RESEARCH COMMUNICATION

Long Term Outcomes and Prognostic Factors of N_0 Stage Nasopharyngeal Carcinoma: a Single Institutional Experience with 610 Patients

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Abstract

Treatment responses of N_0 stage nasopharyngeal carcinoma were firstly analyzed comprehensively to evaluate long term outcomes of patients and identify prognostic factors. A total of 610 patients with N_0 NPC, undergoing definitive radiotherapy to their primary lesion and prophylactic radiation to upper neck, were reviewed retrospectively. Concomitant chemotherapy was administrated to 65 out of the 610. Survival rates of the patients were calculated using the Kaplan-Meier method and compared by log-rank test. Prognostic factors were identified by the Cox regression model. The study revealed the 5-year and 10-year overall, disease-free, disease-specific, local failure-free, regional failure-free, locoregional failure-free and distant metastasis-free survival rates to be 78.7% and 66.8%, 68.8% and 55.8%, 79.9% and 70.4%, 81.2% and 72.5%, 95.8% and 91.8%, 78.3% and 68.5%, 88.5% and 85.5%, respectively. There were 192 patients experiencing failure (31.5%) after radiotherapy or chemoradiotherapy. Of these, local recurrence, regional relapse and distant metastases as the first event of failure occurred in 100 (100/610, 16.4%), 15(15/610, 2.5%) and 52 (52/610, 8.5%), respectively. Multivariate analysis showed that T stage was the only independent prognostic factor for patients with N_0 NPC (P=0.000). Late T stage (P=0.000), male (P=0.039) and anemia (P=0.007) were independently unfavorable factors predicting disease-free survival. After treatment, satisfactory outcome wasgenerally achieved in patients with N_0 NPC. Local recurrence represented the predominant mode of treatment failure, while T stage was the only independent prognostic factor for overall survival. Late T stage, male gender, and anemia independently predicted lower possibility of the disease-free survival.

Keywords: Nasopharyngeal carcinoma - radiotherapy - N_0 - outcome - prognosis factors

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Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy normally happening in head and neck, with unique histological features, epidemiology, natural progression behaviors, management approaches, and high prevalence in Southeast Asia and Southern China. It is believed that, because of a rich lymphatic network in the nasopharynx, the incidence rate of cervical lymphatic metastasis in NPC patients is substantially high. The clinically evident cervical lymphadenopathy was reported to occur in more than 85 % of the patients with NPC (Ng et al., 2007; Tang et al., 2009), which was near the rate of approximately 86% in a total of 4,342 NPC patients admitted in our hospital from May 1989 to Oct. 2009.

However, some patients with extensive primary tumors in the nasopharynx did not present detectable neck lymph adenopathy, representing a specific clinical pattern. These N_0 (neck node negative) NPC might differ from NPC with cervical lymph node metastasis in terms of biological characteristics. However, its underlining biological mechanism in tumor progression had yet to be determined.

Although much had been known regarding to the treatment and prognostic factors of this cancer as a whole, there had not been a systematic study on the N_0 NPC, perhaps due to the fact that it only represented a relatively small subgroup in the NPC patient population. For example, it's still remained unclear whether a combination of chemotherapy with radiotherapy could bring any survival benefits for NPC patients with stages T_{3-4}/N_0 tumors.

Our study was designed to evaluate the therapeutic outcomes of N_0 NPC patients treated primarily with external-beam radiation for improving the current N_0 NPC treatment strategies.

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Materials and Methods

Patients and pretreatment evaluation

From May 1989 to Oct. 2009, 610 patients with N_0 NPC were treated with definite radiotherapy (RT) in the Cancer Hospital of Shantou University Medical College. The pretreatment evaluation included history reviews, physical examination, nasopharyngoscopy with biopsy, chest radiography, abdominal ultrasonography, computed tomography (CT) scan of the nasopharynx and skull base, bone marrow function and biochemistry profiles. Bone scan and thoracic CT were performed if indicated. All patients were staged according to 1992 Fuzhou Chinese staging system (Min et al., 1994). Patients with no palpable lymph nodes in the neck were defined as N_0 stage. The case distribution profile in this study was T_1, 9.3%; T_2, 44.6%; T_3, 20.7%; and T_4, 25.4%, and the detailed characteristics of all patients were listed in Table 1. Anemia was defined as hemoglobin lower than 120 g/L and 110 g/L in male and female patients, respectively.

Radiation therapy

Patients initially underwent conventional external beam radiotherapy (EBRT) 5 times a week at 2 Gy/d using a two-dimensional (2D) technique RT. All patients were treated firstly with two block-shielding lateral opposing faciocervical fields which covered the primary tumor and upper neck to a total dose of 36 to 40 Gy, followed by two lateral preauricular fields with matching anterior cervical fields (covered upper neck). An additional boost of 8~10 Gy was given in case of evident skull-base erosion and/or carotid space (CS) involvement. Since January 2002, CT simulation and three-dimensional conformal radiotherapy (3D CRT) were routinely performed. At the same time, some patients were treated with intensity modulated radiation therapy (IMRT) by simultaneous modulated accelerated radiation therapy (SMART) boost technique. The prescribe dose of IMRT was 70.4 Gy to nasopharynx, 60 to upper neck (including level II, III, Va) in 32 fractions. Of the 610 patients, 322 were treated with 2D EBRT, 281 with 3DCRT, and 7 with IMRT. 542 patients (88.9%) received prophylactic radiation to upper neck, while the rest to entire neck as recommended by the attending physicians. The total dose delivered to the primary lesion was 34-91 Gy (median, 70 Gy) and 34-70 Gy (median, 50 Gy) to upper neck and regions which might harbor subclinical lesion. Radiotherapy was terminated prematurely in two cases, one due to lung infection and the other to death after receiving a total dose of 34 Gy and 52 Gy, respectively.

Residual disease and boost radiotherapy

After the completion of 70-72 Gy of EBRT, patients with primary residual disease were treated with a boost RT using either 192Ir intracavitary brachytherapy (6-24 Gy in 1-3 fractions, once a week) or 3DCRT depending on the size and location of the residual lesion. 99 patients were found with nasopharyngeal residual lesion in this study. Of them, 3 were treated with 3D CRT, 50 with intracavitary brachytherapy, 2 with 3D CRT plus brachytherapy, and 8 without any further treatment.

Chemotherapy

65 patients (10.7%) received cisplatin alone or cisplatin-based combined chemotherapeutic agents, and 57 of them being concurrent with or without sequential (neoadjuvant/adjuvant) chemotherapy, and 8 with sequential chemotherapy.

Follow-up

The follow-up duration was calculated from the day of treatment commencement to either the day of death or the day of the latest clinic visit. After the completion of treatment, patients were followed every 3 months during the first 2 years, then every 6 months for the subsequent 3 years, and then once every year thereafter. Complete physical and fiberoptic nasopharyngoscopy or indirect nasopharyngeal speculum examinations were also performed. Biochemistry profiles, chest radiography and abdominal ultrasonography were routine elements of the follow-up assessment. CT of the nasopharynx and cervical region was performed at least once a year. Further investigations included enhanced CT of chest or abdomen and bone scan were arranged as indicated. The last follow-up date was Dec. 31st, 2010 and the median follow-up duration was 85 months (3-254), with the 5- and 10- year follow-up rates being 91.8% and 84.5%, respectively.

Statistical analysis

The endpoints of this study included overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), local failure-free survival (L-FFS), regional failure-free survival (R-FFS) and distant metastasis-free survival (DMFS) rates calculated with the Kaplan–Meier method. As few patients received IMRT in this study, they were added into those patients treated with 3D CRT during the univariate analysis. The Statistical Package for Social Sciences, version 18.0 (SPSS, Chicago, III) was used. Potential outcome differences were compared using the log-rank test. Multivariate analysis with Cox proportional hazards model was performed to identify prognostic factors. All P values were based on a 2-sided test, and the differences were regarded as statistically significant when $P < 0.05$.

Results

Local control

A total of 119 patients (19.5%) had local recurrence with a median time of 29 months (10-121), and 84.9% of them happened within 5 years. The 5-year and 10-year actuarial L-FFS rates for the entire group were 81.2% and 72.5%, respectively. The corresponding 5-year L-FFS rates for T_1, T_2, T_3 and T_4 disease were 86.6%, 86.2%, 79.6%, and 70.7%, respectively, and these rates were significantly correlated with the T stages ($P = 0.000$; Figure 1a).

Regional control

31 cases (5.1%) of this cohort developed regional recurrence at a median time of 38.5 months (18-53). Of them, 15 patients (2.5%) had regional recurrence as a first event of treatment failure, and the rest had local recurrence

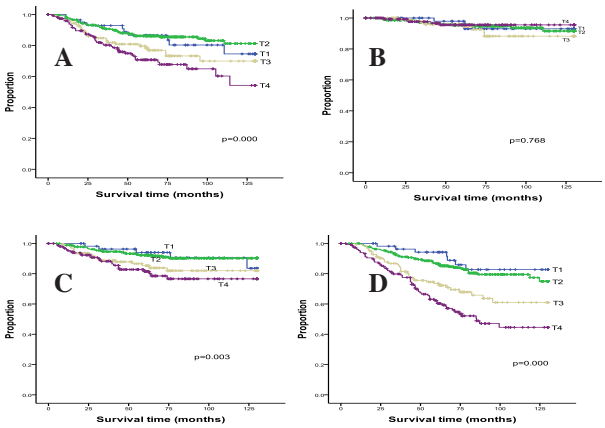

Figure 1. Survival Curves of (a) LFF, (b) RFF Survival, (c) DMF Survival and (d) OS, for the Patients with N_0 Nasopharyngeal Carcinoma According to Different T Stage

Table 1. Characteristics of Patients with N_0 Nasopharyngeal Carcinoma

Characteristics		Number of patients	%
Gender	Male	442	72.5
	Female	168	27.5
Age (y)	Range	17-79	
	Median	48	
Histology	WHO type I	18	3.0
	WHO type II-III	586	96.1
	Unclassified	6	1.0
T stage	T_1	57	9.3
	T_2	272	44.6
	T_3	126	20.7
	T_4	155	25.4
Chemotherapy	No	545	89.3
	Yes	65	10.7
Radiotherapy	2D Conventional	322	52.8
	3D CRT	288	47.2
Cranial nerve paralysis	None	457	74.9
	Anterior	111	18.2
	Posterior	10	1.6
	Both	32	5.2

and/or distant metastasis simultaneously.

Of these regional recurrence, 16 (2.7%) occurred within the elective irradiated area, while 13 (2.1%) out of the area, and 2 (6.5%) both in and out of the areas. The 5-year and 10-year actuarial R-FFS rates for the entire group were 95.8% and 91.8%, respectively. The corresponding 5-year R-FFS rates for T_1, T_2, T_3 and T_4 disease were 97.9%, 95.4%, 96.0%, and 95.5%, respectively. There were no significant differences among them (P=0.768; Figure 1b). The 5-year R-FFS rates in patients with or without local treatment failures were 93.6% and 96.2%, respectively (P=0.006).

28 patients (5.2%) treated with prophylactic irradiation to upper neck developed regional recurrence, while 3 patients (3/68, 4.4%) irradiated with entire neck were found with nodal failure. The 5-year R-FFS rates of these two subgroup were 96.8% and 95.7%, respectively (P=0.964).

Distant metastases

71 patients (11.6%) developed distant metastases

Table 2. Sites of Distant Metastases

Sites	Frequency	%
Bone	25	35.2
Lung	16	22.5
Liver	8	11.3
Bone + Lung	2	2.8
Bone + Liver	1	1.4
Lung + Liver	1	1.4
Bone + Lung + Liver	1	1.4
Others	17	23.9
Total	71	100

Table 3. Causes of Death in Patients with N_0 Nasopharyngeal Carcinoma

Cause	Frequency	%
Local relapse only (L)	69	44.2
Regional relapse only (R)	4	2.6
Distant metastasis only (D)	44	28.2
L+R	2	1.3
L+D	6	3.8
R+D	3	1.9
L+R+D	3	1.9
L+posterior cranial neuropathy	1	0.6
R+posterior cranial neuropathy	1	0.6
Brain damage	2	1.3
Tumor without details	4	2.6
Other disease	5	3.2
Unknown	12	7.7
Total	156	100

Table 5. Patterns of Treatment Failure in Patients with N_0 Nasopharyngeal Carcinoma

Site of failure	Frequency	%
Local failure only (L)	100	52.1
Regional failure only (R)	15	7.8
Distant failure only (D)	52	27.1
Simultaneous		
L+R	6	3.1
R+D	6	3.1
L+D	9	4.7
L+R+D	4	2.1
Total	192	100

with a median time of 29 months (8-48). Of them, 52 were found with isolated distant metastases, the other 19 patients with simultaneous local and/or regional failure. The sites of distant metastasis were depicted in Table 2. The 5-year and 10-year DMFS rates for the entire group were 88.5% and 85.5%, respectively. The corresponding 5-year DMFS rates for T_1, T_2, T_3 and T_4 disease were 94.0%, 92.2%, 85.3%, and 81.5%, respectively (P=0.003; Figure 1c). The 5-year DMFS rates for patients with or without local treatment failures were 86.5% and 88.6%, respectively (P=0.668). Meanwhile, the 5-year DMFS rates for patients with or without regional failures were 65.8% and 89.7%, respectively (P=0.001).

Other survival endpoints

During the analysis, 156 patients (25.6%) died, and 139 of them died of the disease (Table 3). The patterns of treatment failure were shown in Table 4. The 5-year and 10-year OS, DFS and DSS rates for the entire group

Table 4. Five-year OS, DFS and DSS According to the T Stages

Stage	No.	OS (%)	χ^2	P value	DFS (%)	χ^2	P value	DSS (%)	χ^2	P value
T_1	57	94.2			83.1			94.2		
T_2	272	86.7			76.6			88.3		
T_3	126	73.4			66.3			73.6		
T_4	155	62.2	47.266	0.000	51.1	42.739	0.000	63.9	46.736	0.000

OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival

Table 6. Impact of Prognostic Factors on Treatment by Univariate Analysis

Prognostic factors	5-year OS		5-year DFS		5-year DSS	
	%	P value	%	P value	%	P value
Age (y)		0.000		0.001		0.004
≤48	82.2		73.5		82.8	
>48	74.8		63.8		76.8	
Gender		0.043		0.018		0.048
Male	76.5		66.0		77.7	
Female	84.1		75.7		85.6	
T stage		0.000		0.000		0.000
T_1	94.2		83.1		94.2	
T_2	86.7		76.6		88.3	
T_3	73.4		66.3		73.6	
T_4	62.2		51.1		63.9	
Cranial nerve paralysis		0.000		0.000		0.000
No	82.5		72.9		84.0	
Yes	66.4		56.0		67.3	
Dose to nasopharynx (Gy)		0.002		0.033		0.001
≤66	55.6		49.0		55.6	
>66	79.1		69.1		80.5	
Dose to neck (Gy)		0.297		0.232		0.253
≤50	79.1		67.4		79.8	
>50	78.3		71.0		80.5	
Radiotherapy technique		0.311		0.816		0.328
2D- radiation	79.2		68.9		80.8	
3D-radiation	77.7		68.4		78.6	
Chemotherapy		0.847		0.922		0.590
No	79.1		69.1		80.5	
Yes	73.3		62.8		73.3	
Residual disease		0.035		0.042		0.107
No	77.6		67.4		79.1	
Yes	84.2		75.3		84.2	
Boost		0.024		0.029		0.070
No	77.4		67.4		78.9	
Yes	86.4		77.4		86.4	
CS invasion		0.049		0.005		0.076
Absent	84.4		75.1		84.9	
Present	70.7		60.0		74.4	
PPS involvement		0.476		0.287		0.424
Absent	82.3		71.9		83.5	
Present	78.4		69.0		79.9	
Skull base erosion		0.000		0.000		0.000
Absent	86.0		76.8		87.7	
Present	64.7		54.3		65.2	
Hemoglobin level		0.028		0.003		0.042
Anemia	73.5		61.2		75.4	
Normal	79.5		70.4		80.6	

were 78.7% and 66.8%, 68.8% and 55.8%, 79.9% and 70.4%, respectively. Table 4 depicted the 5-year survival rates according to T stage, and the overall survival curves according to T classification were shown in Figure 1d.

Failure patterns and prognostic factors

There were 192 failure (32.0%) after initial treatment. Out of them, 100 patients (16.7%) experienced isolated local failure, and 52 distant metastases as the first event (8.7%). The patterns of treatment failure were shown in Table 5.

The values of various potential prognostic factors, including age, gender, T stage, cranial nerve paralysis, radiation doses to the nasopharynx, radiation doses to the neck, radiotherapy technique, chemotherapy, residual disease, boost, CS invasion, parapharyngeal space (PPS) involvement, skull base erosion, and pre-radiation hemoglobin (Hb) level on predicting different endpoints

Table 7. Significant Factors for Various Endpoints by Multivariate Analysis

Endpoint	Significant factor	Hazard ratio (95% CI)	P value
OS	T stage	1.610 (1.299-1.996)	0.000
DFS	Male	1.589 (1.024-2.465)	0.039
	T stage	1.395 (1.169-1.664)	0.000
	Anemia	1.743 (1.162-2.617)	0.007
DSS	Age>48y	1.649 (1.159-2.348)	0.005
	T stage	1.457 (1.080-1.965)	0.014
	Dose to nasopharynx≤66Gy	3.611 (1.758-7.417)	0.000
L-FFS	Male	1.622 (1.022-2.575)	0.040
	Skull base erosion	1.919 (1.311-2.809)	0.001
	Anemia	1.784 (1.169-2.721)	0.007
	Dose to nasopharynx≤66Gy	2.538 (1.031-6.244)	0.043
DMFS	CS invasion	2.352 (1.208-4.581)	0.012

were evaluated by univariate and multivariate analyses as shown in Table 6 and 7, respectively. Multivariate analysis showed that T stage was the only independent prognostic factor associated with OS. While T stage, male gender and anemia were unfavorable prognostic factors for DFS.

Discussion

Over the past decade, the treatment results of NPC have been substantially improved with a 5-year OS rate in the range of 59-76.1% (Palazzi et al., 2004; Lee et al., 2005; Leung et al., 2005; Yeh et al., 2005; Yi et al., 2006), with even better treatment outcome in the patients with N_0 NPC. The 5-year OS rate in our series was 78.7%, similar to that of other reports (Gao et al., 2010; Xie et al., 2010).

Local recurrences and distant metastases were reported to be the main causes of treatment failures in NPC. With the advances in imaging technology and the advent of modern radiation techniques, local control has been substantially improved, and distant metastases has become the predominant pattern of treatment failure (Lee et al., 2005; Leung et al., 2005; Yi et al., 2006). However, patients with N_0 NPC demonstrated different patterns of treatment failures. In the current analysis, 100 patients failed with local recurrence alone, and 52 patients failed with distant metastases as the main events. The corresponding 5-year local recurrence and distant metastasis rates were 18.8% and 11.5%, respectively. Therefore, local recurrence could be identified as the dominant form of treatment failure in N_0 NPC. It was hoped that an even better survival outcome could be achieved by improving the local control.

Nasopharyngeal carcinoma is a highly radiosensitive tumor. Some reports (Teo et al., 2000; Teo et al., 2006) showed that a significant radiation dose-tumor control relationship was present above the conventional tumoricidal dose level. Dose-escalation significantly improved local control in NPC at early and advanced stages. Similar in the current study, the radiation dose delivered to the nasopharynx was a significant prognostic factor affecting the L-FFS and DSS rates, suggesting that escalating radiation dose to the primary tumor could improve the overall survival of patients.

Yi et al. (2006) found that a boost after 70-72 Gy EBRT to the residual primary lesion improved the treatment outcome in terms of OS rates, locoregional control rates, and DFS rates. In our study, 99 patients had nasopharyngeal residual disease after 70-72 Gy EBRT. 82 of them received a boost. Our results showed that boost irradiation significantly improved OS and DFS. However, the survival difference in other clinical endpoints did not indicate statistical significance. It suggested that boost irradiation delivered higher dose to the primary lesion, in turn improved local control and the treatment outcome.

IMRT represents a technical innovation in NPC management. IMRT could produce customized conformal dose distributions around the tumor, with steep dose gradients at the transition to adjacent normal structures. Hence, it enables the delivery of high radiation dose to the targets without jeopardizing the radiosensitive organs, thereby reducing treatment complications and improving the quality of life. A serial of studies were conducted to investigate the potential benefits of IMRT, using simultaneous integrated multi-target treatment technique (SIMT-IMRT) over highly optimized conventional 3D CRT combined with intracavitary brachytherapy for the treatment of NPC, and came to the same conclusion that a good therapeutic ratio could be achieved with the use of IMRT (Kam et al., 2004; Wolden et al., 2006; Taheri-Kadkhoda et al., 2008; Tham et al., 2009; Han et al., 2010; Wong et al., 2010). Moreover, the severity of xerostomia, neck fibrosis and trismus, and the incidences of xerostomia at 6 months and 1, 2, 3, 4 years after treatment were significantly reduced in IMRT group than in CRT group (Lai et al., 2011). Therefore, it has been proven that IMRT was an effective approach to enhance the local control in NPC. As only limited number of patients who received IMRT (7/610) was included in the current analysis, and the follow-up time was not long enough, it was difficult to come to conclusion whether IMRT could provide a survival benefit to patients with N_0 NPC.

In the present study, most patients (542, 88.9%) received prophylactic radiation to the upper neck, and an excellent 5-year R-FFS rate was achieved, even for advanced T stage NPC. Moreover, few patients experienced regional recurrence out of the irradiation level, with an occurrence rate as low as 2.1%. Our retrospective study also indicated that, compared with upper neck elective irradiation, whole neck irradiation did not result in any additional benefit for N_0 NPC patients in terms of regional control. N_0 NPC was defined as NPC with no palpable lymph nodes in neck, but it was unreasonable to ignore the existence of some impalpable cervical lymph nodes evidenced by imaging studies, as it was obviously not enough to irradiate just the upper neck lymph nodes without elective treatment to the lower neck. During the study, 288 patients received enhanced CT or MRI scans of the head and neck to exclude the existence of some occult lymph node metastases in the cervical region. However, the treatment outcomes of these patients were not significantly different when compared with the rest of patients. The 5-year OS, DFS, L-FFS and DMFS rates in these two subgroups were 77.7%, 68.4%, 81.0%, 88.0% and 79.2%, 68.9%, 81.2%, 88.9%, respectively. Gao once reported an excellent 5-year L-FFS rate of 88.6% in their N_0 NPC series, better than that obtained in our analysis (Gao et al., 2010). One of the possible explanations for this difference was that a considerable proportion of patients

(322, 52.8%) in our analysis were treated with out-of-date radiation techniques in 1990's, while more patients with early stage NPC were recruited in Gao's study.

It was still remained controversial for the value of combined chemoradiotherapy used in N_0 NPC patients. Lee reported their treatment results of 189 patients with T_{3-4} $N_{0-1}M_0$ NPC between 1999 and 2004 (Lee et al., 2006), finding that significant improvement only in failure-free survival was achieved in the concurrent chemoradiotherapy arm, when compared with the radiotherapy arm. The results of other studies also demonstrated that chemotherapy was not the significant prognostic factor for patients with N_0 NPC (Gao et al., 2010; Xie et al., 2010). In the present analysis, combined chemoradiotherapy did neither reduce the risk of local treatment failures and distant metastases nor improve OS, when compared with radiotherapy alone. To date, no consensus has been reached regarding to the magnitude of the effects of chemotherapy on the survival of patients with T_{3-4} N_0. This still warrants additional investigations.

Different researchers reported a 5-year DMFS rate in the range of 75.9-80% for stage III patients, and 56.2-67% for stage IV patients. Though most patients received radiotherapy without chemotherapy, an excellent 5-year DMFS rate of 85.3% in stage III patients, and 81.5% in stage IV patients, respectively, were achieved in our analysis. The risk of distant metastasis was significantly increased for NPC of advanced T stage. Based on our assessment of the DMFS rate in our patient cohort, the T stage was the significant factor on the univariate analysis (P=0.003).

Anemia was indicated to be associated with the low local control rate and survival rate in the head and neck malignancies (Chua et al., 2004; Rades et al., 2008; Gao et al., 2010). Low Hb levels led to tumor hypoxia, which was a well known factor contributing to decreased radiosensitivity and poor treatment outcomes. Our results revealed that low Hb level was an independent factor adversely affecting DFS, suggesting that treating anemia might lead to better survival of N_0 NPC patients. Further investigations were now being conducted.

Ng proved that with better tumor delineation in the help of MRI and improved coverage using modern radiotherapy techniques, neither PPS involvements nor CS invasions predicted for local treatment failure, distant failures and OS (Ng et al., 2008). Similarly, Xie found that prestyloid space involvement was not an independent prognostic factor for N_0 NPC patients (Xie et al, 2010). In the present analysis, PPS involvement showed no statistical significance for any clinical endpoint.

On univariate analysis, the CS invasion was an independent prognostic factor affecting the OS, DFS and DMFS rates. However, the prognostic value of CS invasion was lost for OS and DFS on multivariate analysis, and it only reached statistical significance in predicting DMFS for N_0 NPC patients. The CS invasion was found to be associated with a lower 5-year DMFS rate, suggesting that the tumor invaded the blood vessels in the carotid sheath directly, and then disseminated through blood stream to the distant sites.

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The authors declare that they have no competing interests.

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