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CLINICAL INVESTIGATION **Head and Neck Cancer**

SIMULTANEOUS INTEGRATED BOOST USING INTENSITY-MODULATED RADIOTHERAPY COMPARED WITH CONVENTIONAL RADIOTHERAPY IN PATIENTS TREATED WITH CONCURRENT CARBOPLATIN AND 5-FLUOROURACIL FOR LOCALLY ADVANCED OROPHARYNGEAL CARCINOMA

Sébastien Clavel, M.D., M.Sc.,* David H. A. Nguyen, M.D.,† Bernard Fortin, M.D., M.Sc.,† Philippe Després, Ph.D.,* Nader Khaouam, M.D.,† David Donath, M.D.,* Denis Soulières, M.D.,‡ Louis Guertin, M.D.,§ and Phuc Felix Nguyen-Tan, M.D.†

Departments of *Radiation Oncology, ‡Medical Oncology, and §Head and Neck Surgery, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; and †Department of Radiation Oncology, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada

Purpose: To compare, in a retrospective study, the toxicity and efficacy of simultaneous integrated boost using intensity-modulated radiotherapy (IMRT) vs. conventional radiotherapy (CRT) in patients treated with concomitant carboplatin and 5-fluorouracil for locally advanced oropharyngeal cancer.

Methods and Materials: Between January 2000 and December 2007, 249 patients were treated with definitive chemoradiation. One hundred patients had 70 Gy in 33 fractions using IMRT, and 149 received CRT at 70 Gy in 35 fractions. Overall survival, disease-free survival, and locoregional control were estimated using the Kaplan-Meier method.

Results: Median follow-up was 42 months. Three-year actuarial rates for locoregional control, disease-free survival, and overall survival were 95.1% vs. 84.4% ($p = 0.005$), 85.3% vs. 69.3% ($p = 0.001$), and 92.1% vs. 75.2% ($p < 0.001$) for IMRT and CRT, respectively. The benefit of the radiotherapy regimen on outcomes was also observed with a Cox multivariate analysis. Intensity-modulated radiotherapy was associated with less acute dermatitis and less xerostomia at 6, 12, 24, and 36 months.

Conclusions: This study suggests that simultaneous integrated boost using IMRT is associated with favorable locoregional control and survival rates with less xerostomia and acute dermatitis than CRT when both are given concurrently with chemotherapy.

Head-and-neck cancer, Intensity-modulated radiotherapy chemoradiation, Oropharyngeal carcinoma.

INTRODUCTION

Concurrent chemotherapy and radiotherapy (CTRT) has become the standard of care for locally advanced oropharyngeal cancers (1–3). Although it has been shown to increase survival and quality of life by preserving organ function, CTRT also leads to increased acute toxicities and late complications. Intensity-modulated radiotherapy (IMRT) is a relatively new radiation technique that allows for more precise radiation delivery to target volumes while sparing normal structures (reviewed in references 4 and 5). Intensity-modulated radiotherapy is a promising technique used in a number of clinical sites and potentially helps to decrease side effects and improve local control.

In head-and-neck cancers, IMRT has also shown the ability to preserve salivary function through sparing of the parotid glands. Several studies have shown lower xerostomia in patients treated with this technique (6–8). Some studies also demonstrated that patients treated with IMRT had a better quality of life (9–12). Intensity-modulated radiotherapy potentially leads to better tumor control through the delivery of higher doses to the gross tumor volume. For oropharyngeal cancers, single-institution experiences have suggested that treatment with IMRT gives at least the same outcome as conventional techniques while reducing toxicities (8, 13–16).

The aim of this retrospective study was to compare the toxicity and efficacy of two different radiotherapy regimens used at our institution for patients with oropharyngeal cancers treated with concurrent carboplatin and 5-fluorouracil (5-FU). The first radiotherapy regimen is a simultaneously

Reprint requests to: Sébastien Clavel, M.D., M.Sc., Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Montréal, QC G1K 7P4, Canada. Tel: (514) 890-8254; Fax: (514) 412-7537; E-mail: sebastien.clavel@umontreal.ca

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integrated boost (SIB) using IMRT, and the second is conventional radiotherapy (CRT).

METHODS AND MATERIALS

Study design

In this single-institution, retrospective study, the files of all consecutive patients treated between January 2000 and December 2007 for locally advanced oropharyngeal cancer by concomitant chemoradiation were reviewed. Inclusion criteria were *(1)* Stage III, IVa, or IVb squamous cell carcinoma; *(2)* treatment with a curative intent; and *(3)* treatment with carboplatin and 5-FU, every 3 weeks. Patients were excluded if treated in the adjuvant postoperative setting, with neoadjuvant chemotherapy, or for a tumor recurrence. No patient included in the study had known metastatic disease at presentation. The results are based on a final review of charts as of December 2009. This study was approved by the hospital authorities in the context of a review of the quality of practice.

Radiotherapy

All patients were simulated and treated supine, immobilized by a thermoplastic head and shoulder mask fixed to the treatment couch. Patients were treated using 6-MV photons, and treatment was given in 5 daily fractions per week.

Treatment-planning CT scans with a 1.5-mm slice thickness from the head down through the carina were obtained. The gross tumor volume (GTV) was defined as the gross extent of the tumor by imaging studies as well as physical examination, which included the primary tumor and the involved regional lymph nodes: Clinical tumor volume (CTV1) was defined as the GTV plus margin for microscopic spread. Depending on the primary and the involved lymph nodes, the high-risk subclinical tumor volume (CTV2) was defined as the GTV plus margin for microscopic spread, the retropharyngeal lymph nodal regions, the parapharyngeal space, the oropharynx, and Levels Ib, II, III, V,and IV lymph nodes especially if the above levels were involved. The margin for the GTV varied by anatomic boundaries and critical adjacent tissues and was up to 2 cm. The low-risk CTV3 generally included the contralateral uninvolved lymphatic drainage areas and often Level IV lymph nodes if the above levels were not involved. The planning target volume (PTV) for each above-mentioned target volume was typically 3–5 mm, depending on the relative locations of the tumor and adjacent critical tissues.

For IMRT, the prescription dose was 69.96 Gy in 2.12 Gy per fraction to ≥95% of the PTV1, concurrently with 59.4 Gy in 1.8 Gy per fraction to ≥95% of the PTV2 and 50.4 Gy in 1.8 Gy per fraction to ≥95% of the PTV3. Dose–volume histograms of the PTV1, PTV2, PTV3, and the usual critical normal structures, such as the brainstem, spinal cord, middle and inner ears, mandible, larynx, and parotids, were examined. Typically a margin of 0.5 cm around the spinal cord and brainstem was added to create a planning organ-at-risk volume (PRV). The dose to any point defined as a volume of at least 0.03 cm^3, could not exceed 42 Gy and 45 Gy, respectively, within the spinal cord and spinal cord PRV. The dose to any point defined as a volume of at least 0.03 cm^3 could not exceed 50 Gy and 54 Gy, respectively, within the brainstem and brainstem PRV. We tried to limit the mean dose to at least one parotid gland to <26 Gy, or alternatively, at least 20 cm^3 of the combined volume of both parotid glands to <20 Gy or at least 50% of one gland to <30 Gy. Inverse plans were generated using a commercial inverse planning system (Corvus versions 4 and 5 [NOMOS, Sewickley, PA] as well as Helios version 8.1.20 [Varian Medical Systems, Palo Alto, CA]). Typically five to seven gantry angles were used, and the treatment was delivered in a dynamic fashion.

For conventional radiotherapy using a two-dimensional or three-dimensional technique, two lateral-opposed fields matched with an anterior lower neck field technique were used; an electron field was often given to cover the Level V nodes after 42 Gy. Seventy Gy in 35 fractions was prescribed to the PTV1, 60 Gy in 30 fractions to the high-risk subclinical disease (PTV2), and 50 Gy in 25 fractions was given to the low-risk subclinical disease (PTV3).

Chemotherapy

A combination of carboplatin 70 mg/m^2/d in bolus for 4 days, with 5-FU 600 mg/m^2/d as a continuous infusion for 4 days every 3 weeks, was primarily used in our institution during the study period. Chemotherapy started with the first day of radiotherapy. Most patients were scheduled to receive three cycles of chemotherapy during the course of the radiotherapy. Two cycles were scheduled only for patients with specific comorbidities and/or aged >65 years.

Surgery

A CT scan of the head and neck area was done 6–8 weeks after completion of chemoradiotherapy. If residual disease was observed in the neck on the CT scan or at the clinical examination, a neck dissection was offered to patients. One patient had a planned neck dissection after concurrent chemoradiotherapy as requested by a research protocol.

Patient and tumor characteristics

Patient demographic data were collected, and staging determinations were made according to the 6th edition of American Joint Committee on Cancer (AJCC) staging criteria (17). The choice of treatment modality was determined by a joint committee with representatives from our Departments of Head and Neck Surgery, Radiation Oncology, Medical Oncology, and Diagnostic Radiology. The treatment outcome was analyzed on the basis of the characteristics of the chemotherapy and radiotherapy. Reported outcomes included mucositis and dermatitis during treatment, and hospitalization and deaths during and up to 30 days after treatment. Body weight and xerostomia were also recorded at baseline and at each week of the treatment and at each follow-up visit. Acute and late radiotherapy and/or chemotherapy toxicities were graded according to the National Cancer Institute Common Toxicity Criteria v3.0 (18) or Radiation Therapy Oncology Group scoring scales(www.rtog.org).

Follow-up

At the end of treatment, a weekly follow-up was done systematically at our clinic by a radiation oncologist, an oncology nurse, a nutritionist, and a speech therapist as long as required, usually for 4–6 weeks. The patients were also followed at the joint otorhinolaryngology–radiotherapy outpatient clinic every 2 months for 2 years, then every 4 months for 3 years, and then annually. Every patient had a CT scan 6–8 weeks after definitive treatment and periodically during the first 2 years if symptoms and/or results on physical examination were suspicious for recurrence. A chest radiograph was done annually. Recurrence and deaths were registered during follow-up.