Treatment Outcomes of Patients with Nasopharyngeal Carcinoma Treated with Intensity-Modulated Radiotherapy

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Abstract

Background: Nasopharyngeal cancer shows good response to intensity-modulated radiotherapy. However, there is no clear evidence for the benefits of routine application 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.

Methods: Retrospective analysis was carried out 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.

Results: The 5-year overall survival and disease-free survival rates of these patients were 77.9% and 70.5% respectively. Age, AJCC 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.

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.

Background

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 since 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.

Methods
From September 2004 to October 2015, 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 pretreatment 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. Pretreatment dental assessment was routinely performed. For this study, all patients were restaged with American Joint Committee on Cancer (AJCC) 2017 staging classification [24].

Radiotherapy techniques

All patients were immobilized with 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 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, 83 [25–27]. The Gross Tumor Volume (GTV) is defined as all 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 setup 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 dose for PTV1, PTV2, and PTV3 were 70 Gy, 63 Gy, 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 brainstem, spinal cord, eyeballs, lenses, optic nerves, optic chiasm, middle & 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. 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. IGRT techniques were performed by using cone-beam CT or on-board imager.

Chemotherapy

Chemotherapy was delivered for patients with stage II, III, and IVA diseases providing that there were no major medical comorbidities. Before 2007, concurrent chemotherapy regimen was 100 mg/ m$^2$ of cisplatin every 3 weeks for 2 to 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 below 60 ml / minute.

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 five 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 MRI for skull base or intracranial lesions. Regional recurrences were diagnosed by physical examination and imaging studies (CT scan, MRI, Positron emission tomography CT). Distant metastases were diagnosed by physical examination and suitable imaging studies (bone scan, Positron emission tomography CT, CT scan, MRI, sonography). Acute and late 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. The estimate of LC, RC, DFF, DFS, and OS was calculated actuarially with the Kaplan-Meier method [29]. Comparison between groups for univariate analysis was done with the Log-rank test [30]. Multivariate analysis was performed using the Cox
A proportional hazards model was used to define independent predictors among potential prognostic factors [31]. 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%), N3: 28 (8.6%). The distribution of stages was: I: 33 patients, II: 99, III: 116, 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 were listed in Table 1. The distribution of T and N category was 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.

Before 2007, concurrent chemotherapy with 100 mg/m$^2$ of cisplatin every 3 weeks for 2 to 3 cycles was given to 40 patients. Since 2007, three to seven cycles of weekly concurrent chemotherapy with 30 mg/m$^2$ of cisplatin were delivered to 253 patients. Cisplatin was replaced by carboplatin in 5 patients because the creatinine clearance was below 60 ml/minute.

**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.
Local control

In this study, 30 patients developed local recurrence and the 5-year LC rate was 91.3%. Univariate analysis revealed age and T-category as significant predictors for local control. Multivariate analysis confirmed that T-category was the only independent prognostic factor for local control.

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 regional control. Multivariate analysis confirmed that N-category was the only independent prognostic factor for regional control.

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, 4 sites: 2). 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 5 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. The details of univariate and multivariate analysis were listed in Table 3 and Table 4.

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 TSH value > 5.0 mIU/L and/or FT4 < 0.7 ng/dl. 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). The incidence of acute and late toxicities was listed in Table 5.

Discussion

Radiotherapy is the major treatment modality for NPC. Prior to the advent of IMRT, conventional two-dimensional (2D) or 3DCRT techniques were used and the treatment outcomes were suboptimal. IMRT is a complex form of 3DCRT 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 treated with IMRT. Compared with our historical report for NPC treated with 2D techniques [36], substantial improvement was observed in patients treated with IMRT. Locoregional control is the main goal of radiotherapy. Compared with our historical results of patients treated with conventional techniques, 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]. 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 on local control was still controversial. T-category was ever reported as an independent prognostic factor for local control [20]. Some investigators demonstrated that T-category was no longer a significant predictor for local control in the IMRT era [4,6,15,18,42]. In our study, T-category was demonstrated as the only independent prognostic factor for local control. The 5-year local control 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. Radiation dose-response relationship has been observed in several retrospective studies [43,44]. Therefore, the delivery of higher radiation dose for locally advanced diseases, might play an important role in improving the local control rate. Our further study will explore the impact of the delivery of boost irradiation for patients with T3/4 tumors. Another way to improve the local control might be the use of IGRT techniques. By using the On-Board Imager and Cone Beam CT, radiation dose could be delivered more accurately to the targets. In our study, 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 regional control, 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 frequently observed during the radiotherapy course, the anatomical variations and subsequent loss of adequate immobilization might have impact on the dose distribution and might also cause the residual LAP to move partially outside of the PTV volume. Therefore, the application of IGRT and frequent
replanning to adapt the LN shrinkage and contour change, especially for patients with N3 diseases, should be considered to improve the regional control.

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% (Figure 1). Our results were consistent with other study [12]. Because CT-simulation with contrast enhancement has been the routine workup for NPC, it is less likely to miss the retropharyngeal LAP while defining targets. In our study, underdose of retropharyngeal LAP due to sparing of spinal cord or parotid glands was also not observed. The reason why retropharyngeal LAP was associated with higher incidence of distant failure and leaded to a poor treatment outcomes needed 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 data 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 were associated with significantly better OS and DFS. The 5-year DFS rates for patient without and with IGRT are 66.2% and 77.6% (Figure 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% vs 90.0%, 98.4% vs 95.6% and 88.6% vs 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. 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 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 caused by 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 the randomized clinical trials and meta-analyses, concurrent chemoradiotherapy 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 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.

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 one year after the completion of radiotherapy. Although our result concurred with the findings of other investigators [10,56], this result was far from satisfactory. Recently published research on noncoplanar beam delivery techniques suggests the potential of significant improvement in target coverage and critical organ sparing for head and neck cancer [57]. 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 around 20% [58,59]. 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% [60]. Since subclinical hypothyroidism has been reported to increase the risk of cardiac disease and mortality, thyroid hormone replacement therapy should be considered [61,62]. In our study, the incidence of biochemical hypothyroidism was 46.6%. Because the thyroid glands were very close to the high-risk neck lymphatics 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 [58]. Lee et al. demonstrated that the absolute thyroid volume spared from 45 Gy and 60 Gy should be considered as dose constraints against hypothyroidism during IMRT optimization [59]. In order to reduce the incidence of biochemical hypothyroidism, clinical trials investigating the relationship between radiation dose and the occurrence of hypothyroidism is 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 trial.
Conclusions

IMRT did offer 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. 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.

Abbreviations

NPC: nasopharyngeal cancer;
IMRT: intensity-modulated radiotherapy;
3DCRT: three-dimensional conformal radiotherapy;
IGRT: image-guided radiotherapy;
MRI: magnetic resonance imaging;
AJCC: American Joint Committee on Cancer;
CT: computed tomography;
ICRU: International Commission on Radiation Units and Measurements;
GTV: gross tumor volume;
CTV: clinical target volume;
PTV: planning target volume;
PRV: planning organ at risk volume;
RTOG: Radiation Therapy Oncology Group;
LC: local control;
RC: regional control; DFF: distant failure free; DFS: disease free survival; OS: overall survival;
WHO: World Health Organization;
LAP: lymphadenopathy;
BMI: body mass index;
TSH: thyroid-stimulating hormone; FT4: free thyroxine;
2D: two-dimensional;

**Declarations**

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**Authors' contributions**

conception and design of the study: SAY,

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analysis and interpretation of data: all authors,

manuscript writing: SAY,

All authors read and approved the final manuscript.

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**Availability of data and materials**

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of the E-DA Hospital (approval No. EMRP103063). Informed consent was not required due to the retrospective study design.

**Consent for publication**

Not applicable

**Competing interests**

The authors declare that they have no competing interests.

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Tables

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
Table 2. Distribution of T, N category

|     | 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.
Univariate analysis of prognostic factors

|                | No. | 5-year OS | 5-year DFS | 5-year LC | 5-year RC | 5-year DFF |
|----------------|-----|-----------|------------|-----------|-----------|------------|
| **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%     | 57.1%      | 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%      | 89.4%     | 96.3%     | 86.0%      |
| IVA            | 78  | 64.0%     | 56.4%      | 89.5%     | 92.9%     | 69.1%      |
| **RP LN**      |     |           |            |           |           |            |
| negative       | 148 | 88.5%     | 82.4%      | 92.3%     | 97.9%     | 93.8%      |
| positive       | 178 | 69.0%     | 60.5%      | 90.2%     | 95.7%     | 77.7%      |
| **Level 5 LN** |     |           |            |           |           |            |
| negative       | 272 | 80.9%     | 73.5%      | 91.7%     | 96.9%     | 87.6%      |
| positive       | 54  | 63.0%     | 55.2%      | 87.8%     | 95.9%     | 72.6%      |
| **Multiple LN**|     |           |            |           |           |            |
| 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 LN |     |     |     |     |
|---------------------------|--------------|-----|-----|-----|-----|
|                           | p<0.001      | p= 0.001 | p=0.763 | p=0.004 | P<0.001 |
| 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              | p<0.001      | p=0.001 | p=0.164 | p=0.927 | p=0.008 |
| ≤ 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                      | p=0.008      | p=0.023 | p=0.325 | p=0.144 | p=0.132 |
| 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                       | p=0.011      | p=0.007 | p=0.322 | p=0.875 | P=0.018 |
| ≤ 26                      | 205          | 73.6%| 66.3%| 89.9%| 96.9%| 81.8%|
| > 26                      | 121          | 85.1%| 77.7%| 93.2%| 96.6%| 90.6%|
Table 4.
Multivariate analysis of prognostic factors

|                        | p value | HR   | 95.0% CI  |
|------------------------|---------|------|-----------|
| **Overall survival rate:** |         |      |           |
| Age                    | <0.001  | 2.458| 1.673     |
| Stage                  | 0.001   | 2.100| 1.356     |
| Retropharyngeal LAP    | 0.001   | 1.967| 1.317     |
| Interruption           | 0.007   | 1.679| 1.153     |
| BMI                    | 0.008   | 0.575| 0.381     |
| **Disease-free survival rate:** |         |      |           |
| Age                    | <0.001  | 2.308| 1.614     |
| Stage                  | <0.001  | 2.058| 1.386     |
| Retropharyngeal LAP    | 0.001   | 1.908| 1.314     |
| IGRT                   | 0.024   | 0.631| 0.423     |
| BMI                    | 0.003   | 0.553| 0.376     |
| **Local control rate:** |         |      |           |
| T category             | 0.001   | 3.799| 1.777     |
| **Regional control rate:** |         |      |           |
| N category             | 0.017   | 6.472| 1.397     |
| **Distant failure-free rate:** |         |      |           |
| N category             | 0.001   | 2.677| 1.458     |
| Retropharyngeal LAP    | 0.003   | 2.959| 1.451     |
| BMI                    | 0.023   | 0.471| 0.247     |

Abbreviations: HR, hazard ratio; CI, confidence interval.
Table 5.
Incidence of acute and late toxicities

| Grade        | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--------------|---------|---------|---------|---------|---------|
| Acute        |         |         |         |         |         |
| Salivary     | 5%      | 56%     | 39%     | 0%      | 0%      |
| Mucous membrane | 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     | 51%     | 38%     | 11%     | 0%      | 0%      |
| Larynx       | 96%     | 4%      | 0%      | 0%      | 0%      |
| Subcutaneous tissue | 86% | 12% | 2% | 0% | 0% |
| Skin         | 95%     | 3%      | 2%      | 0%      | 0%      |

Figures
Figure 1

Overall survival rates according to the status of retropharyngeal LN Legend: The 5-year OS rates for patients without and with retropharyngeal LAP are 88.5% and 69% (p<0.001)
Figure 2

Disease-free survival rates according to the status of IGRT Legend: The 5-year DFS rates for patient without and with IGRT are 66.2% and 77.6% (p=0.023)