Outcomes of patients with nasopharyngeal carcinoma treated with intensity-modulated radiotherapy

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ABSTRACT

Nasopharyngeal cancer shows a good response to intensity-modulated radiotherapy. However, there is no clear evidence for the benefits of routine use of image-guided radiotherapy. The purpose of this study was to perform a retrospective investigation of the treatment outcomes, treatment-related complications and prognostic factors for nasopharyngeal cancer treated with intensity-modulated radiotherapy and image-guided radiotherapy techniques. Retrospective analysis was performed on 326 consecutive nasopharyngeal cancer patients treated between 2004 and 2015. Potentially significant patient-related and treatment-related variables were analyzed. Radiation-related complications were recorded. The 5-year overall survival and disease-free survival rates of these patients were 77.9% and 70.5%, respectively. Age, AJCC (American Joint Committee on Cancer) stage, retropharyngeal lymphadenopathy, treatment interruption and body mass index were independent prognostic factors for overall survival. Age, AJCC stage, retropharyngeal lymphadenopathy, image-guided radiotherapy and body mass index were independent prognostic factors for disease-free survival. In conclusion, intensity-modulated radiotherapy significantly improves the treatment outcomes of nasopharyngeal cancer. With the aid of image-guided radiotherapy, the advantage of intensity-modulated radiotherapy might be further amplified.

Keywords: intensity-modulated radiotherapy; image-guided radiotherapy; nasopharyngeal cancer; body mass index

INTRODUCTION

Nasopharyngeal cancer (NPC) is one of the most common malignancies in Taiwan, with annual incidence rate of as high as 6.45 cases per 100,000 persons. Due to high radiosensitivity and anatomic limitation, radiotherapy alone for early disease, or in combination with chemotherapy for advanced lesions, has been the mainstay of treatment for NPC. The most important technical advance in radiotherapy during the past decades was the advent of intensity-modulated radiotherapy (IMRT) techniques. IMRT is a revolutionized form of three-dimensional conformal radiotherapy (3DCRT), and could deliver high non-uniform radiation doses to the targets while minimizing the radiation doses to the surrounding critical normal tissues [1]. Due to the excellent dosimetric advantages for target coverage and normal tissue sparing by using IMRT, promising treatment results have been reported [2–23].

In our institution, IMRT has been routinely employed for the treatment of NPC since 2004. Image-guided radiotherapy (IGRT) was introduced from 2008. This study was conducted to describe the treatment outcomes, treatment-related complications and prognostic factors for patients with NPC treated with IMRT and IGRT techniques with or without chemotherapy.
MATERIALS AND METHODS
From September 2004 to October 2015, a total of 326 consecutive patients with non-metastatic, histology-proven NPC were treated with IMRT at our department. Under the approval of the Institutional Review Board, the medical records of these patients were reviewed. All patients were ethnic Chinese. Patients with a prior or synchronous malignancy were excluded. All patients had a pre-treatment evaluation for oncologic survey and staging, including complete history, physical examination, fiberoptic nasopharyngoscopy, complete blood cell counts, blood biochemistry, chest radiographs, sonography of the abdomen, whole-body bone scan and magnetic resonance imaging (MRI) of head and neck. Pre-treatment dental assessment was routinely performed. For this study, all patients were restaged with the American Joint Committee on Cancer (AJCC) 2017 staging classification [24].

Radiotherapy techniques
All patients were immobilized with a customized thermoplastic head–neck–shoulder cast in the supine treatment position. Computed tomography (CT) scan with contrast enhancement was acquired in helical mode using a 2.5 mm slice thickness from the skull vertex to the middle of the chest. The CT data were transferred to the dosimetric treatment planning workstation for subsequent treatment design. Targets and normal tissues were contoured slice by slice on the axial CT images. The definition of target volumes was in accordance with the International Commission on Radiation Units and Measurements (ICRU) report 50, 62 and 83 [25–27]. The gross tumor volume (GTV) is defined as the whole known gross extent of the primary nasopharyngeal tumor and involved lymph nodes determined from MRI, physical examination and endoscopy. The clinical target volume (CTV) is defined as the tissue volume that contains a demonstrable GTV and/or subclinical microscopic disease. In this study, the GTV was expanded with 5–10 mm margins to generate the CTV1. The CTV2 is defined as the regions at high risk for harboring microscopic disease, including normal structures immediately surrounding the primary tumor with high risk of local tumor invasion (the entire nasopharynx, sphenoid sinus, skull base, clivus, pterygoid fossa, pterygopalatine fossa, parapharyngeal space, posterior third of nasal cavities and maxillary sinuses) and the high-risk lymphatic regions. The CTV3 is defined as the low-risk or electively irradiated lymphatic regions. Selective sparing of level IB lymphatics is considered for N0 disease. The planning target volume (PTV) is generated by adding a suitable margin (3–5 mm) around the corresponding CTV to compensate for the uncertainties of treatment set-up and patient movement. Plans were generated with the simultaneous integrated boost technique, which is characterized by irradiating different targets at different dose levels in a single treatment session. The prescribed doses for PTV1, PTV2 and PTV3 were 70, 63 and 54 Gy in 35 daily fractions, respectively. All plans were normalized such that at least 95% of the PTV1 is encompassed by the 70 Gy isodose surface. No more than 10% of PTV1 would receive ≥110% of the prescribed dose. No more than 1% of any distinct PTV should receive ≤93% of the prescribed dose. Critical normal structures including the brainstem, spinal cord, eyeballs, lenses, optic nerves, optic chiasm, middle and inner ears, temporal lobes, pituitary gland, parotid glands, temporomandibular joints, mandible, oral cavity, brachial plexus, glottis and cervical esophagus were contoured and considered as organs at risk during plan optimization. A margin of 0.5 cm around the spinal cord and brainstem was added to create the planning organ at risk volume (PRV). The dose constraints for critical structures were based on the Radiation Therapy Oncology Group (RTOG) Protocol 0225 and 0615 (the dose constraints are: brainstem: Dmax <54 Gy; spinal cord: Dmax <45 Gy; eyeballs: Dmax <50 Gy; lenses: Dmax <25 Gy; optic nerve and chiasm: Dmax <50 Gy; middle and inner ears: Dmax <50 Gy; temporal lobes: Dmax <60 Gy; pituitary gland: Dmax <50 Gy; parotid glands: Dmax <26 Gy; temporomandibular joints and mandible: Dmax <70 Gy; oral cavity: Dmax <55 Gy; brachial plexus: Dmax <66 Gy; glottis: Dmean <45 Gy; and cervical esophagus: Dmean <45 Gy). An individual plan was tailored to each patient’s anatomy and tumor invasion. Every effort was made to meet the constraints as closely as possible. Adaptive radiotherapy (re-planning) was routinely performed for all patients in this study. IGRT techniques were performed by using cone-beam CT or an on-board imager. Before 2008, we used an Elekta Precise linear accelerator and Pinnacle treatment planning system (Philips Radiation Oncology Systems, Fitchburg, WI, USA). Step-and-shoot techniques with seven fixed beams were used. After 2008, we also used the Varian Rapidarc linear accelerator and Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA). Volumetric-modulated arc therapy techniques were used.

Chemotherapy
Chemotherapy was delivered for patients with stage II, III and IVA diseases providing that there were no major medical comorbidities. Before 2007, the concurrent chemotherapy regimen was 100 mg m⁻² of cisplatin every 3 weeks for 2–3 cycles. Since 2007, we delivered concurrent chemotherapy weekly with 30 mg m⁻² of cisplatin. Cisplatin would be replaced by carboplatin if the creatinine clearance was <60 ml min⁻¹.

Patient follow-up
All patients were evaluated at least once a week by the treating physician for assessment and management of acute radiation-related toxicities during the course of radiotherapy. After the completion of radiotherapy, patients were examined at 4-week intervals until their acute radiation-related toxicities subsided. Patients were subsequently evaluated every 2–3 months for the first 5 years, and every 6 months thereafter. A baseline MRI of head and neck was obtained 2 months post-radiotherapy. Evaluation at each follow-up visit included clinical history and physical examination. Hematology and blood biochemistry, chest radiographs, sonography of abdomen, bone scan and MRI of head and neck were arranged at least yearly and were checked whenever there was any clinical indication. All local recurrences were diagnosed by biopsy for nasopharyngeal lesions or by MRI for skull base or intracranial lesions. Regional recurrences were diagnosed by physical examination and imaging studies (CT scan, MRI or positron emission tomography CT). Distant metastases were diagnosed by physical examination and suitable imaging studies (bone scan, positron emission tomography CT, CT scan, MRI or sonography). Acute and late
Table 1. Characteristics of 326 patients with nasopharyngeal carcinoma

| Characteristics            | No. of patients | Percentage |
|----------------------------|-----------------|------------|
| Gender                     |                 |            |
| Male                       | 258             | 79.1%      |
| Female                     | 68              | 20.9%      |
| Age                        |                 |            |
| ≤50                        | 167             | 51.2%      |
| >50                        | 159             | 48.8%      |
| AJCC stage                 |                 |            |
| Stage I                    | 33              | 10.1%      |
| Stage II                   | 99              | 30.4%      |
| Stage III                  | 116             | 35.6%      |
| Stage IVA                  | 78              | 23.9%      |
| Histology (WHO)            |                 |            |
| Type 1                     | 7               | 2.1%       |
| Type 2a                    | 101             | 31.0%      |
| Type 2b                    | 218             | 66.9%      |

AJCC, American Joint Committee on Cancer
WHO, World Health Organization.

radiation-related adverse effects were assessed and scored according to the RTOG Toxicity Criteria [28].

Statistics

The endpoints of this study were local control (LC) rate, regional control (RC) rate, distant failure-free (DFF) rate, disease-free survival (DFS) rate and overall survival (OS) rate. The time for each endpoint was measured from the first day of radiotherapy to the date of the defined event or the last follow-up visit, including the date of death. Treatment outcomes were analyzed in relation to patient and tumor characteristics using univariate and multivariate analyses. T category was divided into T1–2 and T3–4 groups. N category was divided into N0–1 and N2–3 groups. AJCC stage was divided into stage I–II and stage III–IVA groups. The estimate of LC, RC, DFS and OS was calculated actuarially with the Kaplan–Meier method [29]. Multivariate analysis was performed using the Cox proportional hazards model to define independent predictors among potential prognostic factors [31]. Differences between groups were calculated using the χ² test for categorical variables. All P values were two-sided, and P < 0.05 was considered as the statistical significance limit.

RESULTS

Patient characteristics

The median age was 49.7 years (range 19.4–82.6 years). There were 258 males and 68 females. T category distribution was: T1, 151 patients (46.3%); T2, 57 (17.5%); T3, 64 (19.6%); and T4, 54 (16.6%). N category distribution was: N0, 54 patients (16.6%); N1, 129 (39.5%); N2, 115 (35.3%); and N3, 28 (8.6%). The distribution of stages was: I, 33 patients; II, 99; III, 116; and IVA, 78. Tumor histology according to the World Health Organization (WHO) classification [32] was: type 1, 7 patients; type 2a, 101; and type 2b, 218. The characteristics of these patients are listed in Table 1. The distributions of T and N categories are listed in Table 2.

All patients completed the course of radiotherapy, and the duration of radiotherapy interruption ranged from 0 to 27 days (median 3 days).

Because our health insurance reimbursement did not pay for IGRT, only 125 patients were treated with IGRT techniques. The comparison of patient characteristics between patients with and without IGRT is shown in Table 3.

Before 2007, concurrent chemotherapy with 100 mg m⁻² of cisplatin every 3 weeks for 2–3 cycles was given to 40 patients. Since 2007, 3–7 cycles of weekly concurrent chemotherapy with 30 mg m⁻² of cisplatin were delivered to 253 patients. Cisplatin was replaced by carboplatin in five patients because the creatinine clearance was <60 ml min⁻¹.

Overall survival and disease-free survival

At the time of this retrospective review, 210 patients were alive with a median follow-up of 101.5 months (range 43–183). The 5-year OS rate of the entire cohort of patients was 77.9%. Univariate analysis revealed the following variables as significant prognostic factors for OS: age, T category, N category, AJCC stage, retropharyngeal lymphadenopathy (LAP), level V LAP, multiple LAP, bilateral LAP, interruption of radiotherapy, IGRT and body mass index (BMI). Multivariate analysis confirmed the independent prognostic significance of the following variables: age, AJCC stage, retropharyngeal LAP, interruption of radiotherapy and BMI.

The 5-year DFS rate was 70.5% for all patients. Univariate analysis revealed the following variables as significant prognostic factors for DFS: age, T category, N category, AJCC stage, retropharyngeal LAP, level V LAP, bilateral LAP, interruption of radiotherapy, IGRT and BMI. Multivariate analysis further confirmed the independent prognostic significance of the following variables: age, AJCC stage, retropharyngeal LAP, IGRT and BMI.

Table 2. Distribution of T and N categories

|     | N0 | N1 | N2 | N3 | Total |
|-----|----|----|----|----|-------|
| T1  | 33 | 69 | 39 | 10 | 151   |
| T2  | 6  | 24 | 19 | 8  | 57    |
| T3  | 10 | 17 | 31 | 6  | 64    |
| T4  | 5  | 19 | 26 | 4  | 54    |
| Total | 54 | 129| 115| 28 | 326   |
Table 3. Comparison of patient characteristics between patients with and without IGRT

|            | IGRT   | No IGRT |
|------------|--------|---------|
| T category | P = 0.100 |
| T1         | 67     | 84      |
| T2         | 15     | 42      |
| T3         | 22     | 42      |
| T4         | 21     | 33      |
| N category | P = 0.311 |
| N0         | 19     | 35      |
| N1         | 57     | 72      |
| N2         | 41     | 74      |
| N3         | 8      | 20      |
| Stage      | P = 0.634 |
| I          | 11     | 22      |
| II         | 43     | 56      |
| III        | 43     | 73      |
| IVA        | 28     | 50      |

IGRT, image-guided radiotherapy.

Local control
In this study, 30 patients developed local recurrence, and the overall 5-year LC rate was 91.3%. Univariate analysis revealed age and T category as significant predictors for LC. The 5-year LC rates for T1/2 and T3/4 were 94.8% and 84.8%, respectively (P < 0.001). Multivariate analysis confirmed that T category was the only independent prognostic factor for LC. Salvage treatment included radiotherapy with chemotherapy in 25 patients and operation in 5 patients.

Regional control
Eleven patients developed regional relapse, and the 5-year RC rate was 96.8%. Univariate analysis showed that T category, N category and bilateral LAP were significant prognostic factors for RC. Multivariate analysis confirmed that N category was the only independent prognostic factor for RC. Salvage treatment was operation in 11 patients.

Metastasis
A total of 52 patients developed distant metastases during the follow-up period. The sites of distant metastasis were bone (36 patients), lung (21 patients), liver (20 patients) and others (14 patients). Twenty-seven patients had multiple distant metastases (2 sites, 18 patients; 3 sites, 7 patients; 4 sites, 2 patients). The 5-year DFF rate for the entire cohort of patients was 85.2%. Univariate analysis revealed the following variables as significant predictors for distant metastasis: N category, AJCC stage, retropharyngeal LAP, level V LAP, multiple LAP, bilateral LAP, interruption of radiotherapy and BMI. Multivariate analysis revealed that N category, retropharyngeal LAP and BMI were independent predictors for distant metastasis.

For patients with distant metastasis, the salvage treatment was mainly systemic chemotherapy with or without palliative radiotherapy. The details of univariate and multivariate analysis are listed in Tables 4 and 5.

Treatment toxicity
All patients had radiation-related adverse effects. The most common acute toxicities were xerostomia, oral mucositis, pharyngitis, dermatitis and laryngitis. The most common late toxicity was xerostomia. The blood levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were checked in 262 patients. Biochemical hypothyroidism was defined as a TSH value >5.0 mIU l⁻¹ and/or FT4 <0.7 ng dl⁻¹. There were 122 patients (46.6%) with biochemical hypothyroidism and the interval between the completion of radiotherapy and the first occurrence of biochemical hypothyroidism ranged from 6.1 to 99.4 months (median 29.0 months). Radionecrosis of the mandible was noted on MRI in two patients. They received biopsy of the mandible, and pathology showed necrosis. They subsequently received hyperbaric oxygen therapy. The incidence of acute and late toxicities is given in Table 6.

DISCUSSION
Radiotherapy is the major treatment modality for NPC. Prior to the advent of IMRT, conventional two-dimensional (2D) or 3D CRT techniques were used and the treatment outcomes were suboptimal. IMRT is a complex form of 3D CRT and could deliver non-uniform doses to the targets via multiple intensity-modulated beams. Due to the excellent dosimetric advantages for target coverage and normal tissue sparing by using IMRT, there were results showing significant improvement in treatment outcomes compared with 2D radiotherapy [2, 3, 9, 21, 23]. However, there were also some reports indicating that IMRT has no advantage over conventional 2D or 3D radiotherapy [33–35].

In this article, we reported the treatment outcomes of NPC patients receiving IMRT. Locoregional control is the main goal of radiotherapy. Compared with our historical report for NPC treated with 2D techniques [36], substantial improvement was observed in patients treated with IMRT. The 5-year LC rate improved from 78% to 91.3%. The incidence of local failure decreased from 22% to 9.2%. The reported incidence of local failure for NPC patients treated with IMRT ranged from 4.2% to 10.9% [3, 5, 7, 8, 10–12, 15, 18, 20, 34, 37–41]. The improved treatment outcomes might be mainly attributed to the increased accuracy of target contouring and dose delivery in the IMRT era. For patients with T4 disease treated with IMRT, the reported incidence of local failure ranged from 7.3% to 22.9% [14, 19, 22]. In our study, the incidence of local failure was 9.2% for the entire cohort of patients and 14.8% for those with T4 diseases. Compared with the reported series, there was still room for improvement. The role of T category in LC was still controversial. T category was ever reported as an independent prognostic factor for LC [20]. Some investigators demonstrated that T category was no longer a significant predictor for LC in the IMRT era [4, 6, 15, 18, 42]. In our study, T category was demonstrated as the only independent prognostic factor for LC. The 5-year LC rates for T1/2 and T3/4 were 94.8% and 84.8%, respectively (P < 0.001). According to our current treatment protocol, the prescribed radiation doses were the same between different T categories. A radiation dose–response relationship has been observed in several retrospective studies [43, 44]. Therefore, the delivery of a higher radiation dose for locally advanced diseases might play an important role in improving the LC rate. Our further study will explore the impact of the delivery of boost irradiation for patients with T3/4 tumors. Another way to
Table 4. Univariate analysis of prognostic factors

|                | No. | 5-year OS | P < 0.001 | 5-year DFS | P < 0.001 | 5-year LC | P = 0.048 | 5-year RC | P = 0.895 | 5-year DFF | P = 0.053 |
|----------------|-----|-----------|-----------|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| **Age**        |     |           |           |            |           |           |           |           |           |           |           |
| ≤50            | 167 | 85.6%     | 78.4%     | 93.5%      | 96.2%     | 88.9%     |           |           |           |           |           |
| >50            | 159 | 69.8%     | 62.2%     | 89.0%      | 97.3%     | 80.5%     |           |           |           |           |           |
| **T category** |     |           |           |            |           |           |           |           |           |           |           |
| T1             | 151 | 84.8%     | 79.4%     | 95.1%      | 98.7%     | 88.6%     |           |           |           |           |           |
| T2             | 57  | 71.9%     | 64.9%     | 94.0%      | 89.6%     | 90.3%     |           |           |           |           |           |
| T3             | 64  | 76.6%     | 65.5%     | 84.4%      | 98.4%     | 83.4%     |           |           |           |           |           |
| T4             | 54  | 66.6%     | 57.3%     | 85.6%      | 96.2%     | 72.4%     |           |           |           |           |           |
| **N category** |     |           |           |            |           |           |           |           |           |           |           |
| N0             | 54  | 96.3%     | 87.0%     | 92.3%      | 100%      | 96.3%     |           |           |           |           |           |
| N1             | 129 | 82.2%     | 75.1%     | 89.3%      | 98.4%     | 90.3%     |           |           |           |           |           |
| N2             | 115 | 68.7%     | 60.7%     | 91.1%      | 95.4%     | 78.9%     |           |           |           |           |           |
| N3             | 28  | 60.5%     | 57.3%     | 100%       | 86.9%     | 63.5%     |           |           |           |           |           |
| **Stage**      |     |           |           |            |           |           |           |           |           |           |           |
| I              | 33  | 93.9%     | 87.9%     | 93.5%      | 100%      | 97.0%     |           |           |           |           |           |
| II             | 99  | 88.9%     | 81.8%     | 93.8%      | 99.0%     | 92.7%     |           |           |           |           |           |
| III            | 116 | 73.3%     | 65.4%     | 84.4%      | 96.3%     | 86.0%     |           |           |           |           |           |
| IVA            | 78  | 64.0%     | 56.4%     | 89.5%      | 92.9%     | 69.1%     |           |           |           |           |           |
| **RP LAP**     |     |           |           |            |           |           |           |           |           |           |           |
| Without        | 148 | 88.5%     | 82.4%     | 92.3%      | 97.9%     | 93.8%     |           |           |           |           |           |
| With           | 178 | 69.0%     | 60.5%     | 90.2%      | 95.7%     | 77.7%     |           |           |           |           |           |
| **Level V LAP**|     |           |           |            |           |           |           |           |           |           |           |
| Without        | 272 | 80.9%     | 73.5%     | 91.7%      | 96.9%     | 87.6%     |           |           |           |           |           |
| With           | 54  | 63.0%     | 55.2%     | 87.8%      | 95.9%     | 72.6%     |           |           |           |           |           |
| **Multiple LAP**|   |           |           |            |           |           |           |           |           |           |           |
| Without        | 123 | 86.2%     | 78.0%     | 89.8%      | 98.3%     | 91.6%     |           |           |           |           |           |
| With           | 203 | 72.9%     | 65.9%     | 92.1%      | 95.8%     | 81.2%     |           |           |           |           |           |
| **Bilateral LAP**| |           |           |            |           |           |           |           |           |           |           |
| Without        | 188 | 85.6%     | 78.1%     | 90.4%      | 98.9%     | 91.2%     |           |           |           |           |           |
| With           | 138 | 67.3%     | 60.0%     | 92.5%      | 93.7%     | 76.5%     |           |           |           |           |           |
| **Interruption**| |           |           |            |           |           |           |           |           |           |           |
| ≤5 days        | 211 | 83.4%     | 75.3%     | 92.8%      | 96.5%     | 88.7%     |           |           |           |           |           |
| >5 days        | 115 | 67.8%     | 61.7%     | 88.2%      | 97.1%     | 78.5%     |           |           |           |           |           |
| **IGRT**       |     |           |           |            |           |           |           |           |           |           |           |
| Without        | 201 | 72.6%     | 66.2%     | 90.0%      | 95.6%     | 82.9%     |           |           |           |           |           |
| With           | 125 | 86.4%     | 77.6%     | 93.3%      | 98.4%     | 88.6%     |           |           |           |           |           |
| **BMI**        |     |           |           |            |           |           |           |           |           |           |           |
| ≤26            | 205 | 73.6%     | 66.3%     | 89.9%      | 96.9%     | 81.8%     |           |           |           |           |           |
| >26            | 121 | 85.1%     | 77.7%     | 93.2%      | 96.6%     | 90.6%     |           |           |           |           |           |

RP, retropharyngeal; LAP, lymphadenopathy; IGRT, image-guided radiotherapy; BMI, body mass index; OS, overall survival; DFS, disease-free survival; LC, local control; RC, regional control; DFF, distant failure free.

The LC rates for patients treated with IGRT techniques and their counterpart were 93.3% and 90.0%, respectively (P = 0.325). The RC rates for patients treated with and without IGRT techniques were 98.4% and 95.6%, respectively (P = 0.144). Although the difference is not statistically significant, a trend toward better locoregional control in patients treated with IGRT was observed. Currently, the use of IGRT is not covered by our national health insurance reimbursement. It is necessary to collect more data to confirm the positive impact of IGRT on treatment outcomes and justify the routine use of IGRT.

For RC, compared with our historical results [36], the 5-year RC rate improved from 93.7% to 96.8%. N category was reported to be an independent predictor for regional nodal control [18, 45]. Our results also demonstrated similar results, and those with N3 lesions have the worst 5-year RC rate. Because significant shrinkage of the nodal lesions and change of soft tissue contour due to body weight loss were...
Table 5. Multivariate analysis of prognostic factors

|                        | P value | HR  | 95.0% CI  |
|------------------------|---------|-----|-----------|
| **Overall survival rate:** |         |     |           |
| Age                    | <0.001  | 2.458 | 1.673 | 3.610  |
| Stage                  | 0.001   | 2.100 | 1.356 | 3.251  |
| RP LAP                 | 0.001   | 1.967 | 1.317 | 2.938  |
| Interruption           | 0.007   | 1.679 | 1.153 | 2.444  |
| BMI                    | 0.008   | 0.575 | 0.381 | 0.868  |
| **Disease-free survival rate:** |         |     |           |
| Age                    | <0.001  | 2.308 | 1.614 | 3.301  |
| Stage                  | <0.001  | 2.058 | 1.386 | 3.055  |
| RP LAP                 | 0.001   | 1.908 | 1.314 | 2.771  |
| IGRT                   | 0.024   | 0.631 | 0.423 | 0.940  |
| BMI                    | 0.003   | 0.553 | 0.376 | 0.813  |
| **Local control rate:** |         |     |           |
| T category             | 0.001   | 3.799 | 1.777 | 8.120  |
| **Regional control rate:** |         |     |           |
| N category             | 0.017   | 6.472 | 1.397 | 29.990 |
| **Distant failure-free rate:** |         |     |           |
| N category             | 0.001   | 2.677 | 1.458 | 4.915  |
| RP LAP                 | 0.003   | 2.959 | 1.451 | 6.031  |
| BMI                    | 0.023   | 0.471 | 0.247 | 0.901  |

HR, hazard ratio; CI, confidence interval; RP, retropharyngeal; LAP, lymphadenopathy; BMI, body mass index; IGRT, image-guided radiotherapy.

Table 6. Incidence of acute and late toxicities

| Grade     | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|-----------|---------|---------|---------|---------|---------|
| **Acute:** |         |         |         |         |         |
| Salivary  | 5%      | 56%     | 39%     | 0%      | 0%      |
| Oral      | 0%      | 21%     | 59%     | 20%     | 0%      |
| Skin      | 0%      | 33%     | 60%     | 7%      | 0%      |
| Pharynx   | 0%      | 7%      | 86%     | 7%      | 0%      |
| Larynx    | 94%     | 4%      | 2%      | 0%      | 0%      |
| **Late:**  |         |         |         |         |         |
| Spinal cord | 98%    | 2%      | 0%      | 0%      | 0%      |
| Mandible  | 99.4%   | 0%      | 0%      | 0%      | 0.6%    |
| Salivary  | 52%     | 38%     | 10%     | 0%      | 0%      |
| Larynx    | 97%     | 3%      | 0%      | 0%      | 0%      |
| Subcutaneous tissue | 86% | 12% | 2% | 0% | 0% |
| Skin      | 95%     | 3%      | 2%      | 0%      | 0%      |

frequently observed during the radiotherapy course, the anatomical variations and subsequent loss of adequate immobilization might have an impact on the dose distribution and might also cause the residual LAP to move partially outside of the PTV. Therefore, the application of IGRT and frequent replanning to adapt the lymph node shrinkage and contour change, especially for patients with N3 diseases, should be considered to improve the RC.

In this study, retropharyngeal LAP was found to be an independent prognostic factor for OS, DFS and DFF. The 5-year OS rates for patients without and with retropharyngeal LAP are 88.5% and 69%, respectively (Fig. 1). Our results were consistent with those of another study [12]. Because CT simulation with contrast enhancement has been the routine work-up for NPC, it is less likely to miss the retropharyngeal LAP while defining targets. In our study, undertreatment of retropharyngeal LAP due to sparing of the spinal cord or parotid glands was also not observed. The reason why retropharyngeal LAP was associated with a higher incidence of distant failure and led to a poor treatment outcome needs to be explored by further novel studies.

IGRT is a method of incorporating imaging techniques throughout a course of radiotherapy to maximize the precision and accuracy of the
delivery of radiotherapy and the sparing of critical surrounding tissue. Although there is no large randomized trial of improving outcomes or decreasing radiation-related toxicities with the use of IGRT techniques, some articles reported that IGRT was associated with an improvement in clinical outcomes and radiation-induced complications [46]. In our study, univariate analysis demonstrated that IGRT was associated with significantly better OS and DFS. The 5-year DFS rates for patient without and with IGRT are 66.2% and 77.6%, respectively (Fig. 2). A trend toward better LC, RC and DFF was also noted for patients treated with IGRT techniques. The use of IGRT was further demonstrated as an independent predictor for DFS. For patients with and without IGRT, the 5-year LC, RC and DFF rates were 93.3% versus 90.0%, 98.4% versus 95.6% and 88.6% versus 82.9%, respectively. Therefore, the better OS and DFS for patients with IGRT might be attributed to the lower local, regional and distant failure. It is reasonable that improvement of the precision and accuracy of radiation delivery could lead to improvement of treatment outcomes. However, a randomized study is warranted to validate these results. In the future, in order to amplify the advantage of IGRT, efforts should be made to improve the breadth of personnel experience and to upgrade the software and hardware for IGRT.

Traditionally, higher BMI was considered as unhealthy, and increased body weight was associated with increased death rates for all cancers [47]. However, higher BMI has been reported to be associated with better treatment outcomes in NPC patients [48, 49]. In our study, higher BMI was also found to be an independent prognostic factor for OS, DFS and DFF. Body weight loss was common in patients treated with radiotherapy. In our study, body weight loss ranging from 0.3% to 27.1% (0.2–20.3 kg) occurred in 324 patients (99.4%). For patients with higher BMI, the negative impact of body weight loss and malnutrition might be less and this might account for the better treatment outcomes. However, further research is still warranted to explore the mechanism of the influence of BMI on treatment outcomes.

Treatment interruption was inevitable during the radiotherapy course due to acute radiation-related toxicities, holidays, machine breakdown or personal factors. The prolongation of overall treatment time has ever been reported to be an independent adverse prognostic factor for NPC [20, 50]. On the other hand, a recent study demonstrated that prolonged treatment time had no influence on treatment outcomes for NPC treated with IMRT [17]. Our results showed that treatment interruption was associated with poorer OS, DFS and DFF. Multivariate analysis further confirms its independent prognostic significance for OS. Therefore, we have to recommend that treatment interruption for any reason should be avoided if at all possible.

The importance of age as a determinant of treatment outcomes has been observed by many investigators [4, 11, 12, 17, 18, 40, 48, 50–52], although other studies have not shown its prognostic significance [7, 20, 35, 45, 49]. Our study also showed that older patients had significantly poorer OS, DFS and LC compared with their counterpart. Multivariate analysis also confirms its independent prognostic significance for OS and DFS. Due to the conflicting reports as to the effect of age on prognosis, we currently would not propose a different treatment strategy for older patients.

Based on randomized clinical trials and meta-analyses, concurrent chemoradiotherapy (CCRT) with or without adjuvant chemotherapy is recommended for patients with locally advanced NPC [53–55]. Compared with our prior results of patients treated with radiotherapy alone [36], the 5-year DFF rate improved from 74.7% to 85.2%. The improvement of the distant failure rate might be partly attributed to the addition of chemotherapy. However, the distant failure rate is still far from satisfactory. Although further efforts in improving locoregional control might have some contribution to the decrease of distant failure, a novel strategy of powerful systemic therapy will be most crucial for decreasing the distant failure. In several randomized clinical trials, the addition of induction chemotherapy to CCRT was reported to
suck significantly improve the treatment outcomes with acceptable toxicity in patients with locally advanced NPC [56–58]. Therefore, induction chemotherapy could also be considered as a treatment option for patients with locoregionally advanced NPC.

The most prevalent late radiation-related complication for patients with nasopharyngeal cancer is xerostomia, and it is associated with significant deterioration of quality of life. In our study, 49% of patients still complained of xerostomia at 1 year after the completion of radiotherapy. Although our result agreed with the findings of other investigators [10, 59], this result was far from satisfactory. Recently published research on non-coplanar beam delivery techniques suggests the potential of significant improvement in target coverage and critical organ sparing for head and neck cancer [60]. Further research is needed to validate its use in parotid sparing.

Biochemical hypothyroidism is a common late radiation-related complication. For patients with NPC treated with radiotherapy, the incidence of hypothyroidism has been reported to be ~20% [61, 62]. The 5-year estimated risk of radiation-induced biochemical hypothyroidism after primary radiotherapy for head and neck squamous cell carcinoma was reported to be 25.6% [63]. Since subclinical hypothyroidism has been reported to increase the risk of cardiac disease and mortality, thyroid hormone replacement therapy should be considered [64, 65]. In our study, the incidence of biochemical hypothyroidism was 46.6%. Because the thyroid glands were very close to the high-risk neck lymphatic region, the radiation dose to the thyroid glands was quite high. Lin et al. suggested that keeping the mean thyroid dose below 50 Gy was important in preventing radiation-induced thyroid damage [61]. Lee et al. demonstrated that the absolute thyroid volume spared from 45 and 60 Gy should be considered as dose constraints against hypothyroidism during IMRT optimization [62]. In order to reduce the incidence of biochemical hypothyroidism, clinical trials investigating the relationship between radiation dose and the occurrence of hypothyroidism are necessary for determining the appropriate dose constraint for thyroid glands. Whether sparing of thyroid glands will compromise the neck lymphatics, control also needs to be investigated by further clinical trials.

CONCLUSIONS

IMRT offered good locoregional control for NPC patients. With the aid of IGRT, the advantage of IMRT might be further amplified. Distant metastases remain the major cause of treatment failure. A more efficient systemic treatment strategy should be explored for patients with locally advanced diseases. Novel studies to explore the mechanism of the positive impact of BMI on treatment outcomes are warranted.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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