REVIEW ARTICLE

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Head and Neck Cancer

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Although head and neck cancer is associated with pain, disfiguration, dysfunction, psychosocial distress, and death, recent advances have brought substantial improvements in outcomes. The introduction of immune-checkpoint inhibitors for treatment of recurrent or metastatic head and neck cancer led to a remarkable benefit for some patients. In parallel, improvements in standard therapy, such as minimally invasive, organ-sparing surgical techniques, advances in radiotherapy, and curative multimodal approaches, have enhanced preservation of function and reduced morbidity and mortality. Increased awareness and diagnosis of human papillomavirus (HPV)–associated oropharyngeal carcinoma, alongside decreases in tobacco-related head and neck cancers, are similarly changing the understanding of this disease, its treatment, and the prognosis for affected patients.

DEFINITION

The prognosis and multimodal therapeutic options for patients with head and neck cancer vary depending on epidemiologic factors, anatomical location, and stage. There is marked heterogeneity of tumors arising in the head and neck region (Fig. 1). The focus here is on squamous-cell carcinomas arising from mucosal surfaces of four major anatomical sites: the oral cavity, sinonasal cavity, pharynx, and larynx. (Nasopharyngeal cancer is not discussed because of differences in epidemiology, pathology, natural history, and treatments that are beyond the scope of this review.)

EPIDEMIOLOGY

Head and neck cancer was the seventh most common cancer worldwide in 2018 (890,000 new cases and 450,000 deaths),[1] accounting for 3% of all cancers (51,540 new cases) and just over 1.5% of all cancer deaths (10,030 deaths) in the United States.[2] Typically diagnosed in older patients in association with heavy use of tobacco and alcohol, head and neck cancers are slowly declining globally, in part because of decreased use of tobacco.[3,4]

Conversely, cases of HPV-associated oropharyngeal cancer, induced primarily by HPV type 16, are increasing, predominantly among younger people in North America and northern Europe, reflecting a latency of 10 to 30 years after oral-sex exposure.[4,5] The fraction of head and neck cancers diagnosed as HPV-positive oropharyngeal cancers in the United States rose from 16.3% in the 1980s to more than 72.7% in the 2000s as a result of increased awareness, identification of the association between HPV and cancers of the head and neck, and enhanced diagnostic evaluation for HPV.[6] The effectiveness of prophylactic HPV vaccination is less well defined for oropharyngeal cancer than for anogenital and cervical can-

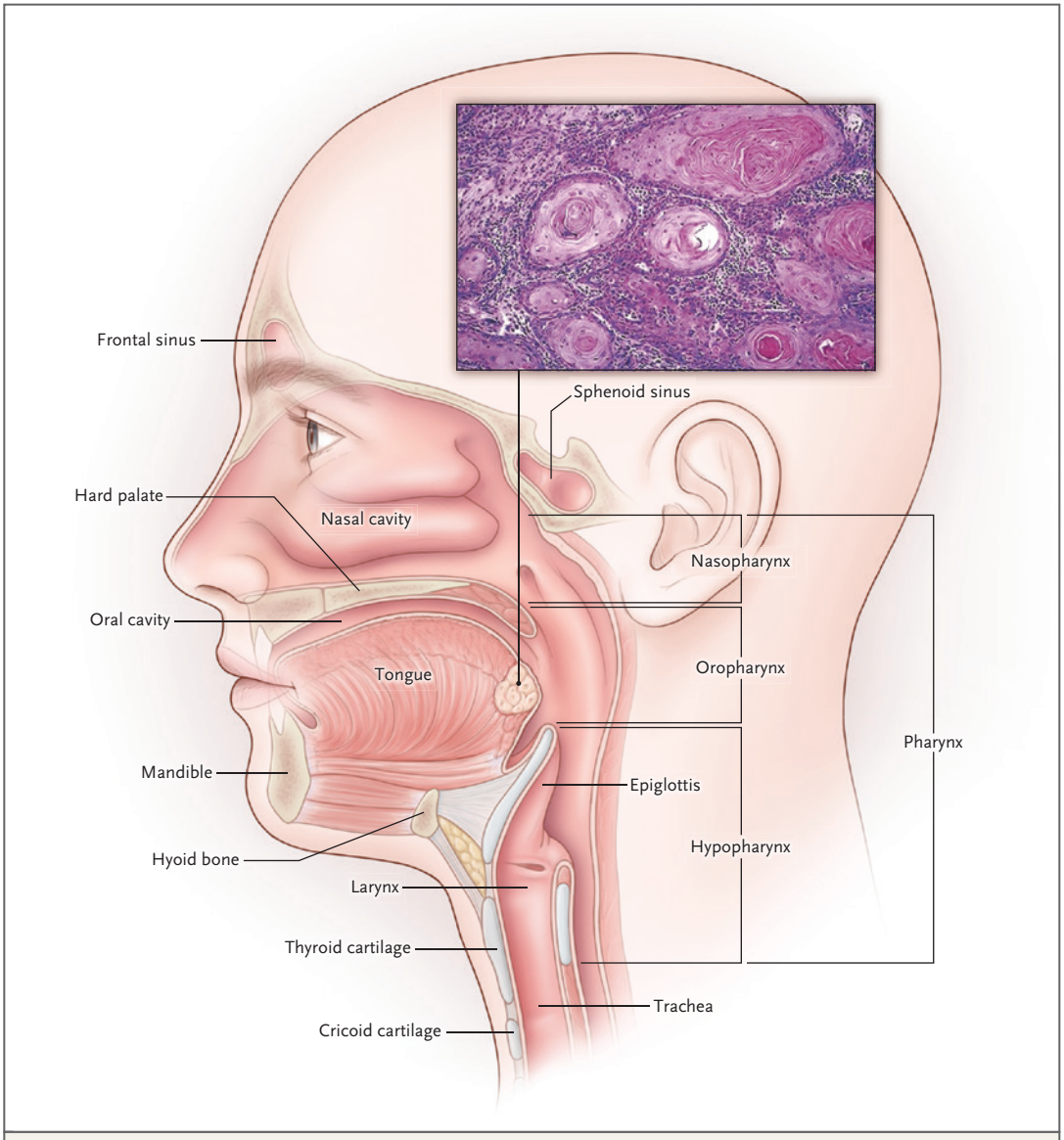

Figure 1. Major Anatomical Sites of Squamous-Cell Carcinoma of the Head and Neck.

The oral cavity includes the lips, buccal mucosa, anterior tongue, floor of the mouth, hard palate, upper and lower gingiva, and retromolar trigone. The pharynx includes the nasopharynx (behind the nasal cavity), oropharynx (comprising the tonsillar area, tongue base, soft palate, and posterior pharyngeal wall), and hypopharynx (comprising the pyriform sinuses, posterior surface of the larynx and postcricoid area, and inferior posterior and inferolateral pharyngeal walls). The larynx includes the supraglottic larynx, glottic larynx (true vocal cords and anterior and posterior commissures), and subglottic larynx. The nasal cavity and paranasal sinuses include the maxillary, ethmoid, sphenoid, and frontal sinuses. The inset shows the typical histologic features of squamous-cell carcinoma that can be seen in head and neck cancer.

cers. Nevertheless, a decreased incidence is expected but may not be evident until after 2060.[5] The prognosis is more favorable for patients with HPV-positive oropharyngeal cancer, who tend to have better responses to chemotherapy and radiotherapy and are generally more fit, with fewer coexisting conditions, than patients with HPV-negative disease, who are often compromised physiologically by chronic tobacco and alcohol use.[6] Furthermore, improved radiother-

apy delivery and the introduction of concurrent radiosensitizing systemic therapy and definitive radiotherapy (chemoradiotherapy) have improved survival among patients with head and neck cancer and especially those with HPV-associated oropharyngeal cancer.[6]

DIAGNOSIS

After a thorough history has been taken and a physical examination has been performed, radiologic imaging ideally should be performed before large biopsy specimens are obtained, to avoid possible biopsy-induced anatomical distortion or biopsy-induced false positive results on positron-emission tomography. Fine-needle aspiration biopsy is highly sensitive, specific, and accurate for the initial histologic diagnosis.[7] If cervical-node biopsy is needed, complete nodal resection is preferable to prevent extracapsular metastatic spread and tumor spillage, which would require more radical treatment.[8]

STAGING

The American Joint Committee on Cancer (AJCC) uses the TNM (tumor, node, metastasis) staging system, along with the Union for International Cancer Control (UICC) system, to classify disease and determine therapy for head and neck squamous-cell cancer.[9] Staging differs at each anatomical site. Generally, early stages (I and II) involve smaller tumors without prominent lymph-node involvement. Later stages (III and IV) are characterized by locally advanced disease and invasion of surrounding structures or an increased number of involved lymph nodes, with distant metastatic spread also defining stage IV.

Oropharyngeal cancer staging requires an assessment of HPV status, which involves in situ hybridization or polymerase-chain-reaction techniques for determining HPV DNA or the viral load, or immunohistochemical testing to detect p16 expression, which is a surrogate marker for HPV positivity. The association between the results of p16 testing and survival is similar to the association between the results of other HPV detection methods and survival.[10] Early-phase trials of immunotherapy with pembrolizumab in patients with advanced head and neck cancer confirmed that there is good diagnostic concordance (81.5%) between p16 immunohistochemical testing and whole-exome sequencing for HPV-associated disease in the oropharynx.[11] In the Radiation Therapy Oncology Group (RTOG) 0129 trial, patients with locally advanced squamous-cell carcinoma of the head and neck were randomly assigned to accelerated or standard fractionated radiotherapy with cisplatin. The study showed that patients with HPV-associated (p16-positive) oropharyngeal cancer were younger, were more likely to be white, and had fewer smoking pack-years, smaller primary tumors, and significantly better outcomes than patients with HPV-negative disease, as well as a higher 8-year overall survival rate (70.9% vs. 30.2%; hazard ratio, 0.30; 95% confidence interval [CI], 0.21 to 0.42; $P<0.001$).[12]

In 2017, the AJCC and the UICC introduced a separate staging system for patients with HPV-positive oropharyngeal carcinoma, in recognition of the improved prognosis for this subgroup (Tables 1 and 2).[9,13] The International Collaboration on Oropharyngeal Network for Staging (ICON-S), using p16 as a marker for HPV-positive disease, validated the differences in prognosis for 1907 patients with HPV-positive oropharyngeal carcinoma according to the new prognostic staging criteria (8th edition, effective as of 2017), as compared with the previous staging system (7th edition, which became effective in 2010).[14,15] The 5-year overall survival rates for HPV-positive oropharyngeal cancer were similar for stages I, II, III, and IVA but were significantly lower for stage IVB. Survival did not differ significantly between patients with T4a tumors and those with T4b tumors, and survival did not differ significantly among patients with N0; N1, N2, or N2a; or N2b nodal subsets. However, survival was reduced among patients with N3 nodal disease. The 7th edition of the staging classification did not differentiate on the basis of HPV status for patients with oropharyngeal cancer, and so the prognosis was shown as worsening with each stage of disease, from stage I through stage IVB.[14,15] That staging system was thought to reflect the prognosis predominantly for HPV-negative disease; therefore, incorporation of the ICON-S findings in the 8th edition of the AJCC–UICC staging manual re-

Table 1. Tumor–Node–Metastasis Classification of Human Papillomavirus (HPV)–Positive and HPV-Negative Oropharyngeal Cancer.*

Classification	HPV-Positive Oropharyngeal Cancer	HPV-Negative Oropharyngeal Cancer
Tumor		
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed
Tis	Carcinoma in situ	Carcinoma in situ
T0	No tumor identified	No tumor identified
T1	Tumor <2 cm in greatest dimension	Tumor <2 cm in greatest dimension
T2	Tumor >2 cm but <4 cm in greatest dimension	Tumor >2 cm but <4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid muscle, hard palate or mandible, or beyond†	
T4a		Moderately advanced local disease; tumor invades larynx, extrinsic muscle of tongue, medial pterygoid muscle, hard palate, or mandible†
T4b		Very advanced local disease; tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Node		
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph-node metastases	No regional lymph-node metastases
N1	Metastases to 1 or more ipsilateral lymph nodes, none >6 cm in greatest dimension	Metastasis to a single ipsilateral lymph node, ≤3 cm in greatest dimension, without extranodal extension
N2	Metastases to contralateral or bilateral lymph nodes, none >6 cm in greatest dimension	
N2a		Metastasis to a single ipsilateral node, >3 cm but <6 cm in greatest dimension, without extranodal extension
N2b		Metastases to multiple ipsilateral lymph nodes, none >6 cm in greatest dimension, without extranodal extension
N2c		Metastases to bilateral or contralateral lymph nodes, none >6 cm in greatest dimension, without extranodal extension
N3	Metastases to one or more lymph nodes, >6 cm in greatest dimension	
N3a		Metastasis to a lymph node, >6 cm in greatest dimension, without extranodal extension
N3b		Metastases to one or more lymph nodes, with clinically overt extranodal extension
Metastasis		
M0	No distant metastases	No distant metastases
M1	Distant metastases	Distant metastases

* Shown is the tumor–node–metastasis (TNM) classification of oropharyngeal tumors issued by the American Joint Commission on Cancer and the Union for International Cancer Control, 8th edition.[9,13]

† Mucosal extension of primary tumors of the base of the tongue and vallecula to the lingual surface of the epiglottis does not constitute invasion of the larynx.

Table 2. Prognostic Stages According to the TNM Classification.*

Stage	HPV-Positive Oropharyngeal Cancer			HPV-Negative Oropharyngeal Cancer		
	Tumor	Node	Metastasis	Tumor	Node	Metastasis
0	Tis	N0	M0	Tis	N0	M0
I	T0, T1, or T2	N0 or N1	M0	T1	N0	M0
II	T0, T1, or T2	N2	M0	T2	N0	M0
	T3	N0, N1, or N2	M0			
III	T0, T1, T2, T3, or T4	N3	M0	T1, T2, or T3	N1	M0
	T4	N0, N1, N2, or N3	M0			
IV	Any T	Any N	M1			
IVA				T4a	N0 or N1	M0
				T1, T2, T3, or T4a	N2	M0
IVB				Any T	N3	M0
				T4b	Any N	M0
IVC				Any T	Any N	M1

* Shown is the classification of prognostic stages issued by the American Joint Commission on Cancer and the Union for International Cancer Control, 8th edition.[9,13] Tis denotes tumor in situ.

sulted in a relative downstaging of HPV-positive disease (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).[9,13]

TREATMENT

Evaluation by a multispecialty team is very important in the choice of treatment for head and neck squamous-cell carcinoma, since treatment differs according to the stage of disease, anatomical site, and surgical accessibility. High-volume centers with expertise in specialized multidisciplinary treatment of patients with head and neck cancers are associated with better outcomes and increased survival.[16] Structural and functional preservation, amelioration of morbidity when feasible, and long-term maintenance of quality of life require multidisciplinary care encompassing surgery, radiotherapy, and medical oncology, with support from dental, nutritional, and speech and language services, as well as audiometry, occupational and physical therapy, and psychosocial services.

HPV-ASSOCIATED DISEASE

Current data are insufficient to recommend changes in treatment or less-intensive treatment for HPV-associated disease on the basis of HPV positivity or to comment on HPV status outside the oropharynx.[17] Moreover, decreasing treatment with downstaging may be detrimental to outcomes. A retrospective analysis of data in the National Cancer Database for 4443 patients with HPV-positive oropharyngeal cancer showed that stratification into disease stage groups (according to the 8th edition of the AJCC–UICC staging manual) for treatment purposes resulted in undertreatment and worse outcomes.[18] Patients with stage I disease who received definitive radiotherapy alone had reduced survival, as compared with patients undergoing chemoradiotherapy, surgery with adjuvant radiotherapy, or surgery with adjuvant chemoradiotherapy. Patients with stage II disease who were treated with surgery alone or radiotherapy alone had poorer survival than those treated with chemoradiotherapy. Patients with stage III disease who received chemoradiotherapy alone had worse survival than those treated with upfront surgery followed by chemoradiotherapy.[18]

Since patients with locally advanced HPV-positive oropharyngeal carcinoma have long-term survival rates as high as 80%, morbidity and quality of life are major concerns.[6,19] Ongoing research seeks to define lower-risk subgroups, reassess risk factors, and evaluate a reduction in treatment intensity or modification of systemic therapy to decrease short-term and long-term

toxic effects (Table S1 in the Supplementary Appendix). Upfront surgery may allow for a reduction in the total radiotherapy, potentially reducing late toxic effects. Case studies and prospective trials involving patient populations with locally advanced oropharyngeal cancer and a high predominance of HPV-positive status (>90%) have shown that transoral robotic surgery and transoral laser microsurgery are feasible and allow adequate visualization with good functional results and survival.[20,21] Early-phase trials suggest that selectively decreasing the radiation dose (e.g., the E1308 trial)[22] or dose and volume (e.g., the OPTIMA trial)[23] in patients with a response to induction chemotherapy may be a promising approach to reducing toxic effects while maintaining overall survival.

EARLY-STAGE DISEASE

Approximately 30 to 40% of patients present with stage I or II disease, which is curable with surgery alone or definitive radiotherapy alone. Surgery alone and radiotherapy alone can provide similar oncologic control and improved long-term survival rates in approximately 70 to 90% of patients with early-stage disease.[24] The choice of treatment depends on anatomical accessibility, with efforts to minimize morbidity and preserve function (see the interactive graphic, available at NEJM.org, as well as a detailed discussion of treatment options, available in the Supplementary Appendix).

Newer techniques of robotic surgery for oropharyngeal cancer[25] and minimally invasive laser microsurgery for laryngeal and hypopharyngeal cancers[26] may increase the likelihood of preserving function, whereas advances in conformal radiotherapy techniques such as intensity-modulated and image-guided radiotherapy may reduce morbidity.[27] Since oral-cavity cancers are easily accessible transorally, surgery is the treatment of choice for such cancers and is associated with high cure rates and reduced morbidity.[28,29] Oropharyngeal cancers may be managed with primary surgery or radiotherapy,[28,30] whereas radiotherapy has an established role in laryngeal preservation for patients with laryngeal cancer.[28] Surgery is preferred for paranasal sinus cancers.[28] At all sites, lymphatic drainage of the primary site and the risk of occult metastatic spread guide decisions regarding additional therapy (Fig. 2).

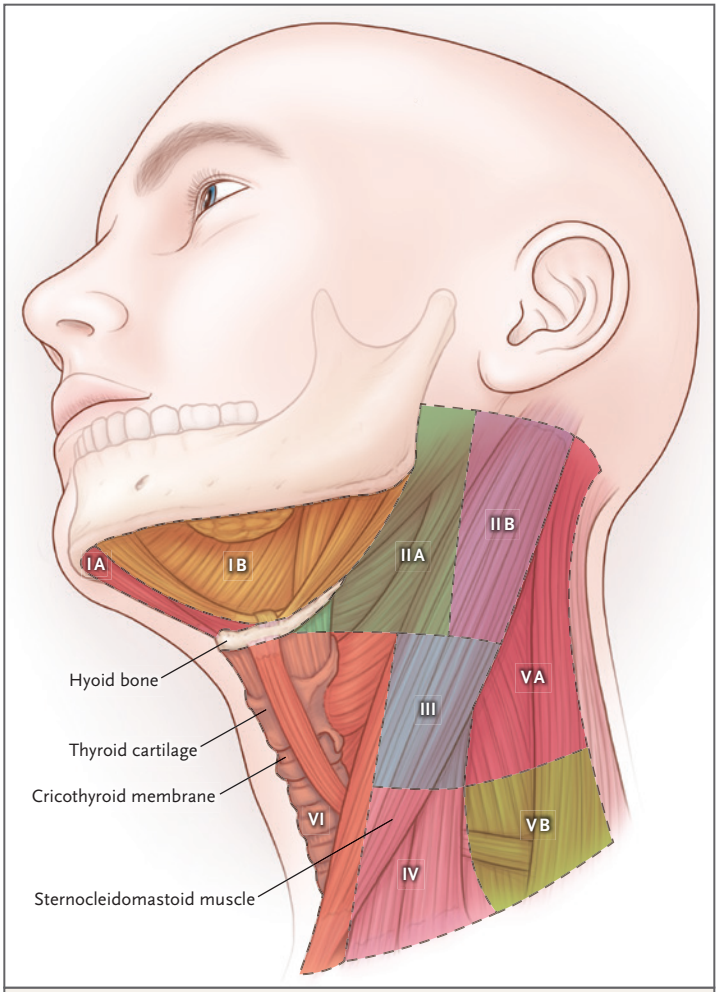

Figure 2. Lymph-Node Stations in the Neck.
Lymph nodes in the neck have historically been divided into anatomical levels (stations) by surgeons and pathologists for the purpose of staging head and neck cancer and planning therapy. Head and neck cancer commonly metastasizes to cervical lymph nodes. The presence and sites of nodal metastases can greatly affect the treatment and prognosis.

Selective neck dissection (i.e., limited removal of cervical lymph nodes), elective neck dissection with more extensive removal of nodes, or prophylactic neck radiotherapy decreases the risk of recurrence and spread to ipsilateral or bilateral nodal sites, with treatment tailored to the site of the primary cancer.[28]

An interactive graphic showing treatment options is available at NEJM.org

LOCALLY ADVANCED DISEASE

More than 60% of patients with squamous-cell cancer of the head and neck present with stage III or IV disease, which is characterized by large

tumors with marked local invasion, evidence of metastases to regional nodes, or both. Locally advanced disease carries a high risk of local recurrence (15 to 40%) and distant metastasis, with a poor prognosis (5-year overall survival, <50%).[31] Multimodal approaches have steadily improved cure rates during the past two decades, while striving to preserve function and quality of life.[32] Curative goals need to be individualized, and the choice of initial therapy, sequencing, and administration of therapy involves expertise in the complex consideration of morbidity, toxic effects, and preservation of function (Table S2 and interactive graphic). Decisions regarding therapy also depend strongly on the size and anatomical site of the primary cancer, stage of disease, age of the patient, patient preferences, performance status, and coexisting conditions.

Surgical resection is preferred for cancer of the oral cavity, in conjunction with elective neck dissection, followed by adjuvant radiotherapy or chemoradiotherapy (depending on an assessment of high-risk features). At other sites, surgery is usually reserved for smaller, accessible primary tumors. Surgery may also be considered in patients with resectable tumors who have poor responses after induction chemotherapy; salvage surgery can also be considered for persistent or recurrent disease in either the primary site or the regional lymph nodes after definitive chemoradiotherapy. When surgical resection is less feasible or would result in poor long-term functional outcomes, chemoradiotherapy is the curative standard of care established by the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study. This study, which originally involved 17,346 patients with resectable or unresectable, locally advanced squamous-cell carcinoma of the head and neck, was updated to involve 19,248 patients and confirmed that the addition of concomitant chemotherapy with radiotherapy showed an absolute decrease in 5-year mortality of 6.5 percentage points (hazard ratio for death, 0.83; 95% CI, 0.79 to 0.87; P<0.001) and decreased locoregional failure rates with chemoradiotherapy as compared with local therapy alone. The addition of induction or adjuvant chemotherapy did not significantly improve overall survival, as compared with local therapy alone.[33,34]

The landmark RTOG 91-11 trial established concurrent chemoradiotherapy for locoregional control and organ preservation in patients with resectable stage III or IV glottic or supraglottic disease.[35] Improved survival when chemotherapy was added to locoregional therapy was supported by the tumor-site–specific MACH-NC analysis.[36] Chemoradiotherapy is preferred for patients with good performance status who have advanced laryngeal or hypopharyngeal cancer without cartilage involvement, whereas salvage laryngectomy is reserved for patients with recurrent or persistent disease or severe functional impairment.

Oropharyngeal cancer requires close multidisciplinary evaluation and collaboration. There are limited data from randomized, prospective studies to guide decisions regarding advanced surgical techniques with adjuvant therapy versus primary chemoradiotherapy. Surgery for T3 or T4 tumors commonly includes prophylactic selective neck dissection (i.e., removal of involved cervical lymph nodes and those at high risk for metastatic involvement) or more extensive elective neck dissection, given the high rates of occult metastases.[30,37] Alternatively, chemoradiotherapy provides excellent locoregional control of more advanced primary tumors.[28,35,38]

DEFINITIVE CONCURRENT CHEMORADIOTHERAPY

High-dose cisplatin (100 mg per square meter of body-surface area, administered intravenously every 21 days for three cycles), given concurrently with radiotherapy as part of a definitive chemoradiotherapy regimen, is the standard of care, with established survival benefits for patients with good performance status; however, because of the substantial short- and long-term toxic effects associated with cisplatin, its use is predominantly reserved for nonelderly patients who have no major coexisting conditions.[28,33,38] For less fit patients and patients in whom high-dose cisplatin is associated with unacceptable adverse effects, alternative systemic therapies have not yet been elucidated but are being investigated. Although data from retrospective and early prospective studies suggest that there are fewer adverse effects associated with low-dose weekly cisplatin,[39] a phase 3 randomized trial showed worse local control with low-dose cisplatin than with high-dose cisplatin, both adminis-

tered concurrently with radiotherapy, without significant differences in survival.[40] Since the majority of patients enrolled in this study had cancer of the oral cavity and were receiving adjuvant chemoradiotherapy, the results do not extrapolate well to definitive treatment or to other disease sites.[40] Carboplatin is commonly substituted for cisplatin in patients with coexisting conditions such as renal impairment, but it is less effective than high-dose cisplatin for definitive therapy.[41] The epidermal growth factor receptor antibody cetuximab, administered concurrently with radiotherapy, became an approved standard therapy in 2006 on the basis of data showing that this regimen provided improvements in locoregional control and overall survival, as compared with radiotherapy alone[42]; however, radiotherapy alone is no longer standard care. In fact, recent randomized trials have shown worse outcomes, including decreased survival, with concurrent cetuximab and radiotherapy in patients with HPV-positive oropharyngeal cancer, in a direct comparison with high-dose cisplatin combined with radiotherapy.[43,44]

Neither intensifying the radiation doses nor accelerating fractionation schedules has yet been shown to improve outcomes, as compared with conventional fractionated, intensity-modulated, and imaging-guided radiotherapy administered concurrently with chemotherapy.[12,45-47] Advances in radiotherapy with specialized approaches, such as proton therapy and intensity-modulated proton therapy, may improve the therapeutic ratio and tumor–dose distribution while decreasing the toxic effects on normal tissue.[48] This potential to decrease radiation-related morbidity is of great interest, particularly for patients with HPV-positive oropharyngeal cancer, many of whom are successfully cured but have long-term consequences of therapy.[48] Studies are ongoing, and prospective trials comparing effectiveness and cost-effectiveness of new techniques are needed.

INDUCTION CHEMOTHERAPY BEFORE CHEMORADIOTHERAPY

Data on the use of induction chemotherapy followed by chemoradiotherapy are conflicting and remain controversial. Taxane-based induction chemotherapy in the TAX 324 and European Organization for Research and Treatment of Cancer [EORTC] 24971/TAX 323 trials improved survival, as compared with non–taxane-based regimens, but with higher toxic effects that required treatment delays.[49-51] Conversely, taxane-based induction in the PARADIGM and DECIDE studies did not improve survival, as compared with chemoradiotherapy alone, but were underpowered.[52-54] Data from meta-analyses support taxane-based induction regimens, showing that such regimens significantly decrease locoregional relapse and death rates, as compared with non–taxane-based regimens. However, differences in trial design, treatment intensity, chemotherapeutic regimens, cycles of therapy, incidence of HPV-positive oropharyngeal cancer, and patient populations limit the conclusions that can be drawn about the use of induction therapy before chemoradiotherapy.[55,56] Furthermore, toxic effects prevent 20 to 30% of patients who are undergoing induction chemotherapy from completing subsequent chemoradiotherapy, which is critical for maximizing locoregional control and overall survival.[49,50,54,56] Induction chemotherapy may best be reserved for patients who are at high risk for locoregional relapse and distant metastases, patients for whom induction chemotherapy is likely to be associated with acceptable adverse-event rates, or patients in whom symptomatic, locally advanced disease prevents adequate delivery of up-front curative chemoradiotherapy.

ADJUVANT THERAPY

For postoperative treatment, the EORTC 22931 and the RTOG 9501 trials established adjuvant chemoradiotherapy with high-dose cisplatin and conventional fractionation radiotherapy (60 to 66 Gy) as the standard of care in high-risk patients with squamous-cell carcinoma of the head and neck.[57-59] The EORTC 22931 trial defined high-risk patients as those with T3 or T4 disease, positive surgical margins, extranodal spread, perineural or lymphovascular invasion, or vascular tumor embolism, or those with oral-cavity or oropharyngeal tumors with level IV or V nodes. The trial showed that chemoradiotherapy improved progression-free survival, locoregional control, and overall survival, as compared with radiotherapy alone, among these high-risk patients.[57,58] The RTOG 9501 trial defined high-risk patients as patients with positive surgical mar-

gins, two or more involved regional nodes, or extranodal extension.[59] An analysis at a median of 46 months of follow-up showed that chemoradiotherapy improved locoregional control and disease-free survival but not overall survival, as compared with radiotherapy alone, among these high-risk patients[59]; however, these improvements were no longer evident at a median follow-up of 9.4 years.[60] Despite differences in patient populations and outcomes in these two studies, a comparative analysis of pooled data from the studies supports the consensus that chemoradiotherapy benefits only patients with extranodal extension or positive surgical margins.[28,57] Research aimed at improving and better defining adjuvant therapy is ongoing.

RECURRENT OR METASTATIC DISEASE

Despite advances in diagnosis and treatment, recurrent or metastatic disease (or both) develops in more than 65% of patients with squamous-cell cancer of the head and neck.[61] Locally recurrent disease that cannot be treated with salvage surgery, radiotherapy, or a combination of the two has a dismal prognosis, which is similar to the prognosis with distant disease (6 to 9 months in the absence of treatment).[61,62] Since previous radiotherapy (in particular, the dose and fields) and the constraints and tolerance of normal tissue limit the feasibility and success of repeat irradiation, systemic therapy with active agents (platinums, taxanes, antifolates, and cetuximab) has been the mainstay of palliation.[28] The choice of one agent or a combination of two or three agents depends on the toxic-effects profile of the drugs, performance status, coexisting conditions, frailty, age, symptoms, and the characteristics associated with prior therapy (the disease stage, specific agents used, combinations of use, response, and interval before progression). The phase 3 EXTREME (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) trial established first-line standard-of-care therapy by showing that cetuximab added to chemotherapy consisting of fluorouracil plus a platinum (cisplatin or carboplatin), as compared with chemotherapy alone, significantly improved overall survival (10.1 months vs. 7.4 months; hazard ratio for death, 0.80; 95% CI, 0.64 to 0.99; P=0.04), progression-free survival (5.6 months vs. 3.3 months), and the overall response rate (36% vs. 20%).[51,63] Unfortunately, the quality of life was less favorable because of the need for weekly administration of cetuximab which resulted in infusion reactions and skin reactions.[51]

The discovery that modulation of the immune system could cause solid tumors to regress has changed our understanding and treatment of cancer. In particular, development of the programmed death 1 (PD-1) immune-checkpoint inhibitors has greatly influenced the treatment of squamous-cell carcinoma of the head and neck. The anti–PD-1 antibodies pembrolizumab and nivolumab showed durable responses and survival improvements in platinum-treated patients with recurrent or metastatic head and neck cancer, leading to approval of these two agents by the Food and Drug Administration (FDA) in 2016.

Accelerated FDA approval of pembrolizumab was based on durable, objective responses (response rate, 16% [complete responses, 5%]; 95% CI, 11 to 22; response duration of ≥6 months, 82%) in the phase 1 KEYNOTE-012 study, in which 174 patients who had disease progression during or after receipt of platinum-containing chemotherapy were evaluated.[64-66] Approval was given pending confirmatory results from the phase 3 KEYNOTE-040 study. Longer-term follow-up (median, 9 months) confirmed the efficacy (response rate, 18%; 95% CI, 13 to 24), durability of the treatment response (≥6 months for 85% of responses), safety, and improvements in survival.[67] The phase 2 KEYNOTE-055 trial, which assessed pembrolizumab in 171 heavily pretreated patients with disease progression within 6 months after platinum and cetuximab therapy, also confirmed efficacy, response durability, and an acceptable adverse events profile.[68] KEYNOTE-040, which compared pembrolizumab with the investigator's choice of therapy (docetaxel, methotrexate, or cetuximab), narrowly missed its primary end point of improved overall survival with pembrolizumab in the intention-to-treat population (8.4 months [95% CI, 6.4 to 9.4] with pembrolizumab vs. 6.9 months [95% CI, 5.9 to 8.0] with standard of care; hazard ratio for death, 0.80; 95% CI, 0.65 to 0.98; P=0.02).[69] Since crossover immunotherapy potentially confounded the survival analyses, and since prolon-

gation of survival and an acceptable safety profile were shown, FDA approval was not withdrawn.[65,69]

FDA approval of nivolumab was based on the phase 3 CheckMate 141 trial, in which patients who were pretreated with platinum were randomly assigned in a 2:1 ratio to nivolumab or the investigator's choice of therapy. Nivolumab was associated with improvements in overall survival (7.5 months [95% CI, 5.5 to 9.1] vs. 5.1 months [95% CI, 4.0 to 6.0]; hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; P=0.01), response rate (13.3% vs. 5.8%), and 6-month progression-free survival (19.7% vs. 9.9%), as well as a lower incidence of severe adverse events (13.1% vs. 35.1%).[70] After more than 2 years of follow-up, the survival benefits (hazard ratio for death, 0.68; 95% CI, 0.54 to 0.86; 24-month overall survival, 16.9% vs. 6.0%) and decreased toxic effects were maintained for nivolumab.[71]

The robustness of programmed death ligand 1 (PD-L1) expression as a predictive biomarker is debatable because of differences in cutoff levels, antibody assays, immune-cell expression, timing, and heterogeneity. The KEYNOTE-012 and KEYNOTE-055 trials showed that the presence of PD-L1 expression (cutoff value, ≥1%) on both the tumor and the tumor-infiltrating immune cells, calculated as a combined positive score, predicted a clinical benefit with pembrolizumab.[64,66,68,72] Incorporation of PD-L1 expression on tumor-infiltrating immune cells, in addition to tumor-cell expression for the combined positive score, enhanced the ability to predict a clinical benefit with pembrolizumab.[66,72] The phase 3 KEYNOTE-040 and CheckMate 141 trials showed that the presence of PD-L1 expression on tumor cells only (tumor proportional score) predicted a greater clinical benefit and improved survival with anti–PD-1 antibody treatment, as compared with the absence of PD-L1 expression.[69,70] The KEYNOTE-040 trial showed that higher PD-L1 expression (>50%) was associated with improved survival, as compared with lower PD-L1 expression.[69] In contrast, higher expression levels did not correlate with improved survival in the CheckMate 141 trial, although the two trials used different PD-L1 assays.[70,71] These findings suggest that PD-L1 expression may help predict the clinical benefit of treatment with PD-1 immune-checkpoint inhibitors, but the absence of PD-L1 expression should not preclude therapy, since some patients with PD-L1–negative tumors may still have a benefit and other treatment options are limited in this disease setting. Analysis of combined tissue samples from the KEYNOTE-012 and KEYNOTE-055 trials for additional biomarkers showed that PD-L1 expression, T-cell inflammatory gene expression profiles, and the tumor mutational burden independently predicted a benefit from pembrolizumab treatment.[11]

These important biomarker evaluations contributed to the success and recent approval[73] of pembrolizumab as standard first-line treatment in the phase 3 KEYNOTE-048 study, which randomly assigned 882 untreated patients with recurrent or metastatic squamous-cell cancer of the head and neck to treatment with pembrolizumab alone, pembrolizumab with chemotherapy (fluorouracil and platinum), or the standard regimen of fluorouracil and platinum plus cetuximab (the regimen in the EXTREME trial).[74] Pembrolizumab monotherapy and pembrolizumab combined with chemotherapy each improved the primary end point of overall survival in patients with PD-L1–expressing tumors at combined positive-score cutoffs of 20% or higher and 1% or higher when separately compared with the EXTREME drug regimen (details are provided in the Supplementary Appendix).[74] Response rates were lower but more durable and there were fewer associated toxic effects with pembrolizumab than with the EXTREME regimen.[74] In the total PD-L1–unselected population, pembrolizumab alone did not improve survival, as compared with the EXTREME regimen, whereas pembrolizumab combined with chemotherapy did improve survival, as compared with the EXTREME regimen (13.0 months vs. 10.7 months; hazard ratio for death, 0.77; 95% CI, 0.63 to 0.93; P=0.003).[74]

Undoubtedly, PD-1–directed immune-checkpoint inhibitor therapy has transformed the lives of a small number of patients, who have durable disease remission, improved survival, or both. Unfortunately, an estimated 85 to 95% of patients with recurrent or metastatic head and neck cancer have no response to this treatment or have a response that is followed by disease progression and, ultimately, death from the disease. Many promising, innovative combinatorial approaches are being evaluated for the treatment of advanced disease, such as HPV vaccines, patient-specific vaccines, T-cell–directed thera-

pies, immunotherapy with various cytokines, oncolytic viruses, and other immune modulators with immune-checkpoint inhibitors. The use of immune-checkpoint inhibitors earlier in the disease course (i.e., neoadjuvant or perioperative treatment, concurrent definitive treatment, or adjuvant therapy) is being explored (Table S3) and will be further investigated in future trials. With increasing knowledge about head and neck cancer, improved prevention, and therapeutic advances, we are poised to see decreased incidence, reduced morbidity, increased survival, and more cures.

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