Nasopharyngeal Carcinoma Treated with Precision-oriented Radiation Therapy Techniques Including Intensity-modulated Radiotherapy: Preliminary Results

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This paper reports preliminary results with intensity-modulated radiotherapy (IMRT) in nasopharyngeal carcinoma (NPC). Between August 2000 and May 2001, we treated 19 patients with NPC using IMRT. Twelve patients had stage I–II disease and seven had stage III–IV disease. Six patients received 9.0–19.8 Gy three-dimensional conformal radiotherapy (3D-CRT) before IMRT and 18 patients received a brachytherapy boost after IMRT. The mean follow-up time was 13.0 months. All patients with stage II–IV disease except one received two cycles of chemoradiotherapy with cisplatin and 5-fluorouracil (5-FU) during radiotherapy, followed by two to four cycles of chemotherapy after radiotherapy. Tumor response was assessed using clinical examination and computerized tomography or magnetic resonance imaging. The mean doses administered to the gross tumor volume and clinical tumor volume were 70.9 Gy and 63.2 Gy, respectively. The mean doses administered to the right and left parotid glands were 38.1 Gy and 38.6 Gy, respectively. All 19 patients had a complete response of primary and lymph node disease. Grade III mucositis developed during chemoradiotherapy in 15 patients (79%). In addition, clinical grade I xerostomia was recorded in nine patients, grade II in nine, and grade III in one. This study demonstrated that 3D-CRT, IMRT, intracavitary brachytherapy, and chemotherapy are effective and safe methods to treat NPC. Although IMRT treatment spared parotid gland function, its efficacy may be significantly influenced by disease stage and location of the neck lymph nodes. More cases and a longer follow-up to assess survival and complications are planned.

Key Words: nasopharyngeal carcinoma, xerostomia, intensity-modulated radiotherapy
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Radiotherapy is the main treatment for nasopharyngeal carcinoma (NPC). Long-term survival rates can reach 40% to 90%, depending on the tumor stage [1,2]. While a high percentage of patients can be cured by radiotherapy, their quality of life is greatly impaired by treatment sequelae [3, 4]. Xerostomia is a chronic complication of treatment that affects eating, swallowing, and speaking. Additionally, the sores may become infected. However, because the salivary glands lie within the treatment field in bilaterally opposed portals, the development of xerostomia is inevitable.

Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) can deliver the radiation dose to the target volume while only exposing

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nearby critical organs to low doses [3,5,6]. IMRT produces more complex three-dimensional dose distributions than 3D-CRT [6,7]. These results suggest that parotid-sparing radiotherapy for NPC may be achievable with IMRT [8,9].

Previous investigators have reported the use of IMRT for NPC, but few reports included simultaneous chemotherapy [8–10]. The safety of the combination of IMRT and chemotherapy, especially with 5-fluorouracil (5-FU), requires further study. This paper reports preliminary results in the first 19 patients treated primarily with IMRT and chemotherapy, with emphasis on the side effects of treatment.

Materials and Methods

From August 2000 to May 2001, 22 patients with histologically proven NPC were treated using IMRT in the Department of Radiation Oncology at Chung Shan Medical University Hospital. Three cases were excluded from the analysis because the gross tumor volume (GTV) received less than 56 Gy or the conventional bilaterally opposed fields received more than 20 Gy. The remaining 19 patients, 14 males and five females, were included in the analysis. Their ages ranged from 21 to 73 years (median, 47.6 years).

Pretreatment evaluation included a complete history and physical examination, complete blood count, liver and renal function tests, fiber optic endoscopy, chest roentgenography, magnetic resonance imaging (MRI) or computerized tomography (CT) of the nasopharynx and neck, bone scan, liver sonography, and dental evaluation. The disease was staged according to the 1997 American Joint Committee on Cancer (AJCC) staging classification [11]. The disease was classified as stage I in seven patients, stage II in five, stage III in five, and stage IV in two (Table 1). Histopathologic analysis confirmed non-keratinizing carcinoma (World Health Organization, WHO, II) in four patients and undifferentiated carcinoma (WHO III) in 15 patients.

Before image acquisition, all patients were immobilized in a supine position with head support and a thermoplastic mask. A volumetric CT image was acquired using a CT simulator (GE HiSpeed CT/1, GE Medical Systems, Milwaukee, WI, USA) coupled with a LAP4 laser (PatPos CTI/DUO; LAP Laser Applikationen GmbH, Lüneburg, Germany), and the image data were transferred to a SomaVision System (Varian Corporation, Palo Alto, CA, USA) for tumor contour and critical organ segmentation. The CT scan slice thickness was 3 mm throughout the scanned region. After all the targets and critical organs were identified, the data were transferred to an inverse planning system (Helio Planning System, Varian Corporation) for IMRT planning. Before treatment, treatment position was verified using portal images acquired using the PortalVision System (Varian Corporation). The GTV of a nasopharyngeal tumor was defined as the volume of gross visible tumor plus margins of 2 mm to 4 mm. The GTV for positive lymph node(s) was defined as the volume of gross visible metastatic lymph node(s) plus margins of 2 mm to 4 mm. The clinical tumor volume (CTV) was defined as the GTV plus a margin including the skull base, inferior two-thirds of the sphenoid sinus, the entire nasopharynx, retropharyngeal nodes, pterygoid fossae, posterior nasal cavity, posterior half maxillary sinuses, and parapharyngeal space. The planning target volume (PTV) was defined as the CTV plus 3 mm margins. To minimize the field-to-field junction error, the upper and lower neck regions were irradiated using an anterior–posterior (AP) portal with the same isocenter as IMRT treatment.

To design an inverse plan with the potential to provide both physical and biologic benefit, we assigned different doses to different targets, similar to the concept of simultaneous integrated boost. The goal was to deliver a minimum dose of 70 Gy to the GTV, 55–60 Gy to the CTV, and 65–70 Gy to the metastatic lymph node(s) with fraction sizes of 2.12 Gy, 1.7–1.8 Gy, and 2.0–2.12 Gy, respectively. The dose regimen was designed to keep the CTV target receiving conventional fractionation but to accelerate the dose to the GTV target. Therefore, this schedule could be considered a semi-accelerated radiotherapy schedule. The dose constraints to critical organs were 50 Gy to the brain stem, 40 Gy to the spinal cord, 45 Gy to the optic chiasm, and 33–35 Gy to the parotid glands. Six patients had received 3D-CRT of 9.0–18.0 Gy before IMRT began. The 3D-CRT treatment consisted of one AP and two bilaterally opposed portals with a daily fraction of 1.8 Gy. IMRT was delivered via seven fixed-gantry angles with a Varian 21EX Linear Accelerator (Varian Corporation). Before treatment, all plans underwent a quality assurance test that included a film isodose curve comparison and absolute dose check with an ion-chamber at the isocenter under a cylindrical water phantom designed in-house.

IMRT plans were prepared using the Helio inverse planning system. Pre-selected coplanar beams were used at non-equiangular spacing for all NPC plans in this study. The spinal cord and brain stem, treated as serial organs, were defined by a dose-based objective function with dose limits of less than 40 Gy and 50 Gy, respectively. As the

Table 1. Characteristics of patients undergoing precision-oriented radiation therapy techniques including intensity-modulated radiotherapy (IMRT)

Gender	Age	T	N	CRT (Gy)	IMRT (Gy)	Brachy	C/T	Xero
F	53	1	0	0	71.3	No	No	2
M	52	2	1	0	72.5	Yes	Yes	2
F	70	2	1	0	71.9	Yes	Yes	2
M	42	1	2	0	70.7	Yes	Yes	1
M	49	1	0	0	71.6	Yes	No	1
M	53	2	2	9.0	64.7	Yes	Yes	1
M	25	1	1	0	69.5	Yes	Yes	1
M	73	2	0	9.0	60.9	Yes	No	2
M	60	1	0	9.0	63.3	Yes	No	2
F	35	3	2	0	71.9	Yes	Yes	1
M	56	1	0	0	70.4	Yes	No	1
M	38	2	2	9.0	60.6	Yes	Yes	2
F	73	2	1	0	71.4	Yes	Yes	2
M	29	1	0	0	69.8	Yes	No	1
F	36	1	0	0	70.6	Yes	No	1
M	21	2	2	0	69.8	Yes	Yes	2
M	41	4	1	9.0	65.9	Yes	Yes	2
M	51	1	0	0	71.4	Yes	No	1
M	47	4	2	19.8	54.7	Yes	Yes	3

T = tumor status according to 1997 AJCC TNM staging system; N = nodal status according to 1997 AJCC TNM staging system; CRT = 3-dimensional conformal radiotherapy; Brachy = intracavitary brachytherapy boost; C/T = chemotherapy; Xero = xerostomia clinical grading [3].

parotid glands were proximal to the CTV, a high dose could not be prevented from reaching the parotid–CTV overlap region. We utilized a dose volume constraint for the parotid glands to allow less than 50% of the parotid volume to receive a dose higher than 35 Gy. After clinical parameters were set for the objective function, an engine based on a conjugate gradient algorithm searched for the optimal fluences to minimize the score function, or the general form of the objective function combined from the separate target and organ-at-risk objective functions with different priority factor settings.

Eighteen cases received a brachytherapy boost of 7.0 Gy given in two fractions after IMRT treatment. The dose calculation point was defined at the skull base. Distances from this point to the sources ranged from 1.2 cm to 2.5 cm as measured by lateral simulation film. All stage II–IV cases except one received concurrent chemoradiotherapy with cisplatin (60 mg/m^2 on days 1 and 28) and 5-FU (600 mg/m^2 on days 1–4 and 28–31), with two cycles given during radiotherapy and two to four cycles following radiotherapy.

Salivary function was evaluated by both subjective and objective methods. The subjective method for grading xerostomia was based on clinical symptoms: grade 0, no symptoms; grade 1, mild mouth dryness, able to eat meals without liquid; grade 2, moderate mouth dryness, always needs liquid while eating; grade 3, severe or complete dryness, usually wakes up at night to drink liquids [3]. Functional radioisotope (RI) sialography, sialoscintigraphy, was the objective method to evaluate parotid gland function. Tests were carried out before the start of radiotherapy and repeated 1, 3, and 6 months after the completion of radiotherapy. The secretion ratio (SR) at 6 months was used as the post-irradiated value for statistical comparison. Functional RI sialography has been described in detail by Tsujii [12]. SR is calculated by dividing the decrease in RI count after acid stimulation by the RI count before stimulation. Parotid gland SR is used as an objective method for estimation of salivary function pre- and postradiotherapy.

After completing radiotherapy, patients were evaluated every month for the first 3 months, then every 2–3 months for the next 6–15 months. A physical examination including a mirror examination or fiber optic endoscopy and palpation of the neck was performed at each visit. Post-treatment MRI or CT scan from the skull base to the neck was obtained 2–3 months after the completion of radiotherapy. MRI or CT examination was repeated every 6 months, while fiber optic endoscopy was performed every 3–6 months. The

follow-up time was defined from the end of radiotherapy to March 2002 and ranged from 8 to 18 months (mean, 13.0 months).

The Wilcoxon signed-rank test was used to compare differences in the SR of parotid glands pre- and post-radiotherapy. The α error was defined as 0.05. SPSS version 10 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Results

Table 2 lists the doses prescribed and delivered to the targets and critical organs. The GTV was prescribed a total dose of 70.0 Gy to 73.6 Gy (mean, 70.8 Gy). Five patients received 3D-CRT with 9.0 Gy in five fractions and one received 19.8 Gy in 11 fractions prior to IMRT. The fraction size in IMRT was 2.12 Gy in 18 patients and 2.0 Gy in one patient. The CTV was prescribed a total dose of 56 Gy in 17 patients and 50 Gy and 60 Gy, respectively, in the remaining two patients. The mean doses to the GTV and the CTV were 70.9 Gy and 63.2 Gy, respectively. The mean 95% volume dose to the GTV and the CTV were 70.0 Gy and 55.0 Gy, respectively. For the total dose, we calculated the sum of the doses from 3D-CRT and IMRT plans. The spinal cord, brain stem, and optic chiasm received mean doses of 36.4 Gy, 34.9 Gy, and 39.9 Gy, respectively, which was lower than the preset dose constraint. However, the mean dose to the bilateral parotid glands (37.5 and 38.1 Gy) was slightly higher than the mean preset constraint of 50% volume dose (34.6 and 34.5 Gy). The dose per fraction to the parotid glands ranged from 0.47 to 1.8 Gy.

Seventeen patients completed the entire course of radiotherapy within 54 days; the remaining two patients completed it within 60 days due to treatment interruption for grade III mucositis. All stage II–IV patients received concurrent chemoradiotherapy and 18 patients (94.7%) received treatment using a semi-accelerated dose schedule. All stage II–IV patients (12 cases) and three of seven stage I patients developed grade III mucositis (79%). Tube feeding during concurrent chemoradiotherapy was necessary for five patients (26.3%). Weight loss of at least 10% of pretreatment body weight occurred in 11 patients (57.8%). Only one patient had a grade III skin reaction at the field-to-field junction line. Grade I and II skin reactions occurred in 11 and 7 patients, respectively. Nine patients each developed grade I and II xerostomia 6 months after radiotherapy. One patient who had grade III xerostomia had received a 3D-CRT dose of 19.8 Gy prior to IMRT treatment. All 19 patients had an initial complete response evaluated at 2–3 months after completion of IMRT treatment. No locoregional recurrence was found during a mean follow-up of 13 months (range, 8–18 months). One patient (5.3%) developed metastasis to the right iliac bone 5 months after radiotherapy.

The mean preradiation parotid SR was 0.21 ± 0.18 (range, 0.0–0.49), and the mean postradiation parotid SR at 6 months was 0.12 ± 0.10 (range, 0.0–0.32). A significant difference ($p = 0.002$) was found between pre- and postradiation parotid gland SRs (Figure).

Discussion

Radiotherapy is the main treatment modality for NPC. Long-term locoregional control rates of more than 70% to 80% have been reported when the disease is treated in the early stages [2,10]. With the addition of chemotherapy, the outcome for advanced disease can be improved compared with radiotherapy alone [13,14]. With this established efficacy of radiotherapy with or without chemotherapy,

Table 2. Dose (Gy) prescribed and delivered to the targets and critical organs

	GTV	CTV	Parotid		Chiasm	Spinal cord	Brain stem
			Right	Left			
Prescribed*	70.8 ± 1.2	56.1 ± 1.1	34.6 ± 0.8	34.5 ± 0.9	45.2 ± 0.7	40.8 ± 1.4	45.8 ± 1.8
Minimum*	63.9 ± 10	42.0 ± 20	15.6	30.9	16.6	19.5	27.1
Maximum*	74.0 ± 1.8	72.5 ± 10.6	43.6	43.2	59.3	46.6	47.0
Mean*	70.9 ± 1.9	63.2 ± 13.2	37.5 ± 6.6	38.1 ± 3.2	39.9 ± 10.2	36.4 ± 7.2	34.9 ± 4.7
Median*	71.1 ± 1.8	63.8 ± 13.2	36.7 ± 9.5	33.8 ± 3.0	41.7 ± 8.5	39.6 ± 3.6	34.9 ± 4.5
95% volume*	70.0 ± 2.1	55.0 ± 19.7	–	–	–	–	–
50% volume*	–	–	34.9 ± 3.3	34.1 ± 2.9	40.1 ± 9.8	39.4 ± 3.7	34.6 ± 4.6

*Mean ± standard deviation. GTV = gross tumor volume; CTV = clinical tumor volume.

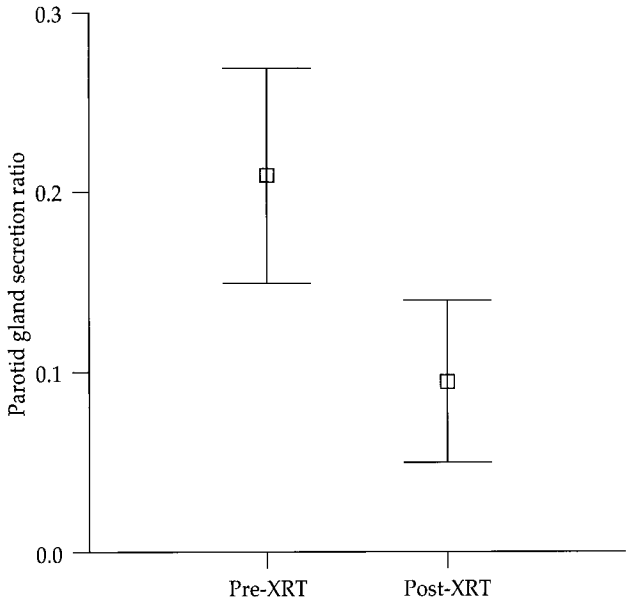

Figure. *Parotid gland saliva secretion ratios for all patients preradiation (pre-XRT) and postradiation (post-XRT). The bars represent the 95% confidence intervals for the means, and the central markers (□) represent the means.* p = *0.002.*

prevention of treatment-related sequelae is an important issue because the number of long-term survivors is increasing.

Xerostomia, the most frequent late complication, impairs the quality of life of NPC patients [3,4,15]. It affects speech, swallowing and chewing, and may increase susceptibility to dental caries and frequent oral infections [4]. In NPC, the CTV and PTV volume are adjacent to or even overlap portions of the bilateral parotid glands. Without IMRT or 3D-CRT, it is difficult to reduce the dose to the parotid glands. The goal of this study was to test the feasibility of concurrent chemotherapy with semi-accelerated radiotherapy using IMRT techniques. We also attempted to preserve parotid function by reducing the dose to the parotid glands. Mean doses to bilateral parotid glands were slightly higher than we expected. We also used intracavitary brachytherapy to boost doses at the primary site of the nasopharyngeal tumor because the dose contribution to bilateral parotid glands would be less than 0.5 Gy (5–7% of prescription dose). The doses to the parotid glands were much lower than if CRT or IMRT with the same doses had been used to boost the dose in the nasopharyngeal cavity. We found that at 6 months after radiotherapy, the mean postradiation parotid SR (0.12 ± 0.10) was significantly less than the preradiation SR (0.21 ± 0.18) (p = 0.002).

Several treatment plan comparison studies have concluded that IMRT plans achieve better parotid gland sparing than bilateral opposed or 3D-CRT plans [5–7]. Butler et al [8] and Sultanem et al [10] reported original data for IMRT treatment of head and neck tumors. In these studies, no patients developed clinical grade 3 xerostomia. Sultanem et al reported that grade 0 xerostomia developed in 50% of patients and grade 1 xerostomia in 50% [10]. In our series, nine patients (47.4%) developed grade 1 xerostomia, nine (47.4%) developed grade 2 xerostomia, and one patient (5.3%), who received 3D-CRT treatment (18 Gy) before IMRT, developed grade 3 xerostomia. These results are similar to those of Sultanem et al's [10]. The mean dose (34.5 Gy) to the left parotid gland was also similar to the 34 Gy used by Sultanem et al [10]. With a longer follow-up period, it might be expected that parotid function would be further improved. The results of objective and subjective salivary function tests demonstrated that, in a more aggressive attempt to preserve parotid gland function, lower dose constraints should be set. In our study, it was below 35 Gy to the parotid glands.

It is important to appreciate the acute toxic effects of IMRT and concurrent chemotherapy. In our study, all 12 chemoradiotherapy patients and three radiotherapy alone patients developed grade III mucositis (79%). Sultanem et al used a similar fraction size but had a lower percentage of grade III mucositis (51%) [10]. We offer two reasonable explanations for this difference. First, the regimens of concurrent chemotherapy were different: Sultanem et al used cisplatin alone while we used cisplatin with 5-FU. Second, the inclusion criteria for chemotherapy were different: Sultanem et al included 75% of stage III–IV cases while we included all stage II–IV cases. Although the incidence of grade III mucositis was 79%, 17 patients (89.5%) completed the whole course of radiotherapy within 54 days without grade IV mucositis or life-threatening complications. With careful, supportive management, this semi-accelerated fractionation plus concurrent chemotherapy with cisplatin and 5-FU is safe and practical.

In this study, 36.8% of patients had stage III–IV disease. The locoregional complete remission rate of 100% was achieved during a mean follow-up of 13 months. Our finding is compatible with the results of Sultanem et al [10], who reported 100% locoregional progression-free survival over 48 months. Although additional investigation with more patients and a longer follow-up is necessary, IMRT with or without chemotherapy demonstrated marked improvement in the preservation of parotid gland function while maintaining or even improving the locoregional control rate when compared with conventional treatment.

Conclusions

The excellent initial tumor response and decreased damage to the parotid glands with the combination of IMRT and chemotherapy suggest that this technique is efficacious as well as safe for the treatment of NPC. Although IMRT treatment spares parotid gland function, its efficacy may be significantly influenced by the disease stage and location of neck lymph nodes. Future research should incorporate a larger series of patients and a longer period of follow-up to better assess these initial promising results.

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以包含強度調控之精準導向放射治療鼻咽癌之初步結果

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本研究報告鼻咽癌患者經強度調控放射治療的初步結果及治療相關的急性反應。從2000 年 8 月到 2001 年 5 月共有 19 位鼻咽癌患者接受以強度調控放射治療為主的治療，其中第一至第二期與第三至四期的患者各有 12 及 7 位。有六位患者在接受強度調控放射線治療前先接受了三度空間順形放射治療，劑量是 9.0–19.8葛雷。平均患者追蹤時間為 13 個月（8–18 個月）。除了一位患者外，其餘第二期至第四期的患者皆在接受放射治療期間，接受兩個療程同步 cisplatin 及 5-FU 的化學治療；放療結束後再給予二至四個療程的輔助性化學治療。治療結果發現這 19 位患者原發及淋巴結的腫瘤均完全消失。在同步化學放射治療期間所發生的急性副作用包括：第三級黏膜反應有 15 位 (79%)，臨床上屬第一級的口乾症有 9 位，第二級的有 9 位，第三級的有一位。本研究結果發現合併三度空間順形療法、強度調控放射療法、腔內近接療法及化學療法是治療鼻咽癌的有效方法之一。雖然此方式對於耳下腺之保護較易達成但是保護成效仍然會受腫瘤期別、頸部淋巴結位置等因素所影響，因此更多的病例與更長時間的追蹤在此方面是必須的。

關鍵詞：鼻咽癌；口乾症；強度調控放射療法

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