-FU x 3 → Carbo + RT B: Doc, Cis, 5-FU x 3 → Carbo + RT	3-y survival A: 48% B: 62%*	

\*Statistically significant difference.

Abbreviations: RT, radiation therapy; Cis, cisplatin; 5-FU, 5-Fluorouracil; Sx, surgery; Doc, docetaxel; Pac, paclitaxel; Carbo, carboplatin; NS, not significant; CR, complete response; PFS, progression-free survival.

function at 2 years were equivalent among all arms. With the reporting of this trial, the induction chemotherapy approach fell out of favor.

Numerous other clinical trials have evaluated the role of induction chemotherapy followed by radiotherapy for a survival endpoint. These trials have largely been negative, except for 2 trials from the 1990s—the Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC)<sup>133</sup> and Gruppo di Studio sui Tumori della Testa e del Collo (GSTTC)<sup>75</sup> studies (Table 4). There are several reasons that induction chemotherapy trials have been negative for their survival endpoints. Firstly,

the definitive therapy delivered in the trials used radiotherapy alone, which is inadequate to achieve the locoregional control rates of concurrent chemoradiotherapy. Secondly, the induction regimens used have been variable, and many trials used suboptimal chemotherapy. Thirdly, many trials were underpowered to address the survival endpoint. Using pooled data from various heterogeneous randomized induction chemotherapy trials, several meta-analyses have postulated that induction may provide minimal survival benefit.<sup>84,137–139</sup> The MACH-NC meta-analysis provided important information to further research

in this area. After analyzing approximately 60 induction chemotherapy trials, only 15 trials utilized effective drugs such as cisplatin-5-FU. Pooled data from these trials showed a significant survival improvement of 5% with the use of effective induction chemotherapy.<sup>84,138</sup>

#### More Potent Chemotherapy

Both paclitaxel<sup>140,141</sup> and docetaxel<sup>142,143</sup> induction combinations resulted in high response rates. Induction chemotherapy with carboplatin-paclitaxel was reported by the University of Chicago to achieve complete and partial response rates of 33% and 57%, respectively.<sup>144</sup> The EORTC 24971 trial compared 2 induction regimens, cisplatin/5-FU with docetaxel/cisplatin/5-FU, followed by radiotherapy.<sup>134</sup> Complete response rates to cisplatin/5-FU and docetaxel/cisplatin/5-FU were 7% and 9%, respectively. The triple induction-regimen arm showed significantly improved progression-free and overall survival rates, but higher toxic death rates and hematologic toxicities. Estimated 3-year survival rates were 24% for the cisplatin/5-FU arm and 37% for the docetaxel/cisplatin/5-FU arm.

With the taxanes proving efficacious as part of an induction regimen before definitive radiotherapy, the taxane-containing induction regimens were then evaluated with concurrent chemoradiotherapy. Hitt et al performed a randomized Phase II trial to compare the antitumor activity of 2 induction chemotherapy treatments of paclitaxel/cisplatin/5-FU versus cisplatin/5-FU, both followed by chemoradiotherapy with cisplatin.<sup>135</sup> Induction with paclitaxel/cisplatin/5-FU resulted in significantly higher complete response rates compared with cisplatin/5-FU (33% versus 14%). Median time-to-treatment failure was 20 months in the paclitaxel/cisplatin/5-FU arm compared with 12 months in the cisplatin/5-FU arm.

Similarly, the docetaxel/cisplatin/5-FU induction regimen was tested in a randomized study by Posner et al.<sup>136</sup> The study compared 2 induction chemotherapy regimens: docetaxel/cisplatin/5-FU versus cisplatin/5-FU for 3 cycles. After induction chemotherapy, patients in both arms received concurrent chemoradiotherapy with carboplatin (AUC 1.5, weekly). The complete

response rates to induction chemotherapy with the cisplatin/5-FU arm and the docetaxel/cisplatin/5-FU arm were 15% and 17%, respectively. Severe neutropenic rates (84%) were higher in the docetaxel/cisplatin/5-FU arm. The 3-year survival rates were 48% for the cisplatin/5-FU arm and 62% for the docetaxel/cisplatin/5-FU arm ( $P = .0058$ ). This trial is noteworthy for its concurrent chemoradiotherapy regimen utilizing carboplatin. The contribution of carboplatin to this regimen is unknown.<sup>145</sup> Together, these 3 trials prove that taxanes, when added to a standard induction regimen (cisplatin/5-FU), result in a superior induction regimen, but are associated with increased toxicities.<sup>135,136,146</sup>

#### Future Investigations

With the development of more effective induction chemotherapy regimens as described above, we are now poised to answer the question on whether induction chemotherapy confers a survival benefit over concurrent chemoradiotherapy. Early evidence from a randomized Phase II study by Paccagnella et al showed that the complete response rates after chemoradiotherapy were 47% in the induction chemotherapy followed by concurrent chemoradiotherapy arm versus 20% in the immediate concurrent chemoradiotherapy arm.<sup>146</sup> This trial lends support to the premise that an effective induction chemotherapy regimen is needed to have a stronger impact on outcome.

There are several ongoing induction chemotherapy randomized trials targeting different SCCHN patient populations. The University of Chicago "DeCIDE" trial (Docetaxel based Chemotherapy plus or minus Induction Chemotherapy to Decrease Events) is comparing chemoradiotherapy using the DFHX platform (docetaxel/5-FU/hydroxyurea/RT) with or without induction chemotherapy comprising docetaxel/cisplatin/5-FU (TPF) for 2 cycles. A completed Southwest Oncology Group/Eastern Cooperative Oncology Group Phase III trial is investigating the role of TPF induction chemotherapy followed by concurrent cisplatin and radiotherapy in patients with locally advanced but resectable oropharyngeal cancer. Nonresponders to induction therapy will undergo

surgical resection. A third trial led by the Dana-Farber Cancer Institute randomizes patients to receive TPF induction chemotherapy or immediate concurrent cisplatin and accelerated fractionation/concomitant boost radiotherapy. For patients in the induction chemotherapy arm, partial responders will receive concurrent docetaxel and accelerated fractionation radiotherapy, while complete responders will receive concurrent carboplatin and conventionally fractionated radiotherapy.

Since the induction chemotherapy approach was tested 3 decades ago, one key observation was made: complete responders following induction chemotherapy have a significant survival benefit over partial or nonresponders.<sup>147-149</sup> Among complete responders, patients with complete pathological tumor response to induction chemotherapy have significantly better outcomes than patients with microscopic residual disease.<sup>150</sup> In addition, it was noted that initial response to chemotherapy correlates with subsequent response to radiotherapy and, ultimately, survival.<sup>147</sup> These observations are crucial in launching a new concept for selection of therapy for patients based on their initial response to therapy. Urba et al administered 1 cycle of neoadjuvant cisplatin and 5-FU.<sup>151</sup> Patients who achieved less than 50% response had immediate laryngectomy, while those who achieved more than 50% response went on to concurrent chemoradiotherapy. The overall survival rate at 3 years is 85%, and larynx preservation was achieved in 70% of patients. Trials like this allow individualization of therapy based on the nature of specific tumors.

#### Metastatic Disease

The prevalence of distant metastasis *at presentation* commonly involving the lung, bones, and liver varies from 2% to 17%.<sup>55-58,152</sup> The incidence of distant metastasis is correlated with presence of neck lymph node involvement at the time of diagnosis, in particular bilateral nodal metastasis.<sup>56,153-155</sup> Due to the propensity for SCCHN to metastasize to the lungs and the presence of second primary tumors within the aerodigestive tract, the thorax should be imaged. The role of PET is increasing in clinical practice. PET has a higher sensitivity than computed

tomography (CT) to detect occult metastasis, which may significantly alter the treatment plan.<sup>156-159</sup> One important use of PET is in evaluating for occult neck metastasis in clinically node-negative SCCHN. Occult neck metastases identified on PET with CT correlation were found in 3% of T1 tumors, 9% of T2 tumors, 13% of T3 tumors, and 25% of T4 tumors.<sup>158</sup> Furthermore, PET has been used to evaluate for distant metastasis and to determine the nature of pulmonary nodules found by other imaging tests.<sup>159,160</sup>

Autopsy series report the prevalence of distant metastases in SCCHN patients ranges from 10% to 60%.<sup>152</sup> The most common sites of distant metastases are lungs, mediastinal lymph nodes, bone, and liver.<sup>152</sup> Skin metastases are uncommon in SCCHN (1%) and confer poor outcome.<sup>161</sup> Therapy at this stage of disease is directed toward palliation. Data supporting a positive impact of chemotherapy on quality of life have not been generated. There has only been one study evaluating the benefit of chemotherapy for recurrent and/or metastatic SCCHN in terms of survival, which showed that cisplatin significantly prolonged median survival by 10 weeks over best supportive care.<sup>162</sup>

#### Active Chemotherapy in Metastatic SCCHN

The platinum analogs have been one of the most active agents in metastatic SCCHN. Single-agent response rates of cisplatin are 15% to 40%<sup>163-165</sup> and carboplatin is around 25%.<sup>166</sup> Platinum agents are key in combination chemotherapy for recurrent and/or metastatic SCCHN.<sup>167</sup> This was shown in a large randomized trial comparing methotrexate-bleomycin-vincristine with or without cisplatin. The arm that received cisplatin attained a 50% response rate compared with 28% in the group that did not receive cisplatin. Median survival was slightly longer in the cisplatin arm (18 weeks), but this was not significantly different from the other arm. The closest comparison of efficacy between cisplatin and carboplatin comes from a trial comparing the 2 agents in combination with 5-FU.<sup>168</sup> The cisplatin/5-FU arm had a response rate of 32% compared with 21% in the carboplatin/5-FU arm, but there was no significant difference in overall survival.

The platinum analogs have been combined with other chemotherapy agents, most commonly with 5-FU. Although 5-FU has only a modest single-agent response rate (13%), when combined with cisplatin the response rate of the combination (32%) is significantly augmented.<sup>164</sup> In the 1990s, taxanes were evaluated in SCCHN and their single-agent activity was found to be among the highest of any chemotherapy drug class. Response rates of up to 40% were observed with paclitaxel<sup>169</sup> and docetaxel.<sup>170</sup> Various combinations of the most active chemotherapies in SCCHN—platinums, taxanes, and 5-FU—have been evaluated.<sup>128</sup> To date, no randomized trial has demonstrated improvement in overall survival, even though high response rates have been achieved. The response rates appear greater with platinum-taxane combinations, but the greater toxicity associated with these regimens may preclude their ability to offer palliation.<sup>128</sup> The inability of combination chemotherapy to significantly impact overall survival indicates that a therapeutic plateau has been reached for cytotoxic therapy.

#### Targeted Agents in Metastatic SCCHN

In recent years, several promising agents have emerged. EGFR signaling, which plays an important role in SCCHN, can be inhibited by small-molecule inhibitors (erlotinib, gefitinib) binding to the tyrosine kinase adenosine triphosphate-binding site or by using monoclonal antibodies (cetuximab) to block the ligand-binding site of EGFR.

Gefitinib and erlotinib have demonstrated activity in metastatic SCCHN. Gefitinib administered orally at 500 mg daily resulted in a response rate of 8% to 11%, and median survival was 6 to 8 months.<sup>100,102</sup> Similarly, erlotinib 150 mg orally daily resulted in a 4% response rate with a median survival of 6 months.<sup>104</sup> Both drugs were well tolerated, and adverse effects are mainly mild rash and diarrhea. A strong correlation between skin toxicity and clinical outcome was observed with gefitinib and erlotinib. Erlotinib has since been combined with docetaxel and cisplatin, achieving a 66% response rate without significantly increasing the toxicity profile of the regimen in a single-arm uncontrolled trial.<sup>107</sup>

In platinum-refractory patients, cetuximab monotherapy resulted in a response rate of 13% and 6 months median survival.<sup>171</sup> Addition of cetuximab to cisplatin in a randomized trial resulted in higher response rates in the cisplatin/cetuximab arm (26%) compared with the cisplatin-alone arm (10%).<sup>109</sup> Development of rash was highly correlated with response. However, despite the higher response rate and improved progression-free survival, both arms had similar median overall survivals (9 versus 8 months). A second trial (EXTREME) evaluating cetuximab in combination with cisplatin/carboplatin and 5-FU as first-line treatment of recurrent and/or metastatic SCCHN shows a significant survival impact.<sup>172</sup> This 442-patient randomized study found that the addition of cetuximab to chemotherapy improved median survival from 7.4 months to 10.1 months ( $P = .03$ ), and the toxicity profile of the regimen was not increased. This is the first systemic therapy in the last 3 decades to show a survival benefit over platinum-based chemotherapy in recurrent and/or metastatic SCCHN.

With the mild toxicity profile of novel agents, there is heightened interest in investigating inhibitors of 2 or more targets involved in the pathogenesis of SCCHN. Sorafenib, a multikinase inhibitor of C-Raf, B-Raf, vascular endothelial growth factor (VEGF) receptor, and platelet-derived growth factor receptor, resulted in a 3% response rate in chemotherapy-naïve patients, but the median and progression-free survival were 7 months and 4 months, respectively.<sup>105</sup> In spite of the scientific rationale behind targeted therapies, not all such therapies are effective. Lapatinib, an inhibitor of EGFR and HER2/neu, was ineffective in metastatic SCCHN.<sup>173</sup> In the recent years, several mechanisms of resistance toward upstream signaling inhibition have been identified, such as the presence of independently activated downstream proteins and the upregulation of other cell-surface receptors. There are currently clinical trials underway to target downstream activators such as mTOR (mammalian target of rapamycin). It is known that VEGF upregulation may result in anti-EGFR therapy resistance. By inhibiting both EGFR and VEGF receptor activation with erlotinib and bevacizumab, significantly improved responses have been observed.<sup>108</sup> These trials

represent the first steps toward rational targeting of SCCHN through comprehension of the disease's biology and hold significant promise for the outcome of SCCHN.

### Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a unique type of head and neck cancer with a distinct natural history, etiology, histopathology, and epidemiology. The World Health Organization histological classification of NPC categorized the tumors into 3 histologic groups: type I (keratinizing squamous cell carcinomas, similar to those found in the rest of the upper aerodigestive tract); type II (nonkeratinizing squamous cell carcinomas); and type III (nonkeratinizing undifferentiated carcinomas). Compared with the keratinizing type of NPC, nonkeratinizing NPC tends to be associated with Epstein-Barr virus (EBV) and is commonly seen in endemic areas such as East Asia, North Africa, and the far Northern Hemisphere. The average age at diagnosis of NPC is in the sixth decade of life, but a significant proportion of patients are diagnosed in their 20s and 30s.<sup>174</sup> NPC tends to metastasize early during the course of the disease; cervical lymph node metastases are observed in almost 90% of patients at presentation<sup>175</sup> and distant metastases are found in 5% to 10% at diagnosis.<sup>175,176</sup> The most frequent sites of distant metastases are bone, noncervical lymph nodes, and liver.<sup>177</sup>

NPC is staged by the tumor-node-metastasis staging system or the Ho staging. Two major differences distinguish the systems: (1) the Ho system compresses the 4 current AJCC T categories into 3, and (2) the Ho system categorizes lymph node disease by its anatomic position.<sup>178</sup> The nodal definition of the Ho system provides important prognostic information.<sup>179</sup> In recognition of this important aspect of the Ho system, the AJCC staging system was revised in 1997. For cervical nodal staging, N1 under the revised system referred to unilateral nodal involvement; N2 to bilateral nodal disease that had not reached N3 designation, irrespective of the size, number, or location of nodes; and N3 to lymph nodes larger than 6 cm (N3a) or nodes that had extended to the supraclavicular fossa (N3b). The

new staging system improved the accuracy of predicting prognosis.<sup>180,181</sup>

A close association between EBV and nasopharyngeal carcinoma<sup>182,183</sup> has been established on the basis of the presence of EBV DNA and proteins in NPC cells<sup>182,183</sup> and premalignant lesions,<sup>184</sup> and the presence of high concentrations of antibodies against EBV proteins in healthy people who later develop NPC.<sup>185,186</sup> High pretreatment EBV-DNA levels correlate with higher disease stage, poorer tumor response, greater likelihood of distant relapse, and survival.<sup>187,188</sup> Therapeutic monitoring of plasma EBV DNA provides a noninvasive method to monitor tumor response.<sup>188</sup> Furthermore, this test may allow early detection of recurrences after treatment. Current research efforts are focused on the management of patients with persistent or increasing plasma EBV DNA after definitive therapy, but without any clinical evidence of disease, and risk stratification of patients for treatment.

The Intergroup-0099 study forms the basis for the standard of care for locoregionally advanced NPC in the United States. The Intergroup regimen utilized concurrent chemoradiotherapy with cisplatin 100 mg/m<sup>2</sup> every 3 weeks followed by adjuvant cisplatin and 5-FU for 3 cycles.<sup>189,190</sup> The 5-year survival was 67% in the chemotherapy arm compared with 37% in the RT-alone arm. A quarter of the 147 patients accrued had World Health Organization type I NPC, which has a different natural history from nonkeratinizing NPC. This led to 2 studies that limited enrollment to endemic nonkeratinizing NPC and have recently confirmed the efficacy of concurrent chemoradiotherapy and adjuvant chemotherapy.<sup>191,192</sup> Both studies compared chemoradiotherapy with cisplatin followed by adjuvant chemotherapy with cisplatin-5-FU with radiotherapy alone. The 3-year survivals in both trials were approximately 80% in the chemoradiotherapy arm compared with 65% in the radiotherapy arm. Local control rates were similar in the chemoradiotherapy arms, but distant metastases were significantly less in the chemoradiotherapy arm of one trial,<sup>192</sup> but not another.<sup>191</sup> With these confirmatory trials, concurrent cisplatin chemoradiotherapy followed by adjuvant cisplatin-based chemotherapy is the current standard of care for locoregionally advanced NPC.

### Locoregional Nonmetastatic Recurrence of Head and Neck Cancer

Locoregional recurrence of SCCHN in a previously irradiated field is a therapeutic challenge. Salvage surgical procedure provides the best chance of long-term disease control and possible cure for operable patients with resectable, recurrent cancers. Extensive surgery is often required and may be associated with surgical complications, permanent loss of function, visible deformity, high cost, and even death. Furthermore, surgical salvage is not always feasible. Eligible patients must be free of metastatic disease, have a resectable tumor, and be medically fit to undergo the surgery. Long-term survival is possible from surgery in well-selected patients with 5-year survival rates ranging from 15% to 40%.<sup>193-200</sup> However, if surgery is not feasible, systemic chemotherapy with palliative intent is an alternative, but offers limited therapeutic benefit.

While palliative chemotherapy may be an acceptable option for some patients with widespread metastatic disease, it may not be the best approach for patients with only locoregionally recurrent disease. In carefully selected cases, reirradiation may be delivered with curative intent. However, since the majority of tumors that recur after primary radiotherapy arose from radiation-resistant tumor cells, reirradiation alone may be ineffective. Hence, reirradiation with concurrent chemotherapy may be more effective since both the radiosensitization and direct cytotoxic properties of chemotherapy are utilized. This toxic approach remains investigational and should only be performed at institutions with such experience. There are risks of unacceptable normal-tissue toxicity in reirradiated patients where cumulative radiation doses may reach twice the expected tolerance of normal tissues.

Two concurrent chemoradiotherapy regimens for reirradiation of recurrent head and neck cancer are commonly utilized—cisplatin-paclitaxel-reirradiation and hydroxyurea-5-FU-reirradiation (FHX). A review of the University of Chicago reirradiation experience with the FHX platform found that patients tolerated a median lifetime radiation dose of 131 Gy and achieved a 3-year overall survival, progression-free survival,

locoregional control, and freedom from distant metastasis rate of 22%, 33%, 51%, and 61%, respectively.<sup>201</sup> The treatment-related death rate was 17%. The RTOG 96-10 and Institut Gustave-Roussy trials have also assessed the FHX platform.<sup>202,203</sup> The results of these trials consistently show that about 20% of patients attain long-term survival. Similarly, the cisplatin-paclitaxel-reirradiation platform has been demonstrated to be effective in patients with recurrent SCCHN.<sup>204,205</sup>

Although reirradiation is a potentially curative therapy, this modality carries an increased risk of treatment-related mortality.<sup>201</sup> Mucositis, stomatitis, and dermatitis occur in almost all reirradiated patients. Furthermore, complications such as osteoradionecrosis, severe fibrosis, soft tissue necrosis, vascular necrosis, and mucosal necrosis have been reported. Late complications of reirradiation, such as vascular stenosis and impairment of swallowing or speech, may compromise quality of life. Reirradiation remains investigational, and the benefits of such an aggressive therapy need to be assessed further in randomized trials comparing it with the current standard therapy, chemotherapy.<sup>206</sup>

### CONCLUSION

After years of minimal progress in improving disease control and survival rates, the field of head and neck cancer therapy is rapidly advancing. Although such progress is good for patient care, this adds to the complexity of its management. It must be emphasized that the management of SCCHN today crosses multiple disciplines of medicine, and this will be the case for years to come. In this article, we have highlighted the increasing role of chemotherapy in the management of various stages of SCCHN. The cure rates achievable today, even in advanced disease, are a testament to the years of research that have been invested in this disease. There remains much to be learned; with the number of new targeted therapies that are produced presently, the permutations for combination multimodality therapies are infinite, and with the identification of various pathogenetic pathways in SCCHN, we are hopeful that this disease may one day be history.

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