Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 398–402, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.01.058

CLINICAL INVESTIGATION **Head and Neck**

ORGAN PRESERVATION WITH CONCURRENT CHEMORADIATION FOR ADVANCED LARYNGEAL CANCER: ARE WE SUCCEEDING?

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Purpose: To determine the rates of organ preservation and function in patients with advanced laryngeal and hypopharyngeal carcinomas treated with concurrent chemoradiotherapy (CRT).

Methods and Materials: Between April 1999 and September 2005, 82 patients with advanced laryngeal (67%) and hypopharyngeal carcinomas (33%) underwent conventional radiotherapy and concurrent platinum-based chemotherapy with curative intent. Sixty-two patients were male (75.6%). The median age was 59 years. Eighteen patients (22%) were in Stage III and 64 (78%) were in Stage IV. The median radiation dose was 70 Gy. The median potential follow-up was 3.9 years.

Results: Overall survival and disease-free survival were respectively 63% and 73% at 3 years. Complete response rate from CRT was 75%. Nineteen patients (23%) experienced significant long-term toxicity after CRT: 6 (7.3%) required a percutaneous endoscopic gastrostomy, 5 (6%) had persistent Grade 2 or 3 dysphagia, 2 (2.4%) had pharyngoesophageal stenosis requiring multiple dilations, 2 (2.4%) had chronic lung aspiration, and 7 (8.5%) required a permanent tracheostomy. Four patients (4.9%) underwent laryngectomy without pathologic evidence of disease. At last follow-up, 5 (6%) patients were still dependent on a gastrostomy. Overall, 42 patients (52%) were alive, in complete response, with a functional larynx and no other major complications.

Conclusions: In our institution, CRT for advanced hypopharyngeal and laryngeal carcinoma has provided good overall survival and locoregional control in the majority of patients, but a significant proportion did not benefit from this approach because of either locoregional failure or late complications. Better organ preservation approaches are necessary to improve locoregional control and to reduce long-term toxicities.

Larynx, Hypopharynx, Radiotherapy, Chemotherapy, Adverse effects, Late morbidity.

INTRODUCTION

Larynx cancer is the most common cancer subsite in head and neck oncology. For patients with advanced tumors (Stage III or IV) of the larynx and hypopharynx, treatment options are concomitant chemoradiation (CRT) with surgery as salvage, or up-front surgery followed by adjuvant radiotherapy, with or without concurrent chemotherapy. These multimodal regimens are equivalent in terms of survival, but CRT offers the potential advantage of organ preservation (1–7).

Unfortunately, organ preservation treatment protocols are associated with significant acute and late adverse effects. Therefore, quality of life and morbidity should be considered when a treatment is proposed. Quality of life relates to overall well-being including the functional, emotional, mental, social, and economic components. The most common predictors of quality of life in surviving patients with advanced laryngeal cancer receiving CRT appear to be absence of pain and lower incidence of mood disorder rather than preservation of speech function (8).

Intensity-modulated radiotherapy (IMRT) is starting to be used in the larynx and hypopharynx substites (9). Although experience with this modality is accumulating, we wanted to review our current results with conventional radiotherapy. Our goal was to determine rates of functional organ preservation and late toxicities in patients treated for advanced laryngeal and hypopharyngeal cancer at our tertiary care health center.

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Presented at the 7th International Conference on Head and Neck Cancer, San Francisco, CA. 21st of July 2008.

Conflict of interest: none

Received Dec 10, 2008, and in revised form Jan 28, 2009. Accepted for publication Jan 29, 2009.

METHODS AND MATERIALS

Patient and tumor characteristics

Between August 1998 and September 2005, a total of 105 patients with histologically proven laryngeal and hypopharyngeal squamous cell cancer (SCC) were treated with concurrent CRT at the Centre Hospitalier de l'Université de Montréal. Pretreatment evaluations consisted of a complete history and physical examination including direct laryngoscopy using a flexible fiberoptic endoscope. Dental evaluation was mandatory in all except edentulous patients. All patients had a complete blood count and biochemical profile, chest X-ray, head-and-neck CT scan, and, in some cases, an MRI. All patients were presented to our multidisciplinary team, which includes head-and-neck surgeons, medical oncologists, radiation oncologists, nurses, nutritionists, speech and swallowing specialists, and pharmacists.

Of these patients, 23 were excluded from the analysis for the following reasons: retreatment (6 patients), use of IMRT (4 patients), follow-up less than 2 years (5 patients), or up-front laryngectomy (10 patients).

Of the remaining 82 eligible patients, 57 and 39 were Stage IVa and T3, respectively. All the data were reported according to the 1998 American Joint Committee on Cancer (AJCC). The distribution of the primary site was 55 larynx and 27 hypopharynx. Of the patients, 62 were male and 20 were female, with a median age of 59 years. Patient characteristics are shown in Table 1. Median potential follow-up was 3.9 years (10).

Table 1. Patient and tumor characteristics

Characteristic	Value (%)
Total patients	82 (100)
Gender	
Men	62 (76)
Women	20 (24)
Age (y)	
Median	59
Range	42–77
Site	
Larynx	55 (67)
Hypopharynx	27 (33)
Histological type (SCC)	82 (100)
T stage*	
T1–2	23 (28)
T3	39 (48)
T4a-b	20 (24)
N stage*	
N0	15 (18)
N1	12 (15)
N2	51 (62)
N3	4 (5)
Overall stage*	
III	18 (22)
IVA	57 (70)
IVB	7 (8)

* Based on American Joint Committee on Cancer criteria.

Radiotherapy

Most patients were treated with conventional radiotherapy and standard fractionation, 2 Gy per day, five fractions per week for 7 weeks. Median dose was 70 Gy (16–72 Gy). Four patients received a concomitant boost to 72 Gy in 6 weeks. Nine patients did not receive the prescribed dose of radiotherapy (Table 2), including 4 patients who died during treatment, of which two deaths were from an unrelated cause. One of the 9 patients experienced recurrence in the treatment field.

A planning CT scan with a 5-mm slice thickness was performed in all patients. A thermoplastic head-to-shoulder mask was used for immobilization. Dosimetry was performed with Theraplan v3.8 (Nucletron, Veenendaal, the Netherlands); field arrangement consisted of half-beam blocked lateral opposed fields and supraclavicular field with 4-MV photons. Electrons fields were added as required to the spinal and tracheostomy regions. The target volumes and radiation doses were defined according to International Commission on Radiation Units (ICRU) (12, 13).

Chemotherapy

All patients underwent concurrent platinum-based chemotherapy. Most patients (56%) received cisplatin 100 mg/m^2 every 3 weeks. A total of 23 (28%) had carboplatin-5FU given respectively 70 mg/m^2/day and 600 mg/m^2/day in continuous infusion, both for 4 days every 3 weeks (Table 2).

Surgery

A head-and-neck CT scan was performed 2 months after the completion of treatment. Neck dissection was performed in a patient with persistent clinical or radiographic evidence of residual nodal disease. A salvage total laryngectomy was performed if the primary tumor response was incomplete.

Toxicity assessment

Follow-up was done every 2 months for the first 2 years, then every 4 months up to 5 years, then annually. Patients with locoregional failure or death resulting from cancer were excluded from the assessment. Late toxicity was evaluated more then 3 months after the end of radiation treatment and defined as follow: Grade 2 or higher dysphagia according to the Common Terminology Criteria of Adverse Events (CTCAE) Version 3.0, requirement of a feeding tube/gastrostomy, pharyngoesophageal stenosis, chronic lung aspiration, and laryngectomy or tracheotomy without evidence of tumor recurrence.

Statistical analysis

Statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC). Disease-free survival and overall survival were calculated using the Kaplan-Meier method. Time variables were calculated from the start of radiotherapy. Freedom from local, regional, or distant progression was defined as the absence of demonstrable tumor on physical and radiographic examinations. Follow-up time was calculated using the method described by Schemper and Smith (10).

Table 2. Treatment details

Treatment	Value (%)
Radiation dose (Gy)	
Median	70
Range	16–72
Chemotherapy	
Cisplatin	46 (56)
Carboplatin	10 (12)
Carboplatin/5-fluorouracil	23 (28)
Unknown	3 (4)