

• Clinical Research •

## Radiotherapy of cervical lymph nodes for the patients with stage-N0 nasopharyngeal carcinoma

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**[Abstract] Background and Objective:** The therapeutic level and dose of irradiation for the regional prevention of nasopharyngeal cancer (NPC) for patients with cervical lymph node involvement remains controversial. This study analyzed the effects of radiotherapy on cervical lymph nodes for the patients with stage-N0 NPC. **Methods:** Between January 2002 and December 2004, 205 NPC patients with negative lymphadenopathy diagnosed by imaging, were retrospectively analyzed. Before treatment, each patient underwent CT or MRI. Facial-cervical portals and 6–8 MV photons were used in radiotherapy. Doses applied were 60–80 Gy to the nasopharynx and 46–64 Gy to the neck without lymphadenopathy. Consecutive radiotherapy was performed employing conventional fractionation of 2 Gy/fraction, once a day, for a total of five fractions per week. Chemotherapy was administered to 60 patients. Median follow-up was 44 months. The survival function was calculated according to the Kaplan-Meier method. A log-rank test was used to compare the differences in survival. The Cox proportional hazards model was used for multivariate analysis. A total of 205 patients with stage-N0 NPC were divided into an upper-neck irradiation group and an entire-neck group. **Results:** The 3-year overall survival rate (OS) was 92.9% and the 3-year disease-free survival rate (DFS) was 91.9%. A total of 88 patients received irradiation to the upper neck and 117 to the entire neck. The rate of regional failure for the upper-neck group and the entire-neck group were 2.27% and 0%, respectively ( $P > 0.05$ ). The rates of regional failure in patients with T1-, T2-, T3- and T4-stage disease were 0%, 3.08%, 0%, and 0%, respectively ( $P > 0.05$ ). The rates of regional failure in the patients both without and with local failure were 1.03% and 0%, respectively ( $P > 0.05$ ). The 1- and 3-year OS for the upper-neck group were 97.7% and 94.2%, and the 1- and 3-year OS for the entire-neck group were 97.4% and 91.9% ( $P = 0.950$ ). The 1- and 3-year DFS for the upper-neck group were 96.6% and 92.9%, and the 1- and 3-year DFS for the entire-neck group were 95.6% and 90.9% ( $P = 0.730$ ). In multivariate analysis, sex ( $P = 0.039$ ) and T stage ( $P = 0.004$ ) were independent prognosis factors for patients with stage-N0 NPC. **Conclusions:** Radiotherapy to the upper neck does not influence regional failure or long-term survival in the patients with stage-N0 NPC. Radiotherapy to the upper neck (levels II, III, VA) is recommended for the patients with stage-N0 NPC. Involvement of the parapharyngeal space, T stage, and the rates of local failure do not influence regional failure in these patients. Sex and T stage were independent prognosis factors for the patients with stage-N0 NPC.

**Key words:** Nasopharyngeal carcinoma, radiotherapy, prognosis, lymph node

Nasopharyngeal carcinoma (NPC) is commonly seen in Southeast Asia and China, and is one of the malignant tumors with high incidence in South China. Patients without cervical lymphadenopathy account for 4%–35.9% of all patients with

NPC.<sup>1-3</sup> Various viewpoints still exist regarding the appropriate method and dosage of radiotherapy for NPC patients with negative regional lymphadenopathy. The research presented in this paper retrospectively analyzed the clinical data of patients with stage-N0 NPC confirmed on diagnostic imaging, investigated the method of cervical radiotherapy, and analyzed patterns of treatment failure and factors of prognosis.

## Materials and Methods

### Data collection

Data were collected on 205 patients with pathologically proven

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nasopharyngeal biopsy, no distant metastasis, and imaging-diagnosed stage-N0 NPC who were hospitalized and treated at the Sun Yat-sen University Cancer Center from January 2002 to December 2004. Imaging tests computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography/CT (PET-CT) were performed before treatment and the scanned structures included the nasopharynx

and the neck. Patients had no history of radiotherapy or chemotherapy. The staging of the NPC was according to the 2002 International Union Against Cancer (UICC) staging criteria. Patients were divided into an upper-neck group and an entire-neck group based on different radiotherapeutic methods for cervical lymph nodes. General clinical data are listed in Table 1.

**Table 1 Clinical data of 205 patients with stage-N0 nasopharyngeal carcinoma (NPC) with different modalities of prophylactic irradiation**

	Preventing irradiation with upper neck portal	Preventing irradiation with entire neck portal	<i>t</i> or $\chi^2$	<i>P</i>
Sex (patient No.)				
Male	67	91	0.077	0.782
Female	21	26		
Age (years)	47.6 ± 11.3	46.8 ± 11.9	0.433	0.665
T stage (patient No.)				
T1	26	20	5.464	0.141
T2	28	37		
T3	18	35		
T4	16	25		
Irradiation dose (Gy)				
Nasopharynx	71.64 ± 4.99	72.52 ± 4.36	-1.352	0.178
Cervical	51.80 ± 2.31	52.26 ± 3.73	-1.088	0.278
Treatment modality (patient No.)				
Radiotherapy	66	79	1.357	0.241
Radiochemotherapy	22	38		

## Radiotherapy

The treatment was delivered using 6–8 MV high-energy X-rays generated by linear accelerator. In phase 1, the total conceptus dose (DT) of 32–40 Gy were delivered to the facial-cervical combined fields + anterior tangential field. In phase 2, DT 10–14 Gy were delivered to shrunken facial-cervical fields shielding the spinal cord + posterior auricular electronic fields + anterior tangential field. In phase 3, DT 10–20 Gy were delivered to anterior auricular fields and in cases of severe skull base erosion, the skull base field received a boost of 5–10 Gy. Normal tissue was shielded with low melting-point lead blocks, and received conventional fractions or continuous radiation. The radiation dose to the primary nasopharyngeal tumor was 60–80 Gy, with a median dose of 70 Gy. The skull base boost was 0–10 Gy. The duration of radiation was 5.8–11.7 weeks. In addition, 28 patients were treated by additional brachytherapy with doses of 12–20 Gy, a cervical therapeutic dose of 46–64 Gy, with a median dose of 50 Gy, and the duration of radiation was 4.3–8.1 weeks. Delimiting the upper neck from the lower neck was the inferior border of the cricoid cartilage, which defines levels III and IV. Radiotherapy of the upper neck included lymph nodes in levels II, III, and VA (the half-neck group), and radiotherapy of the lower neck included lymph nodes in levels II, III, IV, and V (the entire-neck group).

## Chemotherapy

Chemotherapy was given to 60 patients, including 13 patients

treated with induction chemotherapy, 53 with concurrent chemotherapy, and 6 with adjuvant chemotherapy. Most of the chemotherapy regimens were 5-fluorouracil (5-FU) plus cisplatin (DDP).

## Follow-up

The duration of follow-up was calculated from the time of diagnosis to December 31, 2007. The patients were followed-up for 3–68 months, with a median follow-up of 44 months. The 1- and 3-year follow-up rates were 95.1% and 80.5%, respectively.

## Statistical analysis

Observational endpoints were death, local or regional relapse, and distant metastasis. Overall survival (OS) and disease-free survival (DFS) were calculated from the final diagnosis to the emergence of the observational endpoints. Sex, age, pathological type, chemotherapy, invasion of either the pre- or post-styloid space, T stage, nasopharynx radiation dose, radiation dose to the cervical lymph nodes, and the radiation area for the cervical lymph nodes were included in the multivariate analysis. SPSS13.0 software was used for data processing and the analyzed index included the OS rate and the DFS rate. Cumulative survival rate was calculated by the Kaplan-Meier method. Differences between survival rates were compared by a log-rank test. Multivariate analysis was performed by the Cox proportional hazards model using forward selection and a two-tailed test. The proportions were compared by  $\chi^2$  test, and measurement data were compared by *t* test. *P* < 0.05 was considered statistically significant.

## Results

### Treatment outcome, recurrence, and metastatic status

The 3-year OS and DFS rates were 92.9% and 91.9% , respectively, with 23 deaths, 13 patients with local recurrence, and 2 patients with regional relapse. Both regional recurrences happened in the upper neck (level II). The cervical recurrence rate was 0.98%. Distant metastasis occurred in 9 patients.

### Cervical lymph node recurrence factors for patients with stage-N0 NPC

**The relationship between radiotherapeutic methods for cervical lymph nodes and lymph node recurrence** Cervical lymph node recurrence occurred in 2 of the 88 patients in the upper-neck group, both with relapses in the upper neck area, showing a recurrence rate of 2.27%. No recurrence in cervical lymph nodes was observed in the 117 patients in the entire-neck group. Comparison between the recurrence rates of the two groups showed no statistical significance ( $P = 0.183$ ).

**The relationship between the parapharyngeal space (pre- and post-styloid) and lymph node recurrence** No recurrence in the cervical lymph nodes was observed into 80 patients with no invasion in the pre-styloid space and 2 cases of cervical lymph node recurrence into 125 patients with invasion in the pre-styloid space, showing a recurrence rate of 1.60%. Comparison between the recurrence rates of the two groups also showed no statistical significance ( $P = 0.522$ ).

Likewise, no cervical lymph node recurrence was observed in the 137 patients with no invasion into post-styloid space and 2 cases of cervical lymph node recurrence occurred in the 68 patients with invasion into post-styloid space, showing a recurrence rate of 2.94%. Comparison between the recurrence rates of the two groups found  $P = 0.109$ .

### The relationship between T stage and lymph node recurrence

No cervical lymph node recurrence was observed in the 46 patients with T1 disease and 2 cases of cervical lymph node recurrence occurred in the 65 patients with T2 disease, showing a recurrence rate of 3.08%. No cervical lymph node recurrence was found in the 53 patients with T3 disease or in the 41 patients with T4 disease. The comparison of the recurrence rates in the four

groups showed no statistical significance ( $P=0.344$ ).

**The relationship between nasopharyngeal relapse and lymph node recurrence** Cervical lymph node recurrence occurred in 2 of the 194 patients with no nasopharyngeal relapse, showing a recurrence rate of 1.03%. No cervical lymph node recurrence was observed in the 11 patients with nasopharyngeal relapse. Comparison between the two groups showed no statistical significance ( $P = 1.000$ ).

### The influence of different methods of cervical radiotherapy on long-term survival

The 1- and 3-year OS rates for the upper- and entire-neck groups were 97.7%, 94.2%, and 97.4%, 91.9%, respectively, yet were not statistically significant ( $\log\text{-rank } \chi^2 = 0.004$ ,  $P = 0.950$ ) (Figure 1). The 1- and 3-year DFS rates for the upper- and whole-neck groups were 96.6%, 92.9%, and 95.6%, 90.9%, respectively, also without statistical significance ( $\log\text{-rank } \chi^2 = 0.119$ ,  $P = 0.730$ ). No influence was found for different methods of cervical radiotherapy on long-term survival.

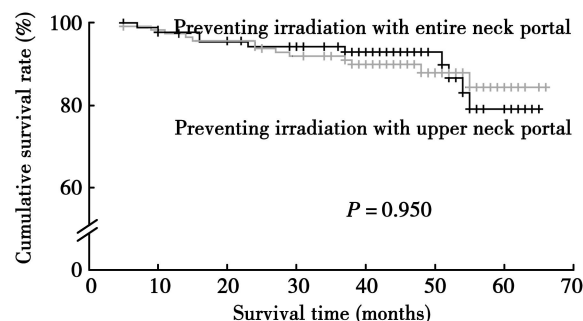


Figure 1 The overall survival in patients with stage-N0 nasopharyngeal carcinoma with different modalities of prophylactic irradiation

### Multivariate analysis on prognosis

The 3-year OS rates for men and women were 91.5% and 97.8%. The 3-year OS rates for patients with T1, T2, T3, and T4 disease were 100%, 98.4%, 88.2%, and 81.8%, respectively. Our results showed that sex and T stage were both independent factors influencing prognosis (Table 2).

Table 2 Multivariate analysis of prognostic factors for the patients with stage-N0 NPC

	Regression coefficient	Variance	Wald	P	Odds ratio	95% confidence interval	
						Upper limit	Lower limit
Sex	-1.578	0.762	4.250	0.039	0.208	0.047	0.925
Age	0.024	0.018	1.746	0.186	1.024	0.989	1.061
Pathologic type	-0.061	0.573	0.011	0.915	0.941	0.306	2.894
Chemotherapy	-0.239	0.499	0.229	0.632	0.788	0.296	2.093
Prestyloid space involvement	1.437	0.790	3.304	0.069	4.208	0.894	19.810
No prestyloid space involvement	-0.135	0.455	0.088	0.766	0.874	0.358	2.131
T stage	0.892	0.311	8.219	0.004	2.441	1.326	4.492
Irradiation dose in nasopharynx	0.024	0.045	0.284	0.594	1.024	0.937	1.119
Subclinical foci	-0.225	0.429	0.276	0.600	0.799	0.345	1.849

## Discussion

NPC has a high incidence in some provinces of Southern and Southwest China, and patients with stage-N0 disease account for 4%–35.9% of all patients.<sup>1-3</sup> In the early 1990s, Li *et al.*<sup>4</sup> from Hong Kong reported that 38% of patients with stage-N0 NPC had lymph node recurrence if no radiotherapy was delivered to the cervical lymph nodes, whereas the recurrence rate was only 11% for those receiving radiation treatment. When no radiotherapy was given, patients with N0 disease had higher recurrent rates than those with N2 disease, whereas for patients with stage-N0 NPC, patients who received radiotherapy had better prognosis than those who did not. As a result, we concluded that for the NPC patients with negative cervical lymphadenopathy, sufficient radiation should be given to the proper neck areas. Sham *et al.*<sup>5</sup> analyzed the data of 271 patients and found that lymph node metastasis progressed from upper to lower levels, radiotherapy for positive lymphadenopathy should cover the next area of lymphatic drainage, and upper-neck radiation treatment should be delivered if no palpable lymph nodes are present.

In our study, all patients with stage-N0 NPC received radiotherapy to the cervical lymph nodes. However, the therapeutic area was in dispute at all times. Data from the Cancer Hospital, China Academy of Medical Science showed that the rate of cervical lymph node recurrence for entire-neck radiotherapy was lower than that for the upper-neck radiotherapy<sup>6</sup>, and metastasis might exist in NPC lymph nodes. As a result, they suggested that entire-neck radiation treatment should be prescribed even for patients with stage-N0 NPC. Radiotherapeutic guidelines from the Chinese Anti-cancer Association suggested that upper half-cervical radiotherapy alone for patients with stage-N0 NPC could achieve a cervical control rate of 95%.<sup>7</sup> Xian *et al.*<sup>8</sup> reported that the rates of cervical lymph node recurrence for their upper- and entire-neck groups were 4.71% and 4.76%, respectively ( $P > 0.05$ ), in patients with stage-N0 NPC diagnosed by CT. Li *et al.*<sup>9</sup> reported that the rates of cervical lymph node recurrence for their entire- and upper-neck groups were 1.14% and 1.08%, respectively ( $P > 0.05$ ), in patients with stage-N0 NPC diagnosed by clinical palpation. Comparison between the two groups showed no statistical significance in the rates of OS or DFS. They suggested that upper-neck irradiation is enough for the patients with stage-N0 NPC.

Our research did not show any statistical difference between either the upper- and whole-neck groups in cervical lymph node recurrent rates or in 1- and 3-year OS and DFS rates. That all patients had a CT or an MRI before treatment basically excludes the possibility of clinically impalpable positive lymph nodes. Besides, the possibility of lymph node metastasis in NPC is

quite low. As a result, upper-neck radiotherapy for patients with stage-N0 NPC is reasonable and sufficient. Neither cervical treatment showed significant influence on long-term survival for patients with stage-N0 NPC.<sup>9-12</sup>

Our research showed that invasion in the parapharyngeal space, late T stage, and high local nasopharyngeal recurrence rate did not increase the rate of cervical lymph node recurrence in our patients. Possible explanations include the following. First, imaging examinations before treatment could help with a precise diagnosis. Second, the facial-cervical combined field technique helped to achieve good conformality and coverage, even when the parapharyngeal space was invaded. Third, the use of CT simulation and the three-dimensional conformal technique helped with more precise target volume delineation and made the severity of the cervical recurrence rate unrelated to the factors mentioned above. Multivariate analysis of OS for our patients indicated that sex and T stage were independent prognostic factors. Women had better prognosis than men, and patients with advanced T stages had worse prognosis.

In the present study, some patients with NPC had unilateral cervical lymph node involvement. And most of these patients received entire-neck irradiation to the lymph node negative side, which lacked support from the published literature. Because it is difficult to form conclusions through retrospective analysis, properly designed prospective cohort studies are needed for confirmation. Because the follow-up period for some of our patients was short, future studies would benefit from longer following-up.

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