# 13 Applications in Head and Neck Cancer

Deepak Khuntia, Anne M. Traynor, Paul M. Harari, and Jean Bourhis

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## 13.1 Introduction

Head and neck (H&N) cancer refers to a heterogeneous group of epithelial tumors involving the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, and paranasal sinuses. In this chapter we focus discussion primarily on squamous cell carcinoma of the H&N, particularly cancers involving the oral cavity, pharyngeal axis, and larynx. In 2006 there will be approximately 43,000 cases of H&N cancer diagnosed in the United States with over 500,000 cases worldwide (American Cancer Society 2005). Tobacco and alcohol use are major risk factors for the development of H&N cancer. For selected H&N tumors, data also implicates Epstein-Barr virus (EBV) and human papilloma viruses (HPV) in the pathogenesis (Gillison et al. 2000).

Historically, patients with early-stage disease (stages I–II) are effectively treated with single modality therapy using radiation (RT) or surgery alone. Patients with more advanced-stage disease (stage III–IVb) have generally received combined modality therapy with surgery and radiation; however, advanced-stage H&N cancer patients commonly experience significant functional and cosmetic deficits that adversely impact both speech and swallowing capacity. In addition, ultimate disease-free survival is modest for advanced stage patients, with 5-year survival rates on the order of 20–40%. Over the past decade, the integration of systemic chemotherapy (CT) has been shown to improve outcome for several cohorts of advanced stage H&N cancer patients. For the future, there is also reason for optimism that new molecular targeted therapies will further enhance the therapeutic approach in advanced H&N cancer.

In this chapter we review the rationale and clinical results for chemoradiation in the management of locoregionally (LR) advanced H&N cancer patients.

D. Khuntia, MD
Assistant Professor, Department of Human Oncology, University of Wisconsin, 600 Highland Avenue, K4 312-3684, Madison, WI 53792, USA
A. M. Traynor, MD
Assistant Professor, Department of Medicine, University of Wisconsin, 600 Highland Avenue, K4 312-3684, Madison, WI 53792, USA
P. M. Harari, MD
Jack Fowler Professor, Department of Human Oncology, University of Wisconsin, 600 Highland Avenue, K4 312-3684, Madison, WI 53792, USA
J. Bourhis, MD
Professor, Head of Radiation Oncology Department, Institute Gustave-Roussy, 39, rue Camille Desmoulins, 94805 Villejuif Cedex, France

## 13.2 Randomized Trials with Definitive Chemoradiation

### 13.2.1 Oropharynx

Primary anatomic subsites of the oropharynx include the tonsil, base of tongue, upper posterior pharyngeal wall, and soft palate. Though surgery

alone may be curative for some of these patients, RT is generally preferred in light of the reduced functional morbidity. For stage-III and stage-IV disease, randomized trials have recently validated a role for the addition of concurrent CT with RT. Potential disadvantages to concurrent chemoradiation regimens include increased acute and late toxicity (Holsti and Mantyla 1988; Calais et al. 1999). The acute toxicities, namely mucositis, can be quite severe such that patients may require treatment breaks that can compromise ultimate outcome.

A major trial validating the use of chemoradiation for oropharyngeal tumors comes from the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC). In this trial, 226 patients were randomized between RT alone (70 Gy in 35 fractions) versus the same RT and three cycles of carboplatin (70 mg/m$^2$) and 5-fluoruracil (600 mg/m$^2$; Calais et al. 1999; Denis et al. 2004). Like cisplatin, carboplatin is a radiosensitizer, but it offers fewer acute toxicities, including less nausea, ototoxicity, and diminished need for hydration. In the most recent update of this trial, 5-year overall survival was improved from 16 to 22% in favor of the chemoradiation arm (Denis et al. 2004). Local control was also improved with CT (see Table 13.1). Pretreatment hemoglobin, stage, and treatment were found to be of prognostic significance. Severe late morbidity rates were reported as similar in both arms; however, feeding tube dependence, swallowing function, and laryngeal function were not rigorously assessed.

Few other randomized trials exist that focus solely on oropharyngeal cancer patients; however, multiple trials, including a variety of H&N tumor subsites, have been conducted to evaluate the role of concurrent CT with RT. Several of these trials identify a survival benefit for combined chemoradiation vs RT alone and are summarized in Table 13.1.

### 13.2.2 Larynx

Patients with advanced-stage tumors of the larynx can be managed with partial laryngectomy, total laryngectomy, RT alone, or combined RT and CT. The choice of therapy depends on a variety of factors, including anatomic extent of disease, patient preference, and local practice patterns. In the U.S., patients receiving radiotherapy often receive induction-CT based on the landmark Veterans Affairs Laryngeal Cancer Study (Department of

**Table 13.1.** Summary of selected chemoradiation randomized trials

| Reference | Primary | Arms | LC (%) | OS (%) |
|---|---|---|---|---|
| Al Sarraf (1998) et al. | NP | RT<br>CRT | 26 PFS[a]<br>66 PFS[a] | 46[a]<br>76[a] |
| VA Larynx (1991) | L | Induction CT→ CRT<br>Surgery/RT | 80[b]<br>93[b] | 68 (NS)[b]<br>68[b] |
| Forastiere (2003) et al. | L | Induction CT→ CRT<br>CRT<br>RT | 61[c]<br>78[c]<br>56[c] | 55 (NS)[c]<br>54[c]<br>56[c] |
| Calais (1999, 2000) et al. | OP | RT<br>CRT | 42[a]/25[c]<br>66[a]/48[c] | 31[a]/16[c]<br>51[a]/22%[c] |
| Brizel (2000) et al. | L, HP, OP, OC | Hyperfractionated RT<br>Hyperfractionated CRT | 44[b]<br>70[a] | 34[b]<br>55[b] |
| Adelstein (2003) et al. | Unresectable: L; HP; OP; OC | RT<br>CRT<br>Split-course CRT | | 23[b]<br>37[b]<br>27[b] |
| Bernier (2004) et al. | Resected: L; HP; OP; OC | Postop RT<br>CRT | 69[c]<br>82[c] | 40[c]<br>53[c] |
| Cooper (2004) et al. | Resected: L; HP; OP; OC | Postop RT<br>CRT | 72[a]<br>82[a] | NS<br>NS |

*NS* not statistically significant, *RT* radiation, *CT* chemotherapy, *CRT* chemoradiation, *NP* nasopharynx, *L* larynx, *OP* oropharynx, *HY* hypopharynx, *OC* oral cavity
[a]Two-year data
[b]Three-year data
[c]Five-year data