

REVIEW ARTICLE

MEDICAL PROGRESS

Recent Advances in Head and Neck Cancer

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MORE THAN HALF A MILLION PATIENTS RECEIVE THE DIAGNOSIS OF squamous-cell carcinoma of the head and neck worldwide each year. In this disease, which primarily affects the oropharynx, oral cavity, hypopharynx, and larynx, smoking and alcohol abuse are major risk factors. Symptoms vary, depending on the site of origin, and can include a sore throat, dysphagia, odynophagia, and hoarseness. On examination, patients often have an identifiable primary site and a palpable neck mass. A multidisciplinary approach is important in treating these patients, given the complexity of the treatment and the acute and long-term complications that result from chemotherapy, radiation therapy, and surgery. Appropriate clinical and radiographic staging is crucial for accurate treatment planning and delivery.

Since this topic was last reviewed in the *Journal*,¹ new findings have emerged, leading to a better understanding of the biologic features of these tumors and, in particular, indicating that human papillomavirus (HPV) is a risk factor for cancer of the oropharynx.² More treatment options are available because of the development of new therapeutic agents directed against multiple molecular targets, including the epidermal growth factor receptor (EGFR).³ In addition, the roles of chemotherapy have expanded so that such therapy is used as a neoadjuvant^{4,5} for larynx preservation⁶ and for postoperative care.^{7,8} Irradiation techniques have also improved with the widespread use of intensity-modulated radiation therapy. New imaging techniques, such as positron-emission tomography, may be helpful in staging, restaging after therapy, and potentially planning radiation therapy. As more patients are cured of their cancers, survivors need help in coping with the long-term complications of therapy.

MOLECULAR PROGRESSION

Squamous-cell carcinoma of the head and neck is a complex disease that is characterized by clinical, pathological, phenotypical, and biologic heterogeneity.⁹⁻¹¹ The evolution and progression of this cancer are thought to result from multiple stepwise alterations of cellular and molecular pathways in the squamous epithelium.¹²⁻¹⁵ Mounting evidence suggests a model of molecular progression from premalignant lesions to invasive disease (Fig. 1).^{10,11,16,17}

Several studies have identified a loss of heterozygosity at particular chromosomes or have detected microsatellite instability that is associated with distinct stages of tumor progression.¹⁸⁻²² Alterations in the p53 tumor-suppressor gene represent an early event in progression, whereas mutations in the p16 gene, an inhibitor of cyclin-dependent kinase that is important in regulating the cell cycle, are associated with later stages of tumor progression.²³⁻²⁶ Studies have suggested that approximately half of all tumor samples from patients with this condition contain p53 mutations,^{27,28}

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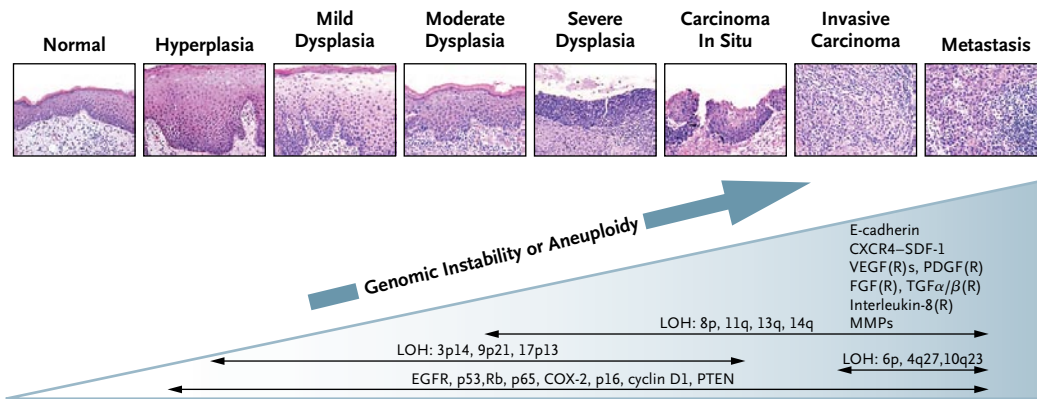


Figure 1. Models of Genetic Instability and Progression in Head and Neck Cancer.

Head and neck cancer is considered to progress through a multistep process from normal histologic features to hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, invasive carcinoma, and metastasis. Underlying genetic instabilities including the loss of heterozygosity (LOH) of certain chromosomes (3p14, 9p21, 17p13, 8p, 11q, 13q, 14q, 6p, 4q27, and 10q23) and amplification or deletion or up-regulation or down-regulation of certain oncogenes or tumor-suppressor genes, including epidermal growth factor receptor (EGFR), p53, Rb, p65, cyclooxygenase 2 (COX-2), p16, cyclin D1, and phosphatase and tensin homolog (PTEN) have been identified as genetic alterations in each of the pathological stages of this disease. Several genes — including those encoding E-cadherin (*CDH1*), chemokine (C-X-C motif) receptor–stromal-cell–derived factor (*CXCR4–SDF-1*), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor α and β (TGF- α and TGF- β), interleukin-8, and the respective receptors, along with matrix metalloproteinase (MMP) — are involved mainly in the progression of metastasis and in early stages of tumor progression.

and about a third contain mutations in cyclin D1.^{25,26} HPV is another important causative factor in some patients, particularly those with tumors of the oropharynx that are not associated with p53 mutations or with other molecular alterations that are more common in tumors related to the use of tobacco, alcohol, or both.²

The major prognostic factors for head and neck cancer are the presence of locoregional metastasis, vascular or lymphatic invasion, positive surgical margins, and extracapsular spread of tumor cells from involved lymph nodes into soft tissue of the neck.^{1,29} The identification of molecular signatures and understanding mechanisms of tumor progression may facilitate the identification of new predictive and prognostic markers and new therapeutic targets for the treatment of this cancer.

Metastatic progression of tumor cells is a multistep and complicated process.³⁰ Each step appears to involve close molecular interactions between tumor cells and the surrounding microenvironment, which are increasingly being explored with the use of genomic and proteomic techniques.³¹ DNA microarray studies have suggested putative metastasis-related proteins that include several keratins, cell-surface proteases, mesenchy-

mal-cell markers, cell-matrix adhesion molecules, chemokines, and factors involved in modulating the extracellular matrix and epithelial-to-mesenchymal transition.^{32–36} Chemokine (C-X-C motif) receptor (CXCR4), and its ligand, stromal-cell–derived factor (SDF-1), appear to bind together to direct tumor cells at primary sites to metastatic organ sites, suggesting that such an interaction may play a key role in the homing of metastatic cells³⁷ and may facilitate the secretion of angiogenic factors, such as vascular endothelial growth factors (VEGFs), and their receptors from vascular endothelial cells.^{38–42}

Most known antiangiogenic compounds target VEGF, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factors α and β (TGF- α and TGF- β), and interleukin-8, along with the receptors of these proteins.^{41–44} Several preclinical and early clinical trials have examined such compounds as single agents or in combination with chemotherapeutic agents in patients with squamous-cell carcinoma of the head and neck.^{45–47} It is hoped that new antiangiogenic or antimetastatic agents will be developed for the treatment of squamous-cell carcinoma of the head and neck as a result of this work.

 SIGNAL TRANSDUCTION OF EGFR

EGFR was initially implicated in cancers because of its tyrosine kinase activity⁴⁸ and the discovery of a truncated EGFR oncogene in avian erythroblastosis virus.⁴⁹ The concept of “inhibition” of EGFR signaling and its adjacent molecular networks has facilitated the development of many new monoclonal antibodies and small-molecule tyrosine kinase inhibitors (Fig. 2A). EGFR consists of four family members, of which EGFR-1 (HER1) and EGFR-2 (HER2/neu) are the best characterized. Ligands for EGFR include epidermal growth factor (EGF), TGF- α , amphiregulin, epiregulin, betacellulin, and heparin-binding EGF-like growth factor (HB-EGF),⁵⁰ whereas EGFR-2 has no known natural ligands.⁵⁰ To initiate growth-signaling cascades, receptor dimerization activates subsequent phosphorylation of tyrosine kinases and downstream signaling mediators (Fig. 2B).^{51,52} Nuclear translocation of EGFR and other growth factor receptors is important for signaling in rapidly growing cells.⁵³⁻⁵⁵ Nuclear translocation is largely abolished by treatment with the human–mouse chimerized anti-EGFR monoclonal antibody C225 (cetuximab), which also strongly inhibits phosphorylation of EGFR.^{56,57} EGFR and two of its ligands, EGF and TGF- α , are overexpressed in many solid tumors, including squamous-cell carcinoma of the head and neck, and are linked to a poor prognosis after treatment.^{58,59} Therefore, EGFR is considered an excellent target for the development of new therapies for this disease.

Preclinical studies investigated how EGFR antibodies and tyrosine kinase inhibitors might work alone or in combination with other agents or treatment approaches. Several chimeric and humanized IgG antibodies that target various EGFR epitopes have been synthesized and shown to prevent EGFR signaling by distinct mechanisms; such antibodies have also been shown to have antitumor activity.^{56,57,60,61} EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, bind within the kinase domain to inhibit kinase activity, thus modulating transcription, cell-cycle progression, cell survival, and motility, all of which facilitate invasiveness and metastasis.⁶²

 HPV AND ANTITUMOR VACCINE

HPV is implicated in the development of tumors. For example, infection with HPV has been shown to cause virtually all female cervical cancers.⁶³ Mo-

lecular evidence also suggests a role for HPV, particularly HPV-16, in the pathogenesis of a subgroup of squamous-cell carcinomas of the head and neck,⁶⁴ and the HPV viral oncogenes E6 and E7 are frequently overexpressed in the oropharynx.⁶⁴ In a case–control study,² it was reported that oropharyngeal cancer was significantly associated with the presence of oral HPV-16 infection. HPV DNA was detected in 72% of 100 oropharyngeal tumor specimens, and 64% of the patients in the study were seropositive for HPV-16 E6, HPV-16 E7, or both.² Although a cause-and-effect relationship cannot be inferred from this single study, such findings confirm those of other case–control studies.⁶⁴⁻⁶⁸ Furthermore, exposure to HPV increased the association with oropharyngeal cancer, regardless of the use of tobacco and alcohol, without evidence of synergy between exposure to HPV and use of tobacco and alcohol. These data suggest that two distinct pathways may be involved in the development of oropharyngeal cancer: one mainly driven by tobacco and alcohol and the other by HPV-induced genomic instability. Additional molecular studies indicated that patients with HPV-positive tumors bearing a unique gene-expression profile with minimal molecular alterations appeared to have more favorable outcomes after therapy, whereas patients with HPV-negative tumors, which show frequent molecular and cytogenetic changes — such as p53 mutations, loss of p16^{INK4a}, p15^{INK4b}, cyclin D1 overexpression, or an increased copy number of EGFR and chromosome 7 — appeared to have less favorable outcomes.⁶⁵⁻⁶⁷ Among young patients, widespread use of oral sexual practices and a trend toward multiple sexual partners may have contributed to an increased incidence of HPV-related head and neck cancers, particularly tonsillar and base-of-the-tongue cancers.⁶⁸⁻⁷⁰ Since HPV vaccination is an important strategy to prevent cervical cancer,⁶⁸ it would seem logical that HPV-vaccination strategies might be tested as a potential means for preventing HPV-induced head and neck cancers.

 TREATMENT

STRATEGIES FOR THERAPY

The majority of patients with head and neck cancer present with locally advanced, stage III or IV disease that requires a combination of chemotherapy, radiation, or surgery. Patients who present with early stage I or II disease are often treated with either radiation or surgery and have an excellent

prognosis. However, these patients are still at high risk for recurrence and second primary tumors and thus should be closely monitored.

A major challenge in treating any cancer is obtaining a high cure rate while preserving vital structures and function. This is especially true for cancers in the anatomically complex region of the head and neck, where major structures and function are affected by both the cancer and its treatment. Organ preservation should be taken into account early on and should be attempted with all treatment approaches. The experience of the treating center plays a big role in this regard.

Advances in treatment strategies have affected all the approaches used in head and neck cancer: radiation therapy, chemotherapy, targeted agents, and surgery. Radiation therapy remains a mainstay of curative therapy for oropharyngeal cancer and advanced hypopharyngeal and laryngeal cancer. Recent advances have focused primarily on fractionation schedules and the use of intensity-modulated radiation therapy, a form of high-precision radiotherapy that delivers radiation more precisely to the tumor while relatively sparing the surrounding normal tissues. Second, chemotherapy is an integral part of treating locally advanced head and neck cancer. It is often administered concurrently with radiotherapy (concurrent chemoradiotherapy) or before radiotherapy in the form of induction chemotherapy. Third, targeted agents such as cetuximab appear to have promise both as single agents and in combination with radiotherapy. Finally, surgical techniques have continued to evolve, with greater focus on minimally invasive procedures where appropriate. Reconstruction and free-tissue-transfer techniques have also improved, resulting in better functional and aesthetic outcomes. Tables 1 and 2 provide a summary of trials involving patients with squamous-cell carcinoma of the head and neck.

CONCURRENT CHEMORADIOOTHERAPY

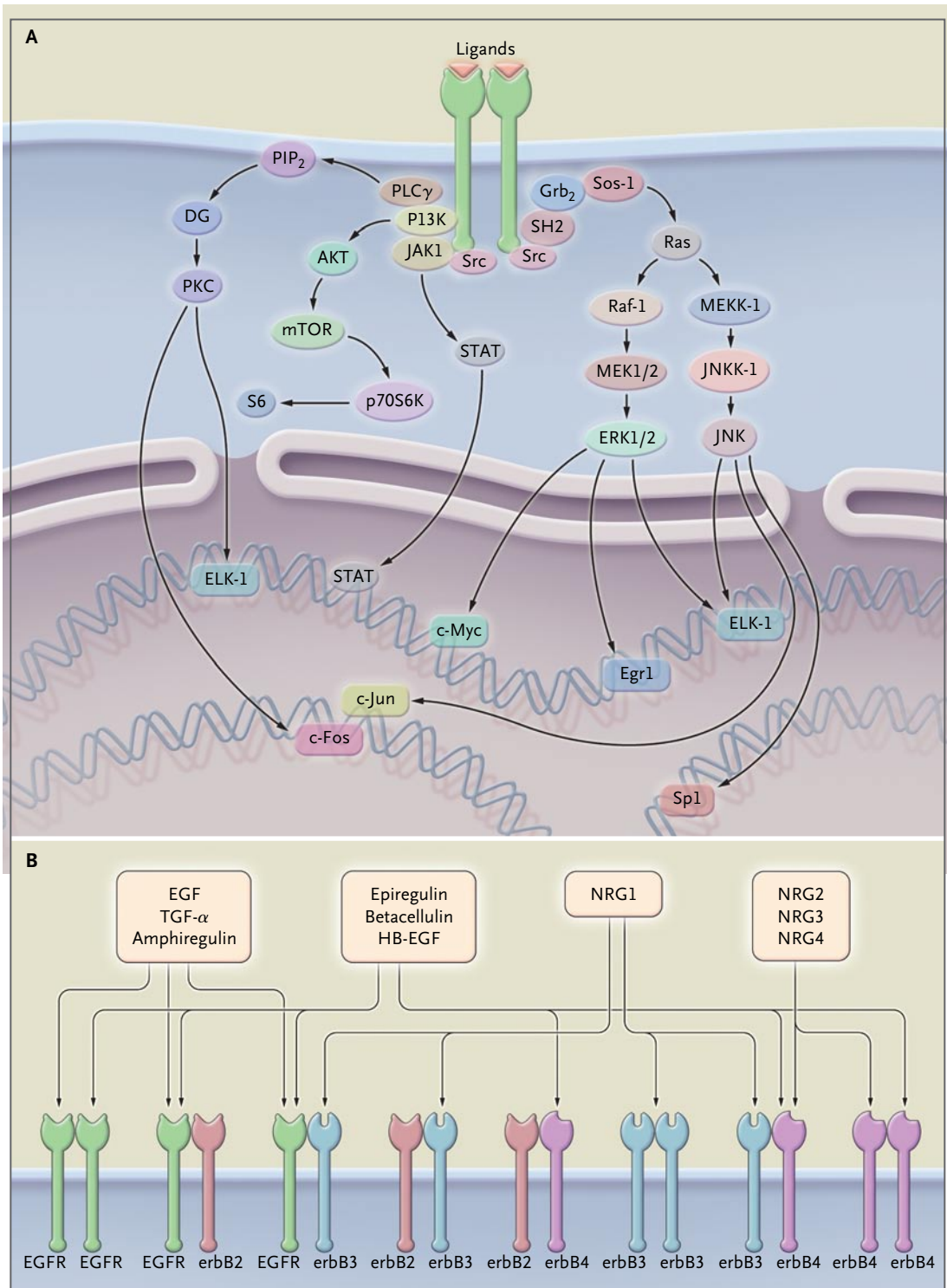
Concurrent or definitive chemoradiotherapy refers to the administration of chemotherapy in combination with radiation therapy in an effort to treat the tumor without previous initial surgical resection. Surgery in this case is used for persistent disease. In contrast, postoperative concurrent chemoradiotherapy is used after surgical resection when the patient is at an increased risk for local and distant recurrence.

Figure 2 (facing page). Signaling Cascades and Dimerization in the EGFR Family.

In Panel A, epidermal growth factor receptor (EGFR) is a transmembrane protein with intrinsic tyrosine kinase activity that regulates cell growth in response to binding of its ligands, such as epidermal growth factor (EGF), transforming growth factor α (TGF- α), and others. Ligand binding induces EGFR dimerization and activates several EGFR-mediated signaling pathways, including Ras/mitogen-activated protein kinases (MAPKs, such as extracellular signal-regulated kinase [ERK] and c-Jun N-terminal kinase [JNK]), Janus kinase-signal transducers and activators of transcription (JAK-STAT), phosphatidylinositol 3-kinase-protein kinase B (PI3K-AKT), phospholipase C- γ -protein kinase C (PLC- γ -PKC), and others. These signaling pathways are responsible for the activation of several transcription factors, such as Sp1, c-Jun, c-Fos, and c-Myc, which consequently regulate gene expression, supporting cell-cycle progression, cell proliferation, invasion, angiogenesis, and metastasis. DG denotes diglyceride, Egr1 early growth response protein, ELK-1 ets-like gene 1, Grb₂ growth factor receptor-bound protein 2, JNKK JNK kinase, MEK MAPK kinase, MEKK MEK kinase, mTOR mammalian target of rapamycin, PIP₂ phosphatidylinositol 4,5-bisphosphate, p70S6K p70 S6 kinase, Raf-1 c-raf-1 protein, SH2 Src homology 2, Sos-1 son of sevenless homolog 1, and S6 subunit protein 6. In Panel B, four receptor proteins have been identified as members of the EGFR family. These include EGFR (or erbB1), HER2/neu (or erbB2), erbB3, and erbB4. Multiple EGF-like ligands bind to EGFR or other receptors of the family, leading to homodimerization or heterodimerization of the receptors. The dimerization of the receptors, except the erbB3 homodimer, results in autophosphorylation of tyrosine residues in the cytoplasmic domain of the receptors and thereby activates signal transducers at corresponding docking sites, followed by activation of downstream signaling cascades. Since erbB2 has no known natural ligands, it can form heterodimers only with other members of the family. HB-EGF denotes heparin-binding EGF-like growth factor, and NRG neuregulin.

DEFINITIVE CHEMORADIOOTHERAPY

A meta-analysis of studies involving patients with head and neck cancer showed an absolute benefit of 8% associated with concurrent chemoradiotherapy, as compared with radiotherapy alone.⁷⁷ Bolus cisplatin at a dose of 100 mg per square meter of body-surface area that was administered every 3 weeks during radiation therapy is often used in patients with advanced disease.^{6,78,79} The side effects of this approach are substantial and can include neuropathy, hearing loss, marked nausea and vomiting, and renal dysfunction. Many patients are not well enough to receive this drug



in bolus form and instead receive weekly cisplatin at a lower dose or weekly carboplatin and paclitaxel. However, bolus cisplatin every 3 weeks remains the reference regimen, and no random-

ized comparisons have been made between this schedule and the weekly regimens.

In one study, patients with newly diagnosed, advanced laryngeal cancer were randomly assigned

Table 1. Phase 3 Studies Involving Patients with Previously Untreated Head and Neck Cancer.*

Study	No. of Patients	Drug Regimen	Radiotherapy Regimen	Population	Median Progression-free Survival ^{m0}	Median Overall Survival
TAX 323 ⁵	358	Docetaxel, cisplatin, and fluorouracil plus radiotherapy vs. cisplatin and fluorouracil plus radiotherapy	Standard, accelerated, or hyperfractionated	Unresectable	11.0 vs. 8.2	18.8 vs. 14.5
TAX 324 ⁴	501	Docetaxel, cisplatin, and fluorouracil plus chemoradiotherapy vs. cisplatin and fluorouracil plus chemoradiotherapy	Standard with carboplatin weekly	Resectable and unresectable	36 vs. 13	71 vs. 30
RT0G-9111 ^{36,71}	547	Cisplatin plus radiotherapy vs. radiotherapy alone vs. cisplatin and fluorouracil plus radiotherapy	Standard	Larynx cancer	47 vs. 34 vs. 45†	55 vs. 54 vs. 59‡
Bonner et al. ³	424	Cetuximab plus radiotherapy vs. radiotherapy alone	Standard, accelerated, or hyperfractionated	Resectable and unresectable	17.1 vs. 12.4	49.0 vs. 29.3
RT0G 9501 ⁸	459	Cisplatin plus radiotherapy vs. radiotherapy alone	Standard	Postoperative	NR	44.9 vs. 31.9
EORTC 22931 ⁷	334	Cisplatin plus radiotherapy vs. radiotherapy alone	Standard	Postoperative	55 vs. 23	72 vs. 32

* EORTC denotes European Organization for Research and Treatment of Cancer, NR not reported, and RT0G Radiation Therapy Oncology Group.

† In this trial, the results are reported as laryngectomy-free survival.

‡ This value is a percentage rather than number of months.

to receive one of three treatments: induction chemotherapy with cisplatin plus fluorouracil followed by radiotherapy (group A), radiotherapy with concurrent administration of cisplatin (group B), or radiotherapy alone (group C). Preservation of the larynx and local control were best achieved in the group that received concurrent chemoradiotherapy, which had an absolute reduction of 43% in the rate of laryngectomy. No differences in survival were noted among the three groups. Laryngectomy-free survival was best achieved with the concurrent and sequential approaches, both of which were superior to radiotherapy alone. Distant metastasis developed in 15% of the patients in group A, 12% of those in group B, and 22% of those in group C. Concurrent chemoradiotherapy is accepted as a standard approach for patients with advanced laryngeal cancer who want to preserve their larynx.

One of the major advances in radiotherapy has been the implementation of intensity-modulated radiation therapy. In this approach, the radiation dose is designed to conform to the three-dimensional shape of the tumor by modulating the intensity of the radiation beam to focus a higher radiation dose to the tumor while minimizing radiation exposure to surrounding normal tissues. By treating specific targets with a different dose each day, such therapy has the potential to improve outcomes by minimizing doses to normal tissues and increasing doses to tumors,^{80,81} leading to reduced long-term toxicity and xerostomia and improved salivary flow.⁸²⁻⁸⁴ Recent data suggest that such therapy is as effective as conventional radiotherapy with regard to local control, but it can reduce late toxicity.^{83,84}

Another important consideration in radiotherapy is the fractionation of treatment. Radiotherapy for head and neck cancer is typically provided in a single fraction on a schedule of 5 days per week for 7 weeks. In the past decade, altered fractionation schedules that allow radiotherapy to be accelerated or hyperfractionated have been studied. In accelerated fractionation, the total treatment time is reduced. This reduces tumor repopulation between sessions and may allow for better local control. In hyperfractionated schedules, two or three lower-dose fractions are given daily, which may reduce late toxicity. A recent meta-analysis⁸⁵ of 15 randomized trials enrolling more than 6000 patients who had mainly stage III and IV tumors of the oropharynx and larynx examined whether

Table 2. Studies in Recurrent Head and Neck Cancer.*

Study	No. of Patients	Regimen	Population	Response Rate	Survival
				%	mo
EXTREME ^{72,73}	442	Cisplatin, fluorouracil, and cetuximab vs. cisplatin and fluorouracil	First-line recurrent	35.6 vs. 19.5	10.1 vs. 7.4†
ECOG 5397 ⁷⁴	117	Cisplatin and cetuximab vs. cisplatin and placebo	First-line recurrent	26.3 vs. 9.8	9.2 vs. 8.0‡
IMEX ⁷⁵	486	Gefitinib (250 mg) vs. gefitinib (500 mg) vs. methotrexate	Second-line recurrent	2.7 vs. 7.6 vs. 3.9	5.6 vs. 6.0 vs. 6.7‡
Vermorken et al. ⁷⁶	103	Cetuximab	Platinum resistant	13	6

* ECOG denotes Eastern Cooperative Oncology Group, EXTREME Erbitux [Cetuximab] in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer, and IMEX Iressa versus Methotrexate in Previously Treated Patients with Recurrent Head and Neck Cancer.

† P=0.03.

‡ P value was not significant.

altered fractionation improved survival. In this analysis, there was a small but significant survival benefit of 3.4 percentage points associated with altered fractionation radiotherapy at 5 years. The survival benefit was significantly greater with hyperfractionated radiotherapy than with accelerated radiotherapy; it was also greater among patients under the age of 50 years who had a good performance status, which was defined according to a tool that assessed patients' overall physical condition and the ability to perform activities of daily living. No effect on distant metastasis was noted. The Radiation Therapy Oncology Group (RTOG) has recently completed a phase 3 study (RTOG 0129; ClinicalTrials.gov number, NCT00047008)⁸⁶ to examine whether the benefit of altered fractionation persists when combined with chemotherapy. No significant difference in acute or late toxicity was noted; efficacy data are not yet available. It should be noted that the benefit of concurrent chemoradiotherapy or altered fractionation radiotherapy decreases with increasing age, and this benefit is uncertain for patients who are older than 70 years.⁸⁷

POSTOPERATIVE CHEMORADIO THERAPY

Postoperative concurrent chemoradiotherapy has been tested in two phase 3 studies conducted by RTOG⁸ (NCT00002670) and the European Organization for Research and Treatment of Cancer (EORTC) (NCT00002555).⁷ Both trials aimed to determine whether the addition of cisplatin to radiotherapy improved the outcome, as compared with radiotherapy alone. In both studies, patients with high-risk surgical or pathological features after surgery were randomly assigned to receive

either radiotherapy alone or radiotherapy plus cisplatin (at a dose of 100 mg per square meter every 3 weeks for three cycles). High-risk features were defined as the presence of a positive margin, extracapsular spread outside the lymph nodes, lymphovascular invasion, perineural invasion, and multiple positive lymph nodes. In RTOG 9501, concurrent chemoradiotherapy significantly reduced the risk of locoregional recurrence, as compared with radiotherapy alone. No benefit on overall survival was noted. In EORTC 22931, both progression-free survival and overall survival were significantly longer in patients receiving concurrent chemoradiotherapy. Both trials showed that adding cisplatin had no significant effect on the incidence of distant metastases. The metastatic rates were 25% with radiotherapy alone and 20% with combined therapy.

Although postoperative concurrent chemoradiotherapy was more effective than radiotherapy alone, it was also more toxic. Both trials reported a significant increase in acute severe adverse events in the combined-therapy group, including mucositis, hematologic toxicity, and muscular fibrosis. A pooled analysis of data from both trials showed that two risk factors were associated with a significant benefit from concurrent chemoradiotherapy: extracapsular extension and positive surgical margins.⁸⁸ It is our practice to offer concurrent chemoradiotherapy to all patients who have a good performance status and any of the high-risk features defined above.

SEQUENTIAL CHEMORADIO THERAPY

Induction chemotherapy has been studied for more than three decades and has been repeatedly associ-

ated with significant tumor shrinkage and with a decrease in the risk of distant metastasis. This is important, since at 2 years, approximately 20% of patients with locally advanced disease who are treated with concurrent chemoradiotherapy have distant metastasis, and their disease is classified as incurable. The effect of induction chemotherapy on overall survival has been more difficult to demonstrate. Various models of induction chemotherapy have been used over the years with different approaches and agents. The interpretation of relevant trials has been difficult, given their heterogeneity. Nevertheless, a meta-analysis of studies of chemotherapy in patients with head and neck cancer showed a survival benefit of 5% for induction chemotherapy with the addition of cisplatin and fluorouracil,⁷⁷ and this regimen has been the reference regimen used in induction-chemotherapy protocols. Two recent randomized, phase 3 trials have shown a significant benefit of adding docetaxel to cisplatin and fluorouracil induction chemotherapy.

DOCETAXEL, CISPLATIN, AND FLUOROURACIL

Induction Therapy

The safety and efficacy of a combination of docetaxel, cisplatin, and fluorouracil as induction chemotherapy for patients with squamous-cell carcinoma of the head and neck were evaluated in a multicenter, randomized, phase 3 trial (TAX 323) (NCT00003888).⁵ In this European study, 358 patients with previously untreated, unresectable, locally advanced stage III and IV tumors and a good performance status received either docetaxel, cisplatin, and fluorouracil or cisplatin and fluorouracil. These regimens were administered every 3 weeks for four cycles. Four to 7 weeks after chemotherapy, patients who did not have progressive disease received radiotherapy alone, either as a conventional, accelerated, or hyperfractionated regimen. The primary end point, median progression-free survival, was significantly longer in the group receiving docetaxel, cisplatin, and fluorouracil (11.4 months) than in the group receiving cisplatin and fluorouracil (8.3 months). Median overall survival was significantly longer in the group receiving docetaxel, cisplatin, and fluorouracil (18.6 months) than in the group receiving cisplatin and fluorouracil (14.2 months).

The TAX 324 study (NCT00273546) took a different approach from that of the TAX 323 study in that instead of undergoing radiotherapy only

after induction chemotherapy, all patients received concurrent chemoradiotherapy. The goal was to combine both induction chemotherapy and concurrent chemoradiotherapy in one study. In this international, multicenter, randomized, phase 3 trial, 501 patients had previously untreated, locally advanced squamous-cell carcinoma of the head and neck (either resectable or unresectable) and had a good performance status.⁴ Patients received either docetaxel, cisplatin, and fluorouracil or cisplatin and fluorouracil every 3 weeks for three cycles. All patients who did not have progressive disease after induction chemotherapy received 7 weeks of concurrent chemoradiotherapy with carboplatin, with an area under the curve (AUC) of 1.5, administered weekly for a maximum of seven doses. The median survival time was 70.6 months in the group receiving docetaxel, cisplatin, and fluorouracil, as compared with 30.1 months in the group receiving cisplatin and fluorouracil ($P=0.006$). These two studies were key parts of the package considered by the Food and Drug Administration (FDA) when they approved induction chemotherapy with docetaxel, cisplatin, and fluorouracil in patients with either operable or inoperable squamous-cell carcinoma of the head and neck.

Toxic Effects

The use of combination therapy with docetaxel, cisplatin, and fluorouracil has been associated with an increased incidence of neutropenia and febrile neutropenia; an increased incidence of stomatitis and diarrhea has been associated with the use of cisplatin and fluorouracil. A substantial number of patients did not receive radiation therapy or concurrent chemoradiotherapy as specified in the protocol in both the TAX 323 and TAX 324 trials (30% and 20%, respectively). Disease progression and adverse events were the major reasons for non-completion. In the TAX 323 study, 44 of 358 patients did not receive any radiotherapy. A total of seven treatment-related deaths occurred in these two studies.

PROS AND CONS OF INDUCTION THERAPY

Concurrent chemoradiotherapy has a long track record of improving local and regional control. However, its effect on distant metastases is at best questionable. Induction chemotherapy clearly reduces distant metastases, and the induction regimen used in the TAX 324 study had an effect on

local control. Ongoing randomized, phase 3 studies are comparing sequential therapy with concurrent chemoradiotherapy; these studies will take 4 to 5 more years to complete. Thus, until that time, the treating multidisciplinary team has two treatment options to choose from: sequential chemoradiotherapy or concurrent chemoradiotherapy. Both approaches are reasonable and have been shown to improve the outcome. For each patient, physicians will need to decide on a treatment plan on the basis of perceived risks of local and distant metastases.

Experience is important during the delivery of induction chemotherapy in order to avoid unnecessary delays in starting radiotherapy. Thus, the use of a multidisciplinary clinic is of extreme importance. The treating team needs to be ready to abort induction chemotherapy and move to radiotherapy if treatment is poorly tolerated by the patient. It seems reasonable, off protocol, to consider induction chemotherapy for patients with a good performance status and fairly advanced primary and nodal presentations — for example, those with grade T3, T4, N2b, N2c, or N3 disease. It is also reasonable to offer induction chemotherapy to symptomatic patients in need of immediate therapy.

CETUXIMAB

Role of Biologic Agents

Cetuximab, a monoclonal antibody, has been approved by the FDA for treating head and neck cancer as a single agent in patients with platinum-resistant disease. It is also approved for use in combination with radiation in previously untreated patients.^{3,76}

With Radiation Therapy

In a recent phase 3 trial (NCT00004227), cetuximab in combination with radiotherapy improved locoregional control and overall survival in patients with locally advanced tumors.³ In a trial involving 424 patients, 213 patients were randomly assigned to receive radiotherapy alone and 211 were assigned to receive cetuximab plus radiotherapy. Concomitant boost radiotherapy was the most common schedule used (56%). Cetuximab was initiated 1 week before radiotherapy with a loading dose of 400 mg per square meter, followed by 250 mg per square meter weekly throughout radiotherapy. Locoregional control and both progression-free and overall survival were significantly improved

with combination radiotherapy plus cetuximab.³ Treatment with the combination regimen decreased the risk of locoregional progression by 32% and the risk of death by 26%. However, the rates of distant metastases at 1 year and 2 years were similar in the two study groups. In an unplanned analysis, the survival benefit was increased in patients with primary oropharyngeal tumors (tonsil and tongue base) and those receiving a concomitant boost schedule, a type of accelerated radiation-therapy protocol in which patients receive 4 weeks of once-daily treatment, followed by 2 weeks of two fractions per day, which “boosts” the treatment at the end of the protocol.

The addition of cetuximab to radiotherapy was associated with similar rates of grade 3 or 4 toxic effects in the two study groups. The incidence of acneiform rash and infusion reactions was significantly higher in the combination cetuximab–radiotherapy group than in the group receiving radiotherapy alone. Rash and nail changes appeared to be the most common side effects associated with cetuximab, as with other EGFR inhibitors.

The interpretation of the results of the cetuximab–radiotherapy trial is quite difficult, since chemotherapy was not part of the study, making it difficult to assess whether the combination of cetuximab and radiotherapy was as effective as concurrent chemoradiotherapy. The RTOG is conducting a large, randomized, phase 3 study comparing chemoradiotherapy with chemoradiotherapy plus cetuximab (RTOG 0522) (NCT00265941). The chemotherapy agent used in RTOG 0522 is cisplatin, and the primary end point is disease-free survival. Until more data become available, it may make sense, in our view, to offer cetuximab in combination with radiotherapy to patients who cannot tolerate chemoradiotherapy.

After Recurrence

Cetuximab was tested as a single agent in 103 patients with recurrent or metastatic head and neck cancer that was resistant to platinum-based therapy.⁷⁶ The response rate was 13%, and the rate of disease control (i.e., patients who had a complete response, a partial response, or stable disease) was 46%. The median time to disease progression was 70 days, and median overall survival was 178 days. There appeared to be no benefit in adding cisplatin to cetuximab in these patients.

The situation was different in patients whose

disease has progressed after curative therapy and who were receiving first-line chemotherapy. For such patients, the addition of cetuximab to cisplatin and fluorouracil was superior to cisplatin and fluorouracil alone in the Erbitux [Cetuximab] in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) (NCT00122460) study.⁷² In this trial, 442 patients were randomly assigned either to group A, which received either cetuximab (at an initial dose of 400 mg per square meter and then 250 mg per square meter weekly) plus cisplatin and fluorouracil every 3 weeks for a maximum of six cycles (at a dose of 100 mg per square meter intravenously on day 1) or carboplatin (at a dose of AUC 5 on day 1) and fluorouracil (a continuous infusion of 1000 mg per square meter per day for the first 4 days of each cycle), or to group B, which received either cisplatin or carboplatin plus fluorouracil in the same regimen as the one used in group A. Median survival was significantly better in the group receiving cisplatin, fluorouracil, and cetuximab (10.1 vs. 7.4 months). Approximately 60% of the patients who were enrolled in this trial had not received chemotherapy before. The benefit appeared to be more pronounced in patients under the age of 65 years who had a good performance status and were receiving cisplatin-based treatment.

Other EGFR inhibitors are being tested as therapeutic agents for patients with head and neck cancer. These agents include cetuximab and other

monoclonal antibodies and tyrosine kinase inhibitors. Tyrosine kinase inhibitors are administered orally. The two agents that have been studied the most are gefitinib⁸⁹ and erlotinib.⁹⁰ Both appear to have only modest antitumor activity in head and neck cancer. For example, a recently completed phase 3 study of gefitinib did not show a survival advantage over methotrexate.⁷⁵

FUTURE DIRECTIONS

The treatment of head and neck cancer is continuing to evolve, and physicians who are treating patients with locally advanced disease have multiple treatment options. The treatment team should consider the patient's overall condition and his or her ability to tolerate aggressive therapy. The risk of local and distant recurrence needs to be considered as a treatment is implemented, and a multidisciplinary approach is crucial. We continue to search for new molecularly targeted agents for head and neck cancer. The incorporation of such therapies into current treatment regimens is a priority, in conjunction with a better understanding of the underlying mechanisms of action of such targeted agents.

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