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CLINICAL INVESTIGATION **Head and Neck**

OUTCOMES OF POSTOPERATIVE SIMULTANEOUS MODULATED ACCELERATED RADIOTHERAPY FOR HEAD-AND-NECK SQUAMOUS CELL CARCINOMA

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Purpose: To evaluate the treatment efficacy and toxicity of postoperative simultaneous modulated accelerated radiotherapy (SMART) for patients with head-and-neck squamous cell carcinoma (HNSCC).

Methods and Materials: Between February 2003 and September 2008, 51 patients with histologically confirmed HNSCC received postoperative intensity-modulated radiotherapy ($N = 33$) or helical tomotherapy ($N = 18$) using SMART after curative surgical resection. The sites included were the oral cavity (OC), oropharynx (OP), larynx, and hypopharynx in 23, 20, 5, and 3 patients, respectively.

Results: The median follow-up duration of all patients and surviving patients were 32 (range, 5–78 months) and 39 months (range, 9–77 months), respectively. The 3-year overall survival, cause-specific survival, disease-free survival, locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS) in all patients were 71%, 77%, 75%, 85%, and 82%, respectively. Although no significant difference in 3-year LRRFS were found between OC (82%) and OP (82%) carcinomas, the 3-year DMFS was worse in cases of OC (66%) carcinoma compared with OP carcinoma (95%; $p = 0.0414$). Acute Grade 3 dermatitis, mucositis, and esophagitis occurred in 10%, 10%, and 2% of patients, respectively. At the last follow-up, Grade 3 xerostomia was documented in 10% of the patients. Young age (≤40 years) ($p < 0.001$) and OC carcinoma primary ($p = 0.0142$) were poor risk factors on univariate analysis for DMFS.

Conclusion: Postoperative SMART was observed to be effective and safe in patients with HNSCC. © 2011 Elsevier Inc.

Intensity-modulated radiotherapy, IMRT, Helical tomotherapy, Postoperative radiotherapy, Head-and-neck cancer.

INTRODUCTION

Surgical resection followed by postoperative radiotherapy (RT) remains the standard of care for most patients with locally advanced head-and-neck squamous cell carcinoma (HNSCC) deemed to be resectable. In an attempt to improve therapeutic outcomes, a variety of altered fractionation schedules of hyperfractionation and acceleration with concomitant boost RT technique were developed in the 1990s and were shown to be better than standard fractionation in terms of locoregional control (LRC) (1). On the other hand, 2 Phase III randomized trials showed that concurrent chemo-radiotherapy (CCRT) yielded better LRC than RT alone, with modest survival advantage for CCRT in disease with positive margin or extracapsular extension (ECE) in the postoperative setting (2–4).

With the advent of intensity-modulated radiotherapy (IMRT), it has been easier and more efficient to deliver higher doses to the tumor while sparing normal structures such as parotid glands, and IMRT is recently becoming more popular in the treatment of HNSCC as well as nasopharyngeal carcinoma. In a previous study of patients with locally advanced nasopharyngeal carcinoma, we showed that IMRT, as a simultaneous modulated accelerated radiotherapy (SMART), was effective in terms of LRC and delayed toxicity (5). Helical tomotherapy (TOMO) is one of the advanced forms of IMRT that can make treatment planning precise and accurate, with dosimetric advantages over IMRT already suggested in head-and-neck carcinoma by some investigators (6–9). Although clinical experiences using SMART on head-and-neck carcinoma have been published and reviewed (10), studies of pure postoperative SMART for HNSCC other than nasopharyngeal carcinoma are rare (11), compared with studies for definitive treatment.

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As an objective of this study, we report our single-institution experience of postoperative SMART in HNSCC patients in terms of treatment efficacy and toxicity.

METHODS AND MATERIALS

Study population

Between February 2003 and September 2008, 51 patients with newly diagnosed HNSCC underwent curative surgical resection, followed by postoperative IMRT (N = 33) and TOMO (N = 18). The sites included were as follows: oral cavity (OC), 23 patients; oropharynx (OP), 21; larynx, 5; and hypopharynx, 3. Patient characteristics are summarized in Table 1. The study was performed in accordance with the guidelines of our Institutional Review Board, and informed consent was obtained from each patient before initiating treatment.

Preoperative evaluation and surgery

All patients underwent a preoperative evaluation, including a complete history, physical examination, complete blood count, biochemical profile, chest radiography, and computed tomography (CT) scan or magnetic resonance imaging (MRI) of the head and neck. Esophagography or esophagoscopy was added for hypopharyngeal carcinoma. Tests to rule out distatant metastases were reserved for patients with any symptom or abnormal finding suspicious on chest radiographs, CT scan, or MRI. An [^{18}F] fluoro-deoxyglucose positron emission tomography (FDG-PET) scan was performed in 31 (60.8%) patients, 14 (45.2%) and 17 (94.4%) of whom had IMRT and TOMO, respectively, because it was not routinely done before the start of 2004. All patients underwent neck dissection, except 2 patients with tonsillar carcinoma referred from outside hospitals. Negative margin were achieved in 33 patients, close margin of <3 mm in 13 patients, and involved margin in 3 patients, including 1 patient with carcinoma *in situ*. Gross residual metastatic lymph nodes were suspicious on planning FDG-PET images in 2 patients after surgical resection. The pathologic stage distribution of patients with OC and OP carcinomas after surgery are summarized according to the 2002 American Joint Committee on Cancer (AJCC) staging system in Table 2. No patient had distant metastasis at the time of diagnosis. The median interval between surgery and the start of RT was 35 days (range, 25–112 days).

Table 1. Patient characteristics (N = 51)

Characteristic	No. of patients	%
Gender		
Male	34	67
Female	17	33
Age (y)		
Median	57	
Range	24–77	
Primary tumor site		
Oral cavity	23	45
Oral tongue	19	
Floor of mouth	1	
Hard palate	1	
Retromolar trigone	1	
Gingiva	1	
Oropharynx	20	39
Tonsil	15	
Base of tongue	3	
Vallecula	2	
Larynx	5	
Supraglottis	5	10
Hypopharynx	3	6
Pyriform sinus	3	
Stage (AJCC)		
I	2	4
II	6	12
III	8	15
IV	35	69

Abbreviation: AJCC = American Joint Committee on Cancer.

Chemotherapy

Two patients with gross residual disease on FDG-PET after surgery underwent CCRT. The concurrent chemotherapeutic regimen at our institution was weekly cisplatin of 40 mg/m^2 on day1, 8, 15, 22, 29, 36 and 43. One patient completed the full schedule of weekly chemotherapy during RT, whereas the other patient received only the first four cycles because of poor compliance.

Simulation, delineation of target volume, and normal structure

The patients were immobilized from the vertex to the shoulders with a thermoplastic mask in the supine position. A treatment planning CT scan (Philips Ultra Z; Philips Medical System, Andover, MA; or LightSpeed 5.X; GE Medical System, Waukesha, WI) from the vertex to the upper mediastinum was acquired at 2.5- to 4-mm intervals. Organs-at-risk (OARs), including the brain stem, spinal cord, parotid glands, eye globes, optic nerves, and chiasm were then contoured in the planning stage.

Gross tumor volume (GTV) was defined as the gross residual extent of the primary tumor or involved lymph nodes determined from planning CT, MRI, and FDG-PET images. The high-risk clinical target volume (CTV) was divided as follows: CTV1a, the at-risk area harboring microscopic disease, such as the nodal areas of extracapsular extension (ECE) or a surgical bed with microscopically involved margin; and CTV1b, the positive nodal areas without ECE or a clear surgical bed. The intermediate-risk CTV (CTV2) and low-risk CTV (CTV3) were defined as the nodal stations next to CTV1 and the volume of elective nodal stations other than CTV1 and CTV2, such as the contralateral level IV and V areas, respectively. All of these targets were contoured with additional circumferential 3- to 5-mm margin to accommodate the daily patient setup uncertainty and defined as PGTV, PCTV1a, PCTV1b, PCTV2, and PCTV3, respectively. Except for the case of ECE, the PTVs were

Table 2. AJCC stage distribution of patients with oral cavity (N = 23) and oropharyngeal cancer (N = 20)

	N0	N1	N2a	N2b	N2c	N3
Oral cavity						
T1	1	2	0	1	0	0
T2	2	3	0	5	0	0
T3	0	0	0	2	0	0
T4a	2	1	0	2	2	0
Oropharynx						
T1	1	0	0	1	1	0
T2	4	2	1	7	1	1
T4a	0	0	0	1	0	0

Abbreviation: AJCC = American Joint Committee on Cancer.