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CLINICAL INVESTIGATION **Head and Neck Cancer**

INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF OROPHARYNGEAL CANCER: AN UPDATE OF THE MEMORIAL SLOAN-KETTERING CANCER CENTER EXPERIENCE

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Purpose: To update the Memorial Sloan-Kettering Cancer Center's experience with intensity-modulated radiotherapy (IMRT) in the treatment of oropharyngeal cancer (OPC).
Methods and Materials: Between September 1998 and April 2009, 442 patients with histologically confirmed OPC underwent IMRT at our center. There were 379 men and 63 women with a median age of 57 years (range, 27–91). The disease was Stage I in 2%, Stage II in 4%, Stage III in 21%, and Stage IV in 73% of patients. The primary tumor subsite was tonsil in 50%, base of tongue in 46%, pharyngeal wall in 3%, and soft palate in 2%. The median prescription dose to the planning target volume of the gross tumor was 70 Gy for definitive (n = 412) cases and 66 Gy for postoperative cases (n = 30). A total 404 patients (91%) received chemotherapy, including 389 (88%) who received concurrent chemotherapy, the majority of which was platinum-based.
Results: Median follow-up among surviving patients was 36.8 months (range, 3–135). The 3-year cumulative incidence of local failure, regional failure, and distant metastasis was 5.4%, 5.6%, and 12.5%, respectively. The 3-year OS rate was 84.9%. The incidence of late dysphagia and late xerostomia ≥Grade 2 was 11% and 29%, respectively.
Conclusions: Our results confirm the feasibility of IMRT in achieving excellent locoregional control and low rates of xerostomia. According to our knowledge, this study is the largest report of patients treated with IMRT for OPC.

Oropharyngeal cancer, IMRT, Head-and-neck cancer, Xerostomia, Dysphagia.

INTRODUCTION

Oropharyngeal malignancies are frequently asymptomatic until reaching significant size or metastasizing to the regional lymphatics and thus most patients present with locally advanced disease. Primary radiotherapy is currently the mainstay of treatment because of the significant functional impairment associated with classical surgical resection in this location (1, 2). With the advent of highly conformal radiotherapy (RT) techniques and level I evidence favoring the use of concurrent chemotherapy in advanced disease (4, 5), relatively high rates of locoregional control have been achieved in the treatment of oropharyngeal cancer (OPC) (6–8). Partly as a result of this success, increased attention has been focused on the avoidance of long-term toxicities associated with chemoradiotherapy, including xerostomia, dysphagia, osteoradionecrosis, and trismus.

Intensity-modulated RT (IMRT) allows for excellent target coverage and minimizes dose to surrounding normal tissues, provided that target delineation and treatment delivery are accurate (9, 10). The dosimetric advantages afforded by IMRT have allowed for parotid-sparing techniques and reduction in rates of late xerostomia (11–13).

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At our institution, IMRT was first implemented in 1998, and an initial report of the first 50 OPC patients treated with this technique has previously been published (6). In this report, we aim to evaluate our single institution experience in the treatment of OPC with IMRT by updating our results with lengthier follow-up and a greater number of patients.

METHODS AND MATERIALS

Patient/staging evaluation

Between September 1998 and April 2009, 472 patients with histologically confirmed squamous cell carcinoma (SCC) of the oropharynx underwent IMRT at our center. Among these patients, 26 had previously received RT to the head and neck, and 4 had metastatic disease at presentation. The 442 remaining patients formed the population for the present analysis. Of these 442, 30 were treated postoperatively, whereas 412 received definitive RT.

Pretreatment evaluation included a complete history/physical examination, flexible fiberoptic endoscopic examination, complete blood counts, liver function tests, chest X-ray, dental evaluation, as well as magnetic resonance imaging and/or computed tomography (CT) scans of the head-and-neck region. Bone scans, CT scans of the chest and abdomen, and positron emission tomography scans were obtained for most patients before the start of treatment.

Table 1. Patient and treatment characteristics

Factor	*n* (%)
Age	
≤55	206 (46.6)
>55	236 (53.4)
Gender	
Male	379 (85.7)
Female	63 (14.3)
Site	
Tonsil	221 (50.0)
BOT	202 (45.7)
Pharyngeal wall	12 (2.7)
Soft palate	7 (1.6)
T stage	
T1	118 (26.7)
T2	185 (41.9)
T3	78 (17.6)
T4	61 (13.8)
N stage	
N0	41 (9.3)
N1	94 (21.3)
N2	296 (67.0)
N3	11 (2.5)
AJCC stage	
I	7 (1.6)
II	17 (3.8)
III	94 (21.3)
IV	324 (73.3)
Chemotherapy	404 (91.4)
Concurrent	389 (88.0)
Cisplatin	244 (55.2)
Carboplatin/5-FU	43 (9.7)
Cetuximab	41 (9.3)
Cisplatin/bevacizumab	39 (8.8)
Other	22 (5.0)
Induction + concurrent	11 (2.5)
Induction only	2 (0.5)
Concurrent + adjuvant	2 (0.5)

Abbreviations: 5-FU = 5-fluorouracil; BOT = base of tongue; SP = soft palate; PW = pharyngeal wall; AJCC = American Joint Committee on Cancer.

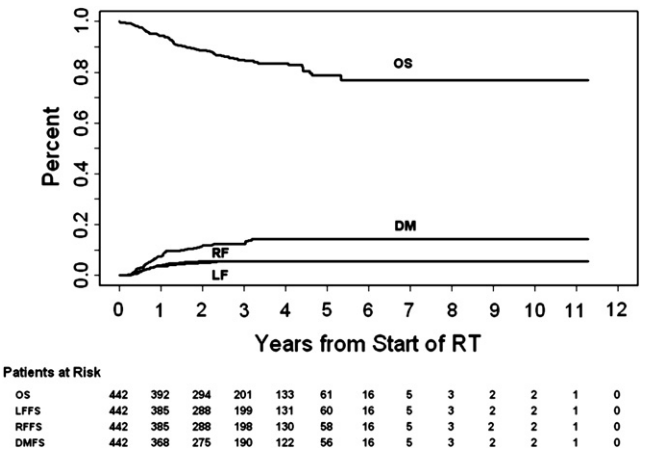

Fig. 1. Kaplan-Meier OS rate and cumulative incidence of LF, RF, and DM. *Abbreviations*: LF = local failure; RF = regional failure; DM = distant metastasis; LFFS = local failure-free survival; RFFS = regional failure-free survival; DMFS = distant metastasis-free survival.

Radiotherapy

Our approach to treatment planning has been previously detailed (6, 14). In brief, all patients received external beam radiotherapy using IMRT. Patients were immobilized in the supine position with a thermoplastic head/neck mask ± shoulder mask to ensure daily reproducibility of treatments. All target volumes were outlined slice by slice at 3-mm intervals on treatment planning CT images. The gross tumor volume (GTV) was defined as the gross extent of tumor visible by imaging studies and clinical examination. On the basis of primary tumor size and extent of regional node involvement, the high-risk clinical tumor volume ($CTV_{59.4}$), or subclinical disease, was defined as the GTV plus a margin for potential microscopic spread, including the lymph node areas at risk. At the primary, the $CTV_{59.4}$ was defined as the GTV plus a 1.0- to 1.5-cm margin. For the node-positive neck,

Table 2. Univariate analysis: treatment outcomes

	OS	LF	RF	DM
Variable	*p* value			
Age (>55 vs. ≤55)	0.46	0.88	0.78	0.95
T stage (T3–4 vs. T1–2)	<0.0001	0.01	0.93	0.02
N stage (N2–3 vs. N0–1)	0.01	0.67	0.37	0.002
Treatment modality (definitive vs. postop)	0.48	0.19	0.66	0.37
Primary subsite				
Tonsil (reference)				
BOT	0.16	0.40	0.67	0.39
SP/PW	0.82	*	*	0.58

Abbreviations: OS = overall survival; LF = local failure; RF = regional failure; DM = distant metastasis; postop = postoperative; BOT = base of tongue; SP = soft palate; PW = pharyngeal wall.

* Excluded from analysis because of insufficient events.