Carcinoma/Undifferentiated Tumor

10

Jennifer W. Mack

Introduction

Squamous cell carcinomas of the head and neck, including carcinomas of the lip, oral cavity, oropharynx, hypopharynx, larynx, and sinus, are common malignancies among adults, often associated with tobacco and alcohol use. However, these tumors are exceedingly rare in children. When they do occur in the pediatric age group, predisposing factors such as Fanconi anemia must be considered. Outcomes appear similar to those in adults, and the mainstay of treatment is aggressive local control, with chemotherapy reserved for special pathologic risk factors and advanced disease.

Key Points

- Squamous cell carcinomas of the head and neck are rare in children, and management, therefore, relies on established treatment strategies in adults.
- Early-stage disease can generally be treated with either surgery or radiation; choice of modality depends on resectability as well as expected functional outcome.
- For patients with advanced disease, chemotherapy improves outcomes over local control alone.
- Especially after radiation therapy, children tend to experience significant acute toxicity and late effects.

Biology and Epidemiology

Squamous cell carcinomas originate in the squamous epithelium that lines the mucosal surfaces of the head and neck. They are classified according to the organ of origination. Oral cavity cancer originates from the lips, anterior two-thirds of the tongue, the buccal and gingival mucosae, the floor of the mouth, and the hard palate. Oropharygeal cancer arises from the soft palate, base of tongue, and tonsils. Additional anatomic locations include the hypopharynx, the larynx, the paranasal sinuses, and the nasal cavity.

Adult squamous cell carcinomas are relatively common, accounting for about 3 % of all cancers in the USA or about 50,000 new incident cancers per year [1], and are frequently associated with smoking and alcohol use. However, these tumors are extremely rare in children. Their presence in childhood should raise the question of predisposing factors. DNA repair defects such as Fanconi anemia [2], Bloom syndrome, ataxia telangiectasia, and dyskeratosis congenita should be considered, as well as xeroderma pigmentosum [3–5]. Even children without characteristic morphologic features of Fanconi anemia should have consideration of appropriate testing, given the frequent use of radiation in treatment of head and neck tumors, and its potential toxicity in this disease [2]. In addition, Li-Fraumeni syndrome, an inherited defect of *TP53*, is associated with squamous cell carcinomas of the larynx [3, 5]. A careful family history may be suggestive, but because not all affected patients have a positive family history, genetic testing may be indicated.

Aside from genetic factors, pediatric cancer survivors, especially those with a history of prior irradiation of the head and neck, are also at risk for developing squamous cell cancers [6]. Oral carcinomas have also been noted in patients with a history of allogeneic bone marrow transplantation and oral graft-versus-host disease [7–9], in which chronic mucosal injury and repair may create a cycle not unlike that seen in adult users of tobacco.

In addition, the human papilloma virus (HPV) has been implicated in squamous cell carcinomas [10, 11], especially

J. W. Mack (✉)
Dana-Farber Cancer Institute, Boston, MA, USA

Department of Pediatric Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
e-mail: Jennifer_mack@dfci.harvard.edu

R. Rahbar et al. (eds.), *Pediatric Head and Neck Tumors,*
DOI 10.1007/978-1-4614-8755-5_10,

oropharyngeal cancers originating from the tonsils and base of tongue. HPV-16 appears to be the subtype that is most commonly involved and is believed to have a role in oncogenesis [10, 11]. The incidence of HPV-associated oropharyngeal cancers is increasing [12], although increasing vaccination rates of children may halt that rise in young people. The existence of HPV infection confers a favorable prognosis and may therefore have implications for treatment [13].

Finally, midline carcinomas with the BRD-NUT translocation t(15;19) have been described in young people and tend to have a highly aggressive course (see also the chapter on nasopharyngeal carcinomas) [14, 15]. Consideration of this entity and evaluation for the translocation should take place in children with midline squamous cell carcinomas.

Presentation

Signs and symptoms of squamous cell carcinomas of the head and neck depend on the tissue of origination. However, oral lesions frequently present as a nonhealing mucosal ulcer, pain or bleeding in the mouth, or mucosal erythema or leukoplakia (Fig. 10.1a). Pharyngeal and laryngeal lesions may present as dysphagia, otalgia, or hoarseness. Nasal and sinonasal lesions commonly present as nasal obstruction, epistaxis, rhinorrhea, chronic sinusitis, or headaches. In addition, a solitary neck mass or bilateral cervical enlargement, evident because of involved regional lymph nodes, is a common presentation with each of these cancers.

Diagnosis and Evaluation

Unfortunately, because of the rarity of these tumors in children, it is not uncommon for patients to come to attention after incomplete resection of what was felt to be a benign lesion. However, such procedures can create greater challenges for local control in the future, and initial resection through tumor is associated with a poorer prognosis [16]. Therefore, whenever possible, initial nasal or oral endoscopy can offer opportunity for biopsy under direct visualization. Careful examination can also help to define the extent of disease. If necessary, the diagnosis can also be made using biopsy of involved cervical lymph nodes in the presence of an identified mucosal lesion.

Imaging studies should include visualization of the primary tumor and nodal areas, including anterior cervical, posterior cervical, and retropharyngeal nodes. Both head and neck magnetic resonance imaging (MRI), for optimal soft tissue involvement, and computed tomography (CT), for evaluation of bony structures and identification of tumor erosion into bones, are indicated. A positron emission tomography (PET) scan should be performed to evaluate for regional and distant disease, and can help to identify involved lymph nodes, although reactive lymph nodes can also be PET positive, so interpretation of results often involves clinical correlation. Finally, evaluation for distant

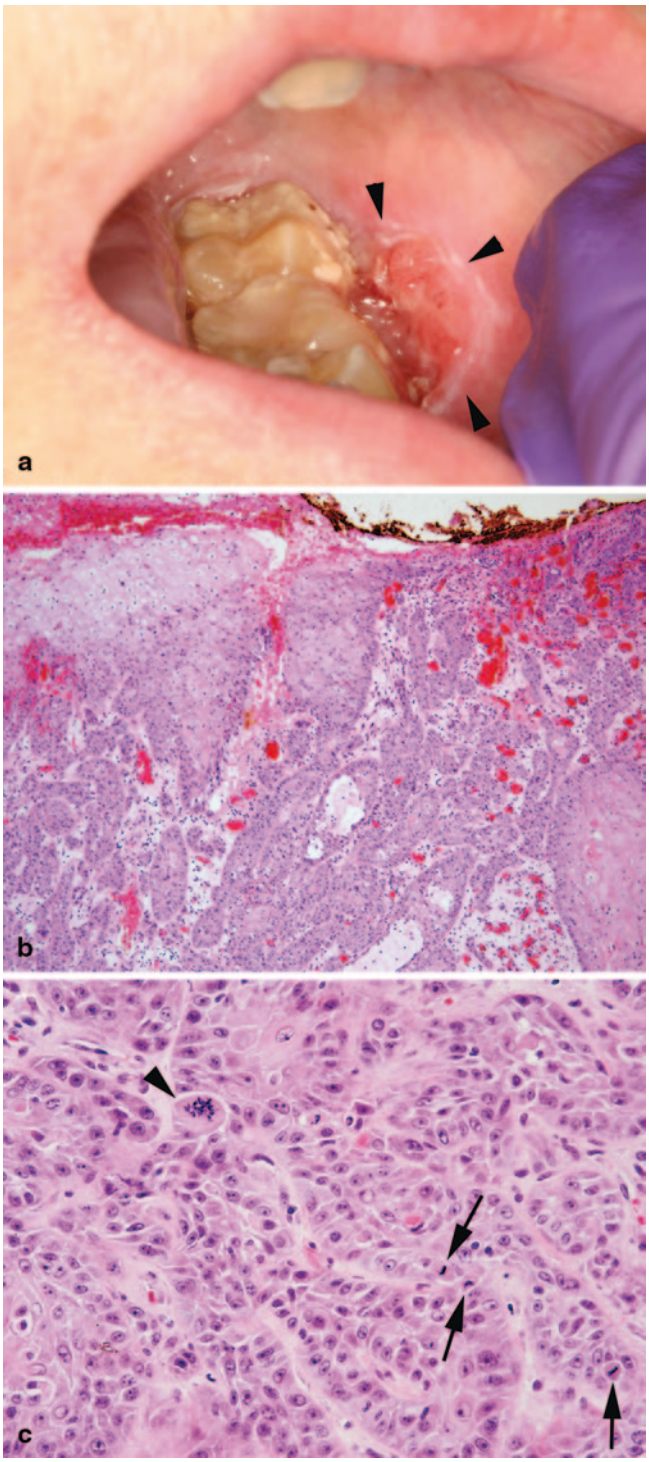

Fig. 10.1 Squamous cell carcinoma of the oral cavity. **a** Large ulceration of the gum (*between arrowheads*) with friable, necrotic surface. Posterior molars are seen to the left of the ulcer. **b** Infiltrating moderately well-differentiated squamous cell carcinoma with ulcerated surface. **c** Nests of pleomorphic, moderately differentiated squamous cells with numerous mitoses (*arrows*), some of them atypical (*arrowhead*)

disease at diagnosis should include a chest CT scan for pulmonary metastases.

Squamous cell carcinomas of the head and neck can be classified pathologically according to the Broder classification [17], which relies on differentiation:

G1 well differentiated
G2 moderately well differentiated
G3 poorly differentiated
G4 undifferentiated

Most squamous cell carcinomas are moderately or poorly differentiated (Fig. 10.1b, c); differentiation is not, however, predictive of survival [18, 19]. Pathology should also be evaluated for lymphovascular and perineural invasion as well as extracapsular lymph node spread, which are predictive of outcomes and response to therapy [20].

Staging of squamous cell carcinomas of the head and neck involves the American Joint Committe on Cancer (AJCC) staging system [21], which predicts clinical outcomes and guides therapy. Each anatomic site has a unique staging system based on the extent of the primary tumor, involvement of regional lymph nodes, and distant metastases. We provide here staging for oral cavity cancer as an illustrative example, but staging should always be based on current AJCC staging for the primary site of origin (Tables 10.1 and 10.2).

In general for squamous cell carcinomas of the head and neck, early-stage cancers are those designated as stages I and II. These tumors are small in size without deep invasion of surrounding structures, and without regional lymph node involvement or distant metastases. Advanced tumors, which are stage III and IV tumors, have significant local invasion, regional lymph nodes, and/or distant metastases. Early-stage and advanced tumors are distinct prognostically and require different treatment modalities.

Table 10.1 AJCC staging system for oral cavity squamous cell carcinoma

Value	Definition
Primary tumor (T)	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose Oral cavity: Tumor invades adjacent structures only
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery
Regional lymph nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, 3–6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 10.2 Summary staging for oral cavity cancer

Stage	T stage	N stage	M stage
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1-3	N1	M0
Stage IVA	T4a	N0-1	M0
	T1-4a	N2	M0
Stage IVB	T1-4a	N3	M0
	T4b	N0-3	M0
Stage IVC	Any T	Any N	M1

Treatment

Overview

Because of the rarity of these cancers in children and the consequent lack of clinical trials, treatment is largely based on adult regimens. This is supported by small series demonstrating similar outcomes in pediatric and adult patients with oral and tongue carcinomas [22, 23], although data in the pediatric setting remain quite limited. Special consideration should be taken of the consequences of aggressive surgery and radiation in children.

Approximately one-third of adult patients present with early-stage (stages I and II) squamous cell carcinomas, and aggressive local control confers excellent survival for most early-stage patients. Use of either surgery or radiation, depending on the resectability of the lesion, is usually sufficient. Treatment modality, including choice of radiation or surgery for local control, should be determined for each patient on an individual basis. Thus, careful discussion with a multidisciplinary team including otorhinolaryngology, oncology, and radiation oncology can offer optimal planning for individual patients before local control is attempted. When high-risk features are found at resection, adjuvant radiation or chemoradiation is recommended.

In contrast, patients with advanced (stage III and IV) disease usually require combined modality therapy, including aggressive local control and systemic chemotherapy, although the optimal sequence of these modalities is not known.

Early-Stage Disease

Because both surgery and radiation can offer excellent cancer control, primary considerations include whether surgical local control is possible and whether surgery or radiation will provide a better functional outcome. In the adult setting, surgery is often the modality of choice for early-stage disease at most anatomic sites. Surgery requires wide local excision [24]; positive margins require re-resection or postoperative radiotherapy. Thus, surgical resection should be attempted only for lesions that are deemed to be resectable with wide margins. For lesions that invade the skull base, for example, radiation alone should be considered, because even an aggressive resection is not expected to obviate the need for radiation. Frozen sections may be used intraoperatively to ensure adequacy of surgical margins.

Even in patients with a clinically negative neck, neck dissection should be considered [25]. Evaluation of the neck helps to determine the extent of disease for consideration of adjuvant radiation or chemoradiotherapy. Typically ipsilateral dissection is adequate in the absence of clinical concerns; however, midline lesions such as those in the palate, base of tongue, and supraglottic larynx may require bilateral dissection, given the high risk of bilateral lymphatic drainage. In addition, lesions of the anterior tongue and floor of mouth require evaluation of the submandibular glands. For oral cavity cancers, the depth of invasion predicts nodal involvement; thus, neck dissection should be considered for lesions with a depth of greater than 4 mm [26]. Any clinically involved nodes should be removed, with bilateral dissections for patients with clinically significant bilateral nodes.

Although surgery is the treatment of choice for many patients with resectable limited-stage disease, patients with laryngeal carcinoma benefit from radiation, which offers the prospect of voice preservation [27]. Similarly, radiation may provide the optimal functional outcome for patients with oropharyngeal cancers at the base of tongue or tonsils. Finally, patients with nasal or sinonasal tumors frequently require postoperative radiation, given high rates of local recurrence with resection alone, except in the smallest (T1) lesions.

For children, the balance of risks and benefits of surgery and radiation is complicated by added pediatric toxicity of radiation, which impairs bony growth for children who are not fully mature, and which confers a lifetime second tumor risk that is magnified over the long hoped-for lifetime of these young patients. The use of proton beam radiotherapy has been proposed as one way to mitigate these risks, but it is not widely available, and the extent to which it mitigates these risks is not known.

Finally, even patients with disease defined preoperatively as early stage may benefit from adjuvant therapy. Postoperative chemoradiotherapy is recommended for adult patients with extracapsular nodal spread or positive surgical margins [20]. Given the morbidity of radiation in children, surgical re-resection could be considered as an alternative strategy for positive margins if a complete resection is deemed possible. In addition, even if lesions are fully resected, histopathologic features including perineural or vascular invasion, or the presence of multiple positive lymph nodes, portend a high risk for recurrence. Thus, postoperative radiation is generally indicated for such patients [20].

Advanced Disease

For patients with advanced disease, three basic strategies have been used: up-front chemoradiotherapy; initial surgery with adjuvant radiation or chemoradiation when indicated, as recommended for early-stage disease; or induction chemotherapy followed by radiation or chemoradiation. To date, no single strategy has been defined as superior [28]; however, concurrent chemotherapy and radiation are generally recommended for most patients. Cisplatin (100 mg/m^2 every 3 weeks concurrent with radiation) offers a modest increase in disease-free survival among patients with locally advanced disease over radiation alone [29, 30]. However, results have been mixed as to whether this regimen improves overall survival, and it comes with a cost of significant toxicity, particularly oral mucositis. Other chemoradiotherapy regimens have been used, including carboplatin/5-fluorouracil [31], cisplatin/paclitaxel [32], and carboplatin/paclitaxel [33], but without clear improvements over cisplatin alone. Cetuximab, which is an IgG1 antibody against the ligand-binding domain of the epidermal growth factor receptor (EGFR), has also been used concurrent with radiation to enhance its cytotoxic effects. An early trial demonstrated survival gain over radiation alone, but without clear improvements over historical findings with cisplatin [34, 35].

Others have advocated for induction chemotherapy followed by radiotherapy or chemoradiotherapy for patients with advanced disease [36, 37]. Neoadjuvant chemotherapy has been proposed as a way to reduce distant metastases as a cause of treatment failure, but results have been mixed, and a reduction in distant recurrence has not been definitively demonstrated. In addition, patients experience significant mucosal toxicity when chemotherapy precedes head and neck radiation. However, because neoadjuvant chemotherapy can offer tumor reduction prior to local control and quick institution of therapy while surgical and radiation planning are underway, it may offer practical benefits to the care of some patients. Regimens are cisplatin based and have included cisplatin/docetaxel/5-fluorouracil [36, 37] or cisplatin/paclitaxel/5-fluorouracil [38]. Following induction chemotherapy, radiotherapy can be used alone or in conjunction with agents such as weekly cetuximab or carboplatin.

Patients with Distant Metastases

Finally, for patients with distant disease, chemotherapy can be used to attempt systemic control, although prognoses remain poor [39]. Therefore, in the adult oncology setting, treatment for metastatic disease usually begins with chemotherapy only, with radiation offered for palliative purposes if local disease is causing significant symptoms. Because of the rarity of this disease in children and the lack of full knowledge about outcomes, it may be appropriate to treat metastatic disease aggressively, with initial chemotherapy and, depending on the systemic response, consideration of aggressive local control with curative intent for those who have responded. Nonetheless, cure of systemic disease is likely to be uncommon in children, just as it is in adults, so evidence of poorly responsive disease merits reconsideration of the aggressiveness of therapy.

Supportive Care

Particularly for patients who will receive chemoradiotherapy, acute toxicity of treatment can be significant, marked by profound mucositis. For patients who present with significant weight loss or swallowing dysfunction, or for patients whose radiation plan involves a large field of mucosa with anticipated significant mucositis, prophylactic gastrostomy tube placement is recommended. Even without these risk factors, close nutritional follow-up and support may be beneficial.

In addition, assessment of speech and swallowing is indicated for patients who either present with deficits or who are expected to have deficits following local control. A careful dental examination prior to therapy also offers the opportunity to treat caries and improve hygiene in mucosal areas that may be compromised during treatment. Finally, patients who develop significant mucositis should have aggressive pain control, as mucosal healing can take weeks or even months after radiation and especially after chemoradiation.

Late Effects

Treatment can have significant long-term effects, especially for children who receive radiation. These include endocrine effects, such as hypothyroidism in children who receive neck irradiation and hypopituitarism in children who receive radiation to the skull base; xerostomia and dental caries after salivary gland radiation; impaired bony growth; swallowing dysfunction and esophageal strictures; speech impairment; and a risk for secondary malignancies in the radiation field. Thus, careful long-term follow-up is indicated for these patients.

References

1. National Cancer Institute: Cancer Statistics. 2012. http://seer.cancer.gov/statfacts/html/lungb.html. Accessed 23 Mar 2012.
2. Kutler DI, et al. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Arch Otolaryngol Head Neck Surg. 2003;129(1):106–12.
3. Trizna Z, Schantz SP. Hereditary and environmental factors associated with risk and progression of head and neck cancer. Otolaryngol Clin North Am. 1992;25(5):1089–103.
4. Jefferies S, et al. The role of genetic factors in predisposition to squamous cell cancer of the head and neck. Br J Cancer. 1999;79(5–6):865–7.
5. Baez A. Genetic and environmental factors in head and neck cancer genesis. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2008;26(2):174–200.
6. Bassal M, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2006;24(3):476–83.
7. Szeto CH, et al., Squamous cell carcinoma of the tongue complicating chronic oral mucosal graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Am J Hematol. 2004;77(2):200–2.
8. Montebugnoli L, et al. Multiple squamous cell carcinomas of the oral cavity in a young patient with graft-versus-host disease following allogenic bone marrow transplantation. Int J Oral Maxillofac Surg. 2011;40(5):556–8.
9. Mawardi H, et al. Oral epithelial dysplasia and squamous cell carcinoma following allogeneic hematopoietic stem cell transplantation: clinical presentation and treatment outcomes. Bone Marrow Transplant. 2011;46(6):884–91.
10. Mork J, et al. Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med. 2001;344(15):1125–31.
11. Mineta H, et al. Human papilloma virus (HPV) type 16 and 18 detected in head and neck squamous cell carcinoma. Anticancer Res. 1998;18(6B):4765–8.
12. Jemal A, et al. Annual report to the nation on the status of cancer, 1975–2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst. 2013;105(3):175–201.
13. Licitra L, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. J Clin Oncol. 2006;24(36):5630–6.
14. Vargas SO, et al. Upper respiratory tract carcinoma with chromosomal translocation 15;19: evidence for a distinct disease entity of young patients with a rapidly fatal course. Cancer. 2001;92(5):1195–203.
15. French CA, et al. BRD4 bromodomain gene rearrangement in aggressive carcinoma with translocation t(15;19). Am J Pathol. 2001;159(6):1987–92.
16. Scholl P, et al. Microscopic cut-through of cancer in the surgical treatment of squamous carcinoma of the tongue. Prognostic and therapeutic implications. Am J Surg. 1986;152(4):354–60.
17. Bansberg SF, Olsen KD, Gaffey TA. High-grade carcinoma of the oral cavity. Otolaryngol Head Neck Surg. 1989;100(1):41–8.
18. Bachar G, et al. Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. Oral Oncol. 2011;47(1):45–50.
19. Janot F, et al. Prognostic value of clinicopathological parameters in head and neck squamous cell carcinoma: a prospective analysis. Br J Cancer. 1996;73(4):531–8.
20. Bernier J. et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843–50.

21. Edge SB, et al., editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
22. Morris LG, et al. Squamous cell carcinoma of the oral tongue in the pediatric age group: a matched-pair analysis of survival. Arch Otolaryngol Head Neck Surg. 2010;136(7):697–701.
23. Morris LG, Ganly I. Outcomes of oral cavity squamous cell carcinoma in pediatric patients. Oral Oncol. 2010;46(4):292–6.
24. Looser KG, Shah JP, Strong EW The significance of "positive" margins in surgically resected epidermoid carcinomas. Head Neck Surg. 1978;1(2):107–11.
25. Ferlito A, et al. Elective and therapeutic selective neck dissection. Oral Oncol. 2006;42(1):14–25.
26. Melchers LJ, et al. Tumour infiltration depth ≥ 4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma. Oral Oncol. 2012;48(4):337–42.
27. Forastiere AA, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349(22):2091–8.
28. Haddad R, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013;14(3):257–64.
29. Bernier J, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945–52.
30. Cooper JS, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937–44.
31. Denis F, et al. Final results of the 94–01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol. 2004;22(1):69–76.
32. Garden AS, et al. Preliminary results of Radiation Therapy Oncology Group 97–03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. J Clin Oncol. 2004;22(14):2856–64.
33. Suntharalingam M, et al. The use of carboplatin and paclitaxel with daily radiotherapy in patients with locally advanced squamous cell carcinomas of the head and neck. Int J Radiat Oncol Biol Phys. 2000;47(1):49–56.
34. Bonner JA, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–78.
35. Bonner JA, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11(1):21–8.
36. Vermorken JB, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007;357(17):1695–704.
37. Posner MR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007;357(17):1705–15.
38. Hitt R, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol. 2005;23(34):8636–45.
39. Fury MG, Pfister DG. Current recommendations for systemic therapy of recurrent and/or metastatic head and neck squamous cell cancer. J Natl Compr Canc Netw. 2011;9(6):681–9.