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CLINICAL INVESTIGATION **Head and Neck**

MATCHED SURVIVAL ANALYSIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED RESECTABLE OROPHARYNGEAL CARCINOMA: PLATINUM-BASED INDUCTION AND CONCURRENT CHEMORADIOTHERAPY VERSUS PRIMARY SURGICAL RESECTION

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Purpose: The outcome of a prospective case series of 47 patients with newly diagnosed resectable locoregionally advanced oropharyngeal squamous cell carcinoma treated with platinum-based induction-concurrent chemoradiotherapy (IC/CCRT) was compared with the outcome of 47 matched historical control patients treated with surgery and postoperative RT.

Methods and Materials: A total of 47 control patients with locoregionally advanced oropharyngeal squamous cell carcinoma were identified from review of a prospectively compiled comprehensive computerized head-and-neck cancer database and were matched with a prospective case series of patients undergoing IC/CCRT by disease stage, nodal status, gender, and age (±5 years). The IC/CCRT regimen consisted of one cycle of induction chemotherapy followed by conventionally fractionated RT to a total dose of 66–70 Gy concomitantly with two cycles of chemotherapy. Each cycle of chemotherapy consisted of cisplatinum, 100 mg/m^2, and a continuous infusion of 5-fluorouracil, 1,000 mg/m^2/d for 5 days. The survival analysis was performed using Kaplan-Meier estimates. Matched-pair survival was compared using the Cox proportional hazards model.

Results: No significant difference was found in the overall survival or progression-free survival rates between the two groups. The matched analysis of survival did not show a statistically significant greater hazard ratio for overall death (hazard ratio, 1.35; 95% confidence interval, 0.65–2.80; $p = .415$) or progression (hazard ratio, 1.44; 95% confidence interval, 0.72–2.87; $p = .301$) for patients undergoing IC/CCRT.

Conclusion: Although the sample size was small and not randomized, this matched-pair comparison between a prospective case series and a historical cohort treated at the same institution showed that the efficacy of IC/CCRT with salvage surgery is as good as primary surgical resection and postoperative RT. © **2011 Elsevier Inc.**

Oropharyngeal carcinoma, Radiotherapy, Chemotherapy, Surgery, Survival.

INTRODUCTION

Oropharyngeal cancer is one of the most common malignant tumors of the head-and-neck region. Recently, a significant increased incidence of oropharyngeal carcinomas has been observed in the United States and Western Europe in people <45 years old (1). Although the risk of developing oropharyngeal malignancies is closely correlated with tobacco use and alcohol abuse, substantial molecular and epidemiologic evidence has suggested that human papillomavirus (HPV) is an emerging etiologic factor in these tumors (2).

Surgery and radiotherapy (RT) alone are considered equally successful for early-stage oropharyngeal carcinoma. However, considerable controversy surrounds the appropriate combined treatment of locoregionally advanced oropharyngeal squamous cell carcinoma (LAOSCC).

Chemoradiotherapy has been perceived by patients and physicians to be a more effective function preservation strategy than surgery. In addition, RT is generally recommended as adjuvant treatment after surgical resection of LAOSCC (5). However, major concerns remain regarding the toxicity of concurrent chemoradiotherapy (CCRT), sometimes

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requiring hospitalization and nutritional support (4). Furthermore, surgical management of persistent or recurrent LAOSCC after failure of chemoradiotherapy is associated with high complication rates because of wound healing difficulties (6) .

Although, the focus of treatment has recently shifted away from surgical approach toward CCRT protocols (3, 4), no anatomic site-specific prospective randomized trials evaluating the outcomes after surgical vs. nonsurgical treatment of LAOSCC are available.

The aim of the present study was to compare the outcome of a prospective case series of patients with resectable LAOSCC treated with platinum-based induction-CCRT (IC/CCRT) with the outcome of matched historical controls who underwent primary surgical resection.

METHODS AND MATERIALS

Criteria for inclusion

A monoinstitution prospective case series of 47 consecutive patients who satisfied the following criteria underwent cisplatinum-based IC/CCRT with curative intent between January 2000 and June 2006: *(1)* previously untreated, histologically proven, resectable LAOSCC (Stage III or IV disease), with tumor considered technically resectable with planned surgical excision if no fixation/invasion to the base of the skull or cervical vertebrae, no involvement of the nasopharynx, no fixed lymph nodes, no carotid encasement, and no invasion of the mediastinum was present; *(2)* age ≤80 years; *(3)* Karnofsky performance status ≥60%; *(4)* no history of head-and-neck cancer; *(5)* absence of synchronous primary lesions; *(6)* absence of distant metastases; and *(7)* acceptable medical and laboratory status to tolerate chemotherapy. Also, all patients provided informed consent. Finally, the institutional review board approved the protocol for the present study.

Pretreatment evaluation

All patients were evaluated by our multidisciplinary team of physicians consisting of head-and-neck surgeons, radiation oncologists, and medical oncologists. All patients were evaluated by complete blood cell count with differential, serum electrolytes, liver function tests, electrocardiography, fiberoptic endoscopy of the upper respiratory tract, tracheobronchoscopy, and esophagoscopy. Baseline imaging included chest X-ray, head-and-neck contrast-enhanced computed tomography with or without magnetic resonance imaging. Computed tomography scans of the chest and abdomen and, in few cases, positron emission tomography scans, were performed as clinically indicated on the basis of abnormal screening test results or symptoms. Using the information included in the medical records, all patients underwent repeat staging according to the American Joint Committee using Cancer TNM 2002.

Treatment

All patients were immobilized in the supine position using a custom-made thermoplastic head mask. A tongue depressor device was placed during the simulation and treatment to reduce the dose to the hard palate. The patients underwent computed tomography-based simulation for treatment planning. Computed tomography with 5-mm slices was done of the entire head-and-neck region. Orthogonal laser beams were used to assess the reproducibility of the treatment position. All patients underwent simulation of all treatment fields. Three-dimensional conformal RT with a multileaf collimator was performed using 4–6-MV photons from a linear accelerator with conventional fractionation (2 Gy/fraction, once daily, five times weekly). The dose was prescribed to the 95% isodose according to the International Commission of Radiation Units and Measurements recommendations.

The first planning target volume (PTV) included the gross tumor volume, which included the primary tumor and involved lymph nodes, as detected on the physical and radiographic examinations, plus a 1.0–1.5 cm expansion. The second PTV included the first PTV plus uninvolved lymph nodes at high risk of harboring microscopic metastatic disease (Level Ib-V, bilaterally).

The prescribed dose to the second PTV was 50 Gy in Stage N0 patients and 60 Gy in Stage N+ patients. The final dose to the first PTV was 66–70 Gy. The maximal dose to the spinal cord was 46 Gy. Bilateral electron fields (6–9 MeV) were used to treat the lymph nodes in Level IIb and V to boost the dose to 50 Gy in Stage N0 patients and 60 Gy in Stage N+ patients in cases in which the dose distribution was not optimal. The energy was chosen according to the depth of nodal volume, as evaluated by computed tomography. An anterior half-beam field was used mainly in Stage N2-N3 patients with a thick neck such that adequate coverage of the lymph nodes using a lateral portal was not achievable.

Induction cisplatinum (100 mg/m^2) was administered on Day 1; 5-fluorouracil (1,000 mg/m^2/d) was administered as a 24-hour continuous infusion for 5 days. Definitive RT started 3 weeks after induction chemotherapy, regardless of the response to induction chemotherapy. Concurrently with the RT, the patients received two cycles of chemotherapy using cisplatinum (100 mg/m^2) on Day 1 and 5-fluorouracil (1,000 mg/m^2/d) as a continuous infusion for 5 days during the first and fourth week of the RT course. Neck dissection was planned for patients with nodal metastasis >3 cm, regardless of the response to therapy and for patients who had suspected persistent neck disease at 8–12 weeks after completing treatment.

Historical cohort of matched pairs

Patients with previously untreated Stage III-IVB oropharyngeal carcinoma who had been treated at our institution since 1985 were identified from a review of a prospectively compiled comprehensive computerized head-and-neck cancer database. The patients had had undergone primary surgery were selected from this database to serve as a matched control group to the patients undergoing IC/CCRT. Patients who satisfied the criteria to undergo IC/CCRT with curative intent between January 2000 and June 2006 but who gave their preference for primary surgical excision were also considered for matching.

Surgery involved resection of the primary tumor using a transoral, transcervical, or combined approach with elective neck dissection of the N0 neck (selective neck dissection or Type III radical modified neck dissection) or therapeutic neck dissection of the N+ neck (radical or radical modified neck dissection depending on N stage). Regional myocutaneous or microvascular free flaps were used for reconstruction. Postoperative RT (PORT) was performed in patients with multiple positive lymph nodes, extracapsular extension, perineural tumor invasion, lymphovascular invasion, positive tumor margins, and those with Stage T4a tumors. Radiotherapy was performed using 4–6-MV photons from a linear accelerator administrated in 2-Gy daily fractions, five times weekly. A volume encompassing the primary site and all draining lymph nodes at risk was prescribed to receive a dose of 60 Gy in 30 fractions within a 6-week period. The dose to the clinically uninvolved nodal region