

the results indicate squamous cell carcinoma, a panendoscopy should be performed, with biopsy of all suspicious-appearing areas and directed biopsies of common primary sites, such as the nasopharynx, tonsil, tongue base, and pyriform sinus. HPV-positive tumors especially can have small primary tumors that spread early to locoregional lymph nodes.

## TREATMENT HEAD AND NECK CANCER

Patients with head and neck cancer can be grossly categorized into three clinical groups: those with localized disease, those with locally or regionally advanced disease (lymph node positive), and those with recurrent and/or metastatic disease. Comorbidities associated with tobacco and alcohol abuse can affect treatment outcome and define long-term risks for patients who are cured of their disease.

### LOCALIZED DISEASE

Nearly one-third of patients have localized disease, that is, T1 or T2 (stage I or stage II) lesions without detectable lymph node involvement or distant metastases. These patients are treated with curative intent by either surgery or radiation therapy. The choice of modality differs according to anatomic location and institutional expertise. Radiation therapy is often preferred for laryngeal cancer to preserve voice function, and surgery is preferred for small lesions in the oral cavity to avoid the long-term complications of radiation, such as xerostomia and dental decay. Overall 5-year survival is 60–90%. Most recurrences occur within the first 2 years following diagnosis and are usually local.

### LOCALLY OR REGIONALLY ADVANCED DISEASE

Locally or regionally advanced disease—disease with a large primary tumor and/or lymph node metastases—is the stage of presentation for >50% of patients. Such patients can also be treated with curative intent, but not with surgery or radiation therapy alone. Combined-modality therapy including surgery, radiation therapy, and chemotherapy is most successful. It can be administered as induction chemotherapy (chemotherapy before surgery and/or radiotherapy) or as concomitant (simultaneous) chemotherapy and radiation therapy. The latter is currently most commonly used and supported by the best evidence. Five-year survival rates exceed 50% in many trials, but part of this increased survival may be due to an increasing fraction of study populations with HPV-related tumors who carry a better prognosis. HPV testing of newly diagnosed tumors is now performed for most patients at the time of diagnosis, and clinical trials for HPV-related tumors are focused on exploring reductions in treatment intensity, especially radiation dose, in order to ameliorate long-term toxicities (fibrosis, swallowing dysfunction).

In patients with intermediate-stage tumors (stage III and early stage IV), concomitant chemoradiotherapy can be administered either as a primary treatment for patients with unresectable disease, to pursue an organ-preserving approach, or in the postoperative setting for intermediate-stage resectable tumors.

**Induction Chemotherapy** In this strategy, patients receive chemotherapy (current standard is a three-drug regimen of docetaxel, cisplatin, and fluorouracil [5-FU]) before surgery and radiation therapy. Most patients who receive three cycles show tumor reduction, and the response is clinically “complete” in up to half of patients. This “sequential” multimodality therapy allows for organ preservation (omission of surgery) in patients with laryngeal and hypopharyngeal cancer, and it has been shown to result in higher cure rates compared with radiotherapy alone.

**Concomitant Chemoradiotherapy** With the concomitant strategy, chemotherapy and radiation therapy are given simultaneously rather than in sequence. Tumor recurrences from head and neck cancer develop most commonly locoregionally (in the head and neck area of the primary and draining lymph nodes). The concomitant approach is aimed at enhancing tumor cell killing by radiation therapy in the presence of chemotherapy (radiation enhancement)

and is a conceptually attractive approach for bulky tumors. Toxicity (especially mucositis, grade 3 or 4 in 70–80%) is increased with concomitant chemoradiotherapy. However, meta-analyses of randomized trials document an improvement in 5-year survival of 8% with concomitant chemotherapy and radiation therapy. Results seem more favorable in recent trials as more active drugs or more intensive radiotherapy schedules are used. In addition, concomitant chemoradiotherapy produces better laryngectomy-free survival (organ preservation) than radiation therapy alone in patients with advanced larynx cancer. The use of radiation therapy together with cisplatin has also produced improved survival in patients with advanced nasopharyngeal cancer. The outcome of HPV-related cancers seems to be especially favorable following cisplatin-based chemoradiotherapy.

The success of concomitant chemoradiotherapy in patients with unresectable disease has led to the testing of a similar approach in patients with resected intermediate-stage disease as a postoperative therapy. Concomitant chemoradiotherapy produces a significant improvement over postoperative radiation therapy alone for patients whose tumors demonstrate higher risk features, such as extracapsular spread beyond involved lymph nodes, involvement of multiple lymph nodes, or positive margins at the primary site following surgery.

A monoclonal antibody to EGFR (cetuximab) increases survival rates when administered during radiotherapy. EGFR blockade results in radiation sensitization and has milder systemic side effects than traditional chemotherapy agents, although an acneiform skin rash is commonly observed. Nevertheless, the integration of cetuximab into current standard chemoradiotherapy regimens has failed to show additional improvement in survival and is not recommended.

### RECURRENT AND/OR METASTATIC DISEASE

Five to ten percent of patients present with metastatic disease, and 30–50% of patients with locoregionally advanced disease experience recurrence, frequently outside the head and neck region. Patients with recurrent and/or metastatic disease are, with few exceptions, treated with palliative intent. Some patients may require local or regional radiation therapy for pain control, but most are given chemotherapy. Response rates to chemotherapy average only 30–50%; the durations of response are short, and the median survival time is 8–10 months. Therefore, chemotherapy provides transient symptomatic benefit. Drugs with single-agent activity in this setting include methotrexate, 5-FU, cisplatin, paclitaxel, and docetaxel. Combinations of cisplatin with 5-FU, carboplatin with 5-FU, and cisplatin or carboplatin with paclitaxel or docetaxel are frequently used.

EGFR-directed therapies, including monoclonal antibodies (e.g., cetuximab) and tyrosine kinase inhibitors (TKIs) of the EGFR signaling pathway (e.g., erlotinib or gefitinib), have single-agent activity of approximately 10%. Side effects are usually limited to an acneiform rash and diarrhea (for the TKIs). The addition of cetuximab to standard combination chemotherapy with cisplatin or carboplatin and 5-FU was shown to result in a significant increase in median survival. Drugs targeting specific mutations are under investigation, but no such strategy has yet been shown to be feasible in head and neck cancer.

### COMPLICATIONS

Complications from treatment of head and neck cancer are usually correlated to the extent of surgery and exposure of normal tissue structures to radiation. Currently, the extent of surgery has been limited or completely replaced by chemotherapy and radiation therapy as the primary approach. Acute complications of radiation include mucositis and dysphagia. Long-term complications include xerostomia, loss of taste, decreased tongue mobility, second malignancies, dysphagia, and neck fibrosis. The complications of chemotherapy vary with the regimen used but usually include myelosuppression, mucositis, nausea and vomiting, and nephrotoxicity (with cisplatin).