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CLINICAL INVESTIGATION **Head and Neck Cancer**

LONG-TERM OUTCOMES OF EARLY-STAGE NASOPHARYNGEAL CARCINOMA PATIENTS TREATED WITH INTENSITY-MODULATED RADIOTHERAPY ALONE

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Purpose: Reports of intensity-modulated radiotherapy (IMRT) for early-stage nasopharyngeal carcinoma (NPC) have been limited. The present study evaluated the long-term survival outcomes and toxicity of early-stage NPC patients treated with IMRT alone.

Methods and Materials: Between February 2001 and January 2008, 198 early-stage (T1-T2bN0-N1M0) NPC patients had undergone IMRT alone. The data from these patients were retrospectively analyzed. The patients were treated to 68 Gy at 2.27 Gy/fraction prescribed to the planning target volume of the primary nasopharygeal gross tumor volume. The Radiation Therapy Oncology Group scoring system was used to assess the toxicity.

Results: At a median follow-up of 50.9 months (range, 12–104), the 5-year estimated disease-specific survival, local recurrence-free survival, and distant metastasis-free survival rate was 97.3%, 97.7%, and 97.8%, respectively. The 5-year local recurrence-free survival rate was 100% for those with Stage T1 and T2a and 94.2% for those with Stage T2b lesions ($p = 0.252$). The 5-year distant metastasis-free survival rate for Stage T1N0, T2N0, T1N1, and T2N1 patients was 100%, 98.8%, 100%, and 93.8%, respectively ($p = .073$). All local recurrence occurred in patients with T2b lesions. Five patients developed distant metastasis. Of these 5 patients, 4 had had Stage T2bN1 disease and 1 had had Stage T2bN0 disease with retropharyngeal lymph node involvement. The most common acute toxicities were mainly Grade 1 or 2. At 24 months after IMRT, no Grade 3 or 4 xerostomia had developed, and 62 (96.9%) of 64 evaluated patients were free of trismus; only 2 patients (3.1%) had Grade 1 trismus. Radiation encephalopathy and cranial nerve injury were not observed.

Conclusions: IMRT alone for Stage T1N0, T2N0, T1N1, and T2N1 yielded satisfactory survival outcomes with acceptable toxicity, and no differences were found in survival outcomes among these four subgroups. Patients with Stage T2b lesions might have relatively greater risk of local recurrence and those with T2bN1 disease mighth have a greater risk of distant metastasis.

Nasopharyngeal carcinoma, Early stage, Intensity-modulated radiotherapy, Prognosis, Toxity.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an endemic disease in southern China. Early-stage NPC was defined as Stage I and II using the American Joint Committee on Cancer (AJCC) 2002 staging system. Definitive radiotherapy (RT) has been the main treatment modality for early-stage NPC, and the overall survival rate has been about 84–90% for those NPC patients with conventional two-dimensional conformal radiotherapy (2D-CRT) alone (1–4).

Different survival outcomes were observed in different subgroups of early-stage NPC treated with the 2D-CRT technique alone. Chua *et al.* (1) reported that the distant metastasis rate for those with Stage T1-T2N1 was much greater than that for those with Stage T1-T2N0 and that chemoradiotherapy is necessary for Stage T1-T2N1 disease to improve the prognosis of this group. In our previous report of 362 early-stage patients treated with 2D-CRT alone, we divided the patients with early-stage NPC into four subgroups (Stage T1N0, T2N0, T1N1, and T2N1) and found that the T2N1M0 subgroup was a unique group with the poorest prognosis because of distant metastasis. We suggested that only patients in the T2N1 group might need combined treatment instead of RT alone (2). Several publications have indicated that the combination of RT and chemotherapy improved the treatment outcomes for Stage II patients (5, 6).

Because it optimizes the radiation deposition in the tumor while sparing the adjacent normal structures, intensity-modulated RT (IMRT) has been widely used for NPC and has improved clinical outcomes, especially local control,

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in the past decades (7, 8). However, published data of IMRT for early-stage NPC with long-term survival and toxicity outcomes have been limited. The question remains of whether with IMRT, instead of 2D-CRT, would chemotherapy still be essential for Stage II patients. Therefore, we performed the present retrospective analysis to analyze the long-term outcomes of patients with early-stage NPC who had undergone IMRT alone and to determine whether differences existed in the survival outcomes among the different subgroups and whether the different subgroups would require different treatment strategies.

METHODS AND MATERIALS

Patients and patient workup

Between February 2001 and January 2008, 198 histologically proven, newly diagnosed, Stage I-IIb NPC patients had undergone primary, full-course definitive IMRT alone at the Cancer Center of Sun Yat-Sen University. None of these patients had received chemotherapy. Of the 198 patients, the male/female ratio was nearly 2.9:1, and the patient age range was 31 to 77 years (median, 45). The routine workup included a complete physical examination, hematologic and biochemistry profiles, fiberoptic endoscope examination of the nasopharynx, magnetic resonance imaging, or contrast-enhanced computed tomography of the head and neck to accurately evaluate the extent of the primary tumor and regional lymph nodes. Chest radiography, bone scintigraphy, and ultrasonography of the abdominal region were used to exclude distant metastases. All patients underwent disease staging using the AJCC 2002 staging system. The clinical characteristics are listed in Table 1, and the distribution by T and N classification is listed in Table 2.

Table 1. Patient characteristics (n = 198)

Characteristic	Value
Age (y)	
Range	31–77
Median	45
Gender	
Male	146 (73.7)
Female	52 (26.3)
Pathologic type	
WHO I	5 (2.5)
WHO II	15 (7.6)
WHO III	178 (89.9)
Staging method	
MRI	159 (80.3)
CT	39 (19.7)
Stage	
I	51 (25.8)
IIa	6 (3.0)
IIb	141 (71.2)

Abbreviations: WHO = World Health Organization; MRI = magnetic resonance imaging; CT = computed tomography.

Data presented as number of patients, with percentages in parentheses, unless otherwise noted.

Table 2. Distribution of T and N categories

	Stage		
Stage	N0	N1	Total
T1	51	12	63
T2a	6	3	9
T2b	74	52	126
Total	131	67	198

Planning technique and target volume delineation

All patients were immobilized in the supine position with a head, neck, and shoulder thermoplastic mask. Two set images, with and without contrast, were obtained from the computed tomography simulator for treatment planning purposes. All patients were scanned with serial 3-mm slices from the vertex through the clavicles. Inverse IMRT planning was performed using the Corvus system, version 3.0 (Peacock, Nomos, Deer Park, IL), and a MiMi multileaf collimator (Nomos, Sewickly, PA) was used for planning and treatment.

The target volumes were defined in accordance with the International Commission on Radiation Units and Measurements reports 50 and 62. All target volumes were delineated slice by slice on the treatment planning computed tomography scan. The primary nasopharygeal gross tumor volume (GTVnx) and that for the involved cervical lymph nodes were determined from the imaging, clinical, and endoscopic findings. The enlarged retropharyngeal nodes were outlined, together with primary GTV, as the GTVnx on the IMRT plans. The first clinical tumor volume (CTV) was defined as the GTVnx plus a 5–10-mm margin for potential microscopic spread, including the entire nasopharynx mucosa plus a 5-mm submucosal volume. The second CTV (CTV2) was defined by adding a 5–10-mm margin to the first CTV (when the CTV2 was adjacent to critical organs, such as the brainstem and spinal cord, the margin was reduced to 3–5 mm) and included the retropharyngeal lymph nodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus, and posterior edge of the nasal cavity and maxillary sinuses. The upper neck was also included in CTV2. For Stage N1 patients, the lower neck area also received conventional anterior cervical field radiation with a midline shield to 50 Gy in 2-Gy daily fractions. For Stage N0 patients, RT did not include the lower neck field. The adjacent critical organs, including the brainstem, spinal cord, temporal lobe, optic nerves, optic chiasm, lens, parotid glands, mandible, and temporomandibular joints, were also delineated.

Evaluation of IMRT planning

Inverse planning was performed on the Corvus System for all patients using Simultaneous Modulated Accelerated Radiation Therapy boost RT (9). The dose–volume histograms of the treatment targets and critical normal structures were evaluated. The prescribed dose was 68 Gy to the planning target volume (PTV) of the GTVnx, 60 Gy to the PTV of the first CTV, 54 Gy to the PTV of the CTV2, and 64–66 Gy to the PTV of the GTV for the involved cervical lymph nodes in 30 fractions. For the GTV and CTV, the target volumes receiving ≥95% of the prescribed dose was used to reflect the target coverage, and the maximal, minimal, and mean doses delivered to the target volumes were also calculated. For the critical organs with functional subunits organized in series, such as the brainstem, optic chiasm, and optic nerves, the dose to 5% of the volumes was examined. For the critical organs with functional subunits organized in parallel (*e.g.,* the parotid glands, temporomandibular joints, and temporal lobes), the dose delivered to 33% of the volumes was evaluated. The dose distribution was also examined slice by slice on the CT images. The actual dose