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Should Tonsillar Carcinoma With Nasopharynx Invasion Alone be Classified as a T4b Disease?

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Abstract

Objective: The aim of this study was to explore the role of nasopharynx (NP) invasion alone in tonsillar carcinoma.

Materials and Methods: From 1987 to 2005, 32 patients with unresectable cT4b tonsillar carcinoma were retrospectively divided into two groups: the NP-only group, that included 11 patients with NP invasion alone without fitting other T4 criteria; and the other-T4b group, that included the remaining 21 patients. Local control and overall survival were the main endpoints of interest.

Results: At the time of this analysis, 28 patients had died, with a median follow-up time for all 32 patients of 13 months (range, 1–228 months). The mean follow-up period for the four living patients was 180 months (range, 125–228 months). When compared with the other T4b patients, patients with NP invasion alone, without fitting other T4 criteria, had greater 5-year local control (63.6% *vs.* 14.3%, $p=0.026$; hazard ratio for local failure, 0.31; 95% confidence interval, 0.11–0.94) and 5-year overall survival (45.5% *vs.* 10.3%, $p=0.022$; hazard ratio for death from any cause, 0.34; 95% confidence interval, 0.13–0.89).

Conclusion: In patients with tonsillar carcinoma, nasopharynx invasion alone should not be considered as an independent criterion of T4b classification in the next version of cancer staging. (*Tzu Chi Med J* 2009; 21(3):204–209)

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1. Introduction

Treating patients with unresectable tonsillar carcinoma is clinically challenging. For these patients, two treatment modalities are available for potential cure: definitive radiotherapy (RT) and concurrent chemoradiotherapy (CCRT) [1,2]. In general, definitive CCRT is the treatment of choice for patients who are medically fit, and RT alone is the alternative for patients who are not [1]. Even if CCRT can be performed, however, treatment outcomes are eventually unsatisfactory and overall survival is often short in these patients [2,3].

Most head and neck surgeons would agree that achieving adequate surgical margins is technically difficult for patients with tonsillar carcinoma with nasopharynx (NP) invasion. Thus, the clinical finding of NP invasion independently indicates a potentially unresectable disease (i.e. cT4b classification) and implies a poor clinical outcome in accordance with the American Joint Committee on Cancer (AJCC) staging systems [4,5]. In our clinical practice, however, we observed some patients with NP invasion alone, who did not fit other T4 criteria, had good disease control, and long survival after definitive RT or CCRT. This observation raises a clinical question of whether these patients really have as poor clinical outcomes as the other cT4b patients; this question has not been well explored.

The aim of this retrospective case-series study was to clarify the following clinical question: should tonsillar carcinoma patients with NP invasion alone be classified independently and absolutely as a T4b disease? We challenged the primarily null hypothesis that there are similar clinical outcomes between patients with NP invasion alone and other T4b patients. Treatment outcomes, chiefly local control and overall survival, were defined as the study endpoints.

2. Materials and methods

2.1. Study design and endpoints

We retrospectively included 32 patients who had histologically-proven unresectable cT4b tonsillar carcinoma and who were treated with definitive RT or CCRT (Fig. 1) from January 1987 through December 2005. All patients had undergone both endoscopy for the upper respiratory tract and cross-section imaging (computed tomography, magnetic resonance imaging, or both) of the head and neck region to define their locoregional disease extension. Cancer stages were retrospectively defined in accordance with the AJCC staging manual, 6th edition [4]. According to inclusion criteria as described below, these 32 patients were divided into the following two groups: the NP-only group, 11 patients with NP invasion alone

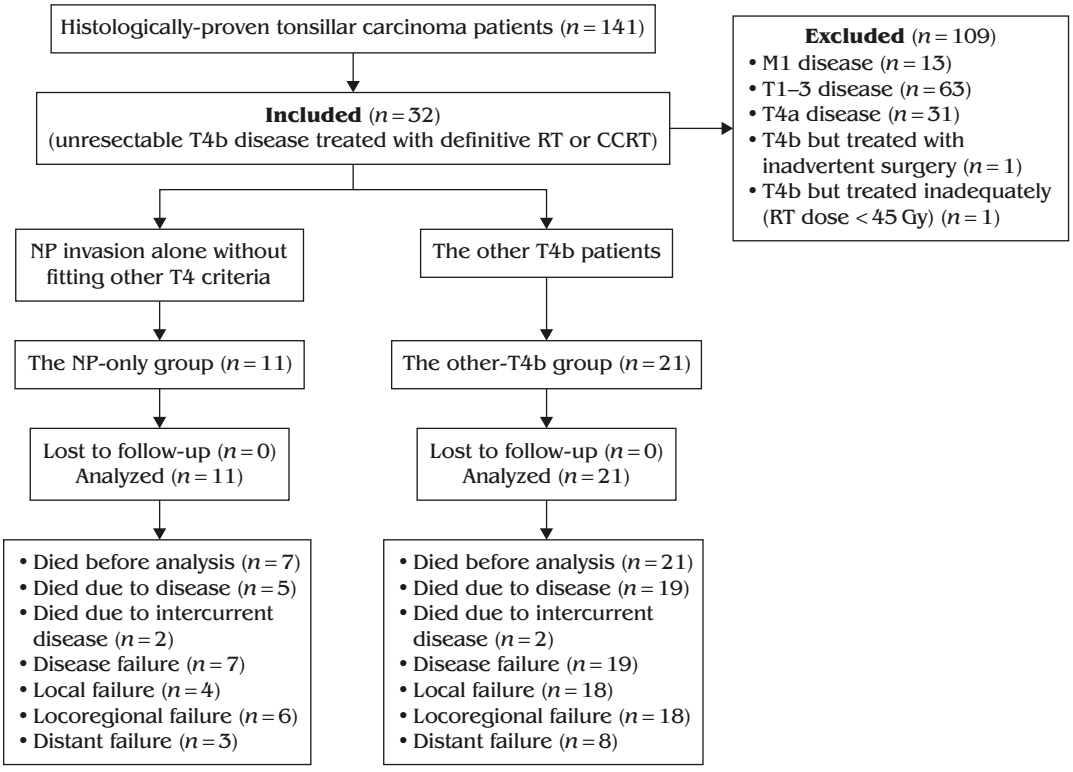

Fig. 1 — Patient allocation diagram. RT=radiotherapy; CCRT=concurrent chemoradiotherapy; NP=nasopharynx.

(without other T4 criteria); and the other-T4b group, the other 21 patients. Table 1 shows no clinically meaningful differences between the two groups in baseline characteristics. Tables 2 and 3 show individual patient profiles of the two groups. The procedures followed were in accordance with the ethical standards of the committee on human experimentation of the institution and with the Helsinki Declaration of 1975, as revised in 1983.

In the NP-only group, all 11 patients met the following three criteria: (I) histologically-proven squamous-cell or undifferentiated carcinomas of the faucial tonsil; (II) treated with definitive RT or CCRT, with a minimum cumulative RT dose of 54 Gy; and (III) classified as a T4b disease due to NP invasion alone without other T4 criteria. In the other-T4b control group, potential candidates fitted the above criteria, from (I) to (II), but did not fit the third criterion, (III).

Local control and overall survival were the main endpoints of interest. Locoregional control, disease-free survival, distant metastasis-free survival, and disease-specific survival were also recorded and analyzed as study endpoints.

Table 1 — Patient characteristics according to study group

	Patients, *n* (%)			*p*
	NP-only group	Other-T4b group	Total	
Age (yr)				0.39
>50	8 (72.7)	12 (57.1)	20 (62.5)	
≤50	3 (27.3)	9 (42.9)	12 (37.5)	
Sex				0.07
Male	8 (72.7)	20 (95.2)	28 (87.5)	
Female	3 (27.3)	1 (4.8)	4 (12.5)	
T classification				*
T4b	11 (100)	21 (100)	32 (100)	
N classification				0.45
N0–1	4 (36.4)	5 (23.8)	9 (28.1)	
N2–3	7 (63.7)	16 (76.2)	23 (71.9)	
Stage				*
IVB	11 (100)	21 (100)	32 (100)	
Histology				0.71
Grade 1–2	5 (45.5)	11 (52.4)	16 (50.0)	
Grade 3–4	6 (54.5)	10 (47.6)	16 (50.0)	
Treatment				0.95
RT	9 (81.8)	17 (81.0)	26 (81.3)	
CCRT	2 (18.2)	4 (19.0)	6 (18.8)	

*p could not be calculated. NP=nasopharynx; RT=radiotherapy; CCRT=concurrent chemoradiotherapy.

2.2. Data collection and follow-up

We reviewed data from the cancer registry database, clinical images, and all original medical charts. Discrepancies were resolved by consensus. The last follow-up was recorded on the basis of the last patient visit at the institution, the last telephone interview, or date of death. No patient was lost to follow-up. Follow-up time intervals were every 1–3 months during the first year after completion of RT, every 3–6 months during the 2nd–5th year, and every 6–12 months thereafter.

2.3. Treatment modality and policy

Radiotherapy was given for all 32 patients: definitive RT, $n=26$; and definitive CCRT, $n=6$. No formal treatment policy existed during the time span of this study. Whether definitive RT or CCRT was actually conducted depended on the patient's age, performance status, associated comorbidities, physician's preference and—more importantly—the patient's choice. The RT technique used in these two groups was the same; conventional RT with bilateral-opposed

Table 2 — Individual patient profiles in the NP-only group

Patient no.	Age (yr)/ sex	Cancer stage (AJCC 2002)	Revised cancer stage*	Local failure	Locoregional failure	Distant failure	Follow-up time† (mo)	Final status
NP-1	62/M	T4bN2c, IVB	T3N2c, IVA	Y	Y	Y	1	DOD
NP-2	63/M	T4bN1, IVB	T3N1, III	Y	Y	N	2	DOD
NP-3	67/M	T4bN3, IVB	T3N3, IVB	Y	Y	Y	6	DOD
NP-4	68/M	T4bN0, IVB	T3N0, III	N	N	Y	12	DOD
NP-5	60/M	T4bN3, IVB	T3N3, IVB	Y	Y	N	13	DOD
NP-6	81/F	T4bN0, IVB	T3N0, III	N	N	N	40	DOD
NP-7	47/M	T4bN2b, IVB	T3N2b, IVA	N	Y	N	125	AWD
NP-8	59/M	T4bN0, IVB	T3N0, III	N	N	N	138	DOD
NP-9	56/F	T4bN2b, IVB	T3N2b, IVA	N	N	N	144	AWD
NP-10	22/M	T4bN2b, IVB	T3N2b, IVA	N	N	N	216	AWD
NP-11	22/F	T4bN2b, IVB	T3N2b, IVA	N	Y	N	228	AWD

*Revised cancer stage from AJCC 2002, assuming that NP invasion alone is not an independent criterion in the T4b classification; †time interval from completion of radiotherapy to death from any cause or to the last follow-up. NP=nasopharynx; AJCC=American Joint Committee on Cancer; M=male; F=female; Y=yes; N=no; DOD=died of disease; AWD=alive with disease.

Table 3 — Individual patient profiles in the other-T4b group

Patient no.	Age (yr)/ sex	Cancer stage (AJCC 2002)	Revised cancer stage*	Local failure	Locoregional failure	Distant failure	Follow-up time† (mo)	Final status
nNP-1	36/M	T4bN3, IVB	T4bN3, IVB	Y	Y	N	2	DOD
nNP-2	47/M	T4bN2b, IVB	T4bN2b, IVB	Y	Y	Y	3	DOD
nNP-3	66/M	T4bN2b, IVB	T4bN2b, IVB	Y	Y	Y	3	DOD
nNP-4	51/F	T4bN1, IVB	T4bN1, IVB	Y	Y	N	6	DOD
nNP-5	53/M	T4bN2b, IVB	T4bN2b, IVB	Y	Y	N	6	DOD
nNP-6	44/M	T4bN3, IVB	T4aN3, IVB	Y	Y	Y	8	DOD
nNP-7	36/M	T4bN2b, IVB	T4bN2b, IVB	Y	Y	N	9	DOD
nNP-8	78/M	T4bN0, IVB	T4bN0, IVB	Y	Y	N	10	DOD
nNP-9	62/M	T4bN2b, IVB	T4bN2b, IVB	Y	Y	Y	10	DOD
nNP-10	65/M	T4bN2c, IVB	T4bN2c, IVB	Y	Y	N	13	DOD
nNP-11	65/M	T4bN0, IVB	T4bN0, IVB	Y	Y	N	13	DOD
nNP-12	38/M	T4bN0, IVB	T4bN0, IVB	Y	Y	N	13	DOD
nNP-13	69/M	T4bN3, IVB	T4bN3, IVB	Y	Y	N	13	DOD
nNP-14	44/M	T4bN2c, IVB	T4aN2c, IVA	Y	Y	Y	15	DOD
nNP-15	71/M	T4bN3, IVB	T4bN3, IVB	Y	Y	Y	15	DOD
nNP-16	46/M	T4bN2b, IVB	T4bN2b, IVB	Y	Y	N	15	DOD
nNP-17	81/M	T4bN0, IVB	T4bN0, IVB	Y	Y	Y	16	DOD
nNP-18	42/M	T4bN2c, IVB	T4bN2c, IVB	Y	Y	N	19	DOD
nNP-19	44/M	T4bN2b, IVB	T4bN2b, IVB	N	N	Y	62	DOD
nNP-20	66/M	T4bN2b, IVB	T4bN2b, IVB	N	N	N	70	DID
nNP-21	68/M	T4bN2c, IVB	T4bN2c, IVB	N	N	N	72	DID

*Revised cancer stage from AJCC 2002, assuming that NP invasion alone is not an independent criterion in the T4b classification; †time interval from completion of radiotherapy to death from any cause or to the last follow-up. AJCC=American Joint Committee on Cancer; NP=nasopharynx; M=male; F=female; Y=yes; N=no; DOD=died of disease; DID=died of intercurrent disease.

cone-down portals encompassed the primary tumor and bilateral upper neck. The median RT dose to the primary gross tumor was as follows: definitive RT, 68.0 Gy with a range of 63.0–82.8 Gy; and, CCRT, 73.8 Gy with a range of 59.4–79.2 Gy. No brachytherapy or intraoral cone boost was used. A single anterior-posterior portal with a dose of 45–50 Gy was used for the lower neck irradiation down to the bilateral supraclavicular fossae. Cisplatin alone was given concurrently with RT for patients treated with CCRT. Dose regimens of cisplatin ranged from 60 to 100 mg/m^2 every 21–28 days during RT. The median cycle of cisplatin was 2 (range, 1–3).

2.4. Definition

We defined the study endpoints as follows: local/locoregional failure, persistent local/locoregional disease 3 months after completion of RT, or local/locoregional recurrence after a disease-free time interval; distant failure, cancer failure at distant sites; disease failure, cancer failure at any site; and overall survival, the time interval from completion of RT to death from any cause or to the last follow-up.

2.5. Statistical analyses

We used commercial statistical software (SPSS version 10.0; SPSS Inc., Chicago, IL, USA) to conduct statistical analyses as follows: the Kaplan-Meier method to cumulatively estimate survival and disease-control rates; the log-rank test to assess curve difference between groups; Pearson's χ^2 test to evaluate differences between variables; and Cox proportional hazard regression to perform multivariate analyses for hazard ratio (HR) assessment. For estimating the effective size, HR was provided with a 95% confidence interval (CI) in addition to a conventional p value. All tests were two-tailed and considered to be statistically significant when $p < 0.05$.

3. Results

3.1. Patients

At the time of our analysis, 28 patients died. The median follow-up time for all 32 patients was 13 months (range, 1–228 months) and for the four living patients was 180 months (range, 125–228 months; all in the NP-only group). There were 28 men and four women, with a median age of 60 years (range, 22–81 years).

3.2. Disease control and survival

Five-year local control rates by groups were 63.6% in the NP-only group and 14.3% in the other-T4b group, $p=0.026$ (Fig. 2). In addition, we found an HR for local failure of 0.31 (95% CI, 0.11–0.94) in the NP-only

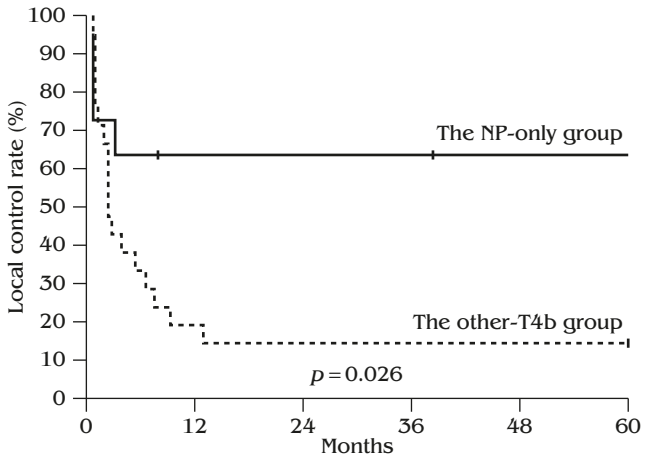

Fig. 2 — Kaplan-Meier estimates of local control according to study groups: the NP-only group included patients with NP invasion alone and the other-T4b group included the other T4b patients. NP=nasopharynx.

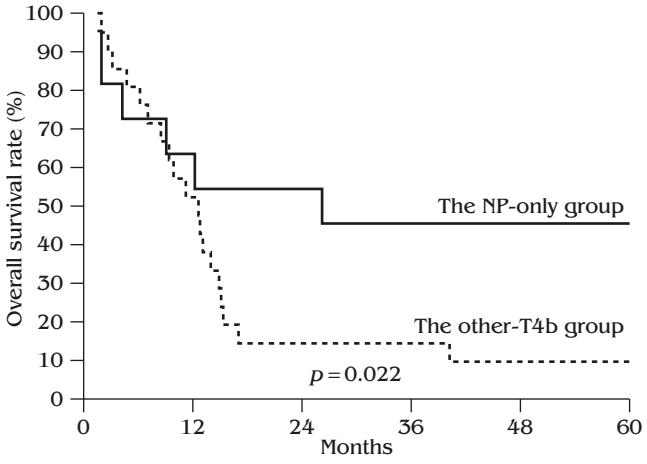

Fig. 3 — Kaplan-Meier estimates of overall survival according to study groups: the NP-only group included patients with NP invasion alone and the other-T4b group included the other T4b patients. NP=nasopharynx.

group when compared with the other-T4b group. Treatment modalities, namely definitive RT versus CCRT, had no statistically significant impact on the local control (29.6% *vs.* 33.3%, $p=0.92$).

Five-year overall survivals were 45.5% in the NP-only group and 10.3% in the other-T4b group ($p=0.022$; Fig. 3). We observed an HR for death from any cause of 0.34 (95% CI, 0.13–0.89) in the NP-only group when compared with the other-T4b group. In addition, five patients in the NP-only group had their survival time of more than 10 years, but no patients in the other-T4b group had such a long survival. The statistical significance on local control, however, did not translate into locoregional control and disease-free survival, as shown in Table 4.

3.3. Salvage treatments

At the time of our analysis, 26 patients had disease failures: seven in the NP-only group and 19 in the other-T4b group (Fig. 1). For the 11 patients who failed with a component of distant metastases, only palliative treatments were given: three in the NP-only group and eight in the other-T4b group. For the other 15 patients who failed without distant metastases, salvage treatments were given as follows: three re-irradiation and one palliative treatment in the NP-only group; and, four salvage re-irradiation and seven palliative treatments in the other-T4b group. Palliative treatments included best supportive care, low-dose chemotherapy, and low-dose re-irradiation (i.e. re-RT dose <45 Gy). For the four patients who died due to causes other than cancer disease, the causes of death were as follows: one falling injury with lethal intracranial hemorrhage, one myocardial infarction, one traffic accident, and one acute cerebral vascular infarction.

4. Discussion

Poor local control and short overall survival are the hallmarks of unresectable cT4b tonsillar carcinoma (6). In this study, when compared with the other cT4b patients, patients with NP invasion alone, without fitting other cT4 criteria, had better 5-year local control (63.6% *vs.* 14.3%, $p=0.026$; HR for local failure, 0.31; 95% CI, 0.11–0.94) and 5-year overall survival (45.5% *vs.* 10.3%, $p=0.022$; HR for death from any cause, 0.34; 95% CI, 0.13–0.89). The findings opposed the primary null hypothesis and strongly suggest that the clinical factor of NP invasion alone should be reconsidered as an independent criterion of T4b disease in tonsillar carcinoma.

Death from any cause is one event with a solid endpoint in oncology investigations. In this study, we observed a better 5-year overall survival in patients with NP invasion alone than in the other T4b patients. In addition, five patients in the NP-only group had survival times of more than 10 years, but no patient in the other-T4b group had such long survival times. These findings suggest that patients with NP invasion alone may behave differently from the other cT4b patients.

The T classification is clinically useful to represent local cancer burden in patients with tonsillar carcinoma (4,5). Our study, however, hinted at a possible pitfall of the T classification (i.e. heavily constructed on the basis of anatomic cancer extension). Some anatomic cancer extensions, such as NP invasion, could be ominous signs for patients treated with primary surgery, but may not be so clinically meaningful for patients treated with definitive RT or CCRT. This limitation has been presented in a prior study that

Table 4 — Five-year clinical outcome by groups

Outcomes (%)	NP-only versus other-T4b					
	NP-only	Other-T4b	p^*	HR	95% CI	$p^\dagger$
Local control	63.6	14.3	0.026	0.31	0.11–0.94	0.04
Overall survival	45.5	10.3	0.022	0.34	0.13–0.89	0.03
Locoregional control	42.4	14.3	0.09	0.44	0.17–1.13	0.21
Disease-free survival	36.4	9.5	0.11	0.49	0.20–1.17	0.25
DM-free survival	70.0	40.4	0.45	0.60	0.16–2.29	0.66
Disease-specific survival	54.6	14.3	0.07	0.39	0.15–1.07	0.09

*p values calculated by log-rank test; †p values calculated by Cox proportional hazard regression method. NP=nasopharynx; T4b=T4b classification; HR=hazard ratio; CI=confidence interval; DM=distant metastasis.

suggested the quantitative primary tumor volume is a better factor than the T classification in terms of estimating local cancer burden (7). Our study results confirmed this limitation of the T classification.

In most head and neck cancers, including tonsillar carcinoma, the T classification has its primary role in predicting local control (8). In our previously published data on tonsillar carcinoma, we found 5-year local control rates of 78% in T1–3 patients and 32% in T4a patients (9). In the present study, in patients with NP invasion alone, we observed a 5-year local control rate of 63.6%, which is much higher than the 32% reported in T4a patients. This observation also suggested that patients with NP invasion alone behaved differently from the other T4 patients.

For unresectable oropharyngeal carcinoma patients, including tonsillar carcinoma patients, CCRT has shown better treatment outcomes than definitive RT (2,3,10). For that reason, in these locally advanced patients, CCRT is the treatment of choice if the patient is medically fit. Our data, however, did not show this treatment benefit in CCRT. This may be due to inevitable selection bias and rare CCRT cases (n=6) in this study.

This study had several limitations. Two main limitations were the retrospective study design and the small number of cases examined; thus, the conclusions of this study should be confirmed by further investigations. Despite these limitations, this study showed that patients with NP invasion alone had better clinical outcomes, in terms of local control and overall survival, than the other T4b patients. Our observation, therefore, is a hint for revising future cancer staging systems in patients with tonsillar carcinoma.

In conclusion, for unresectable tonsillar carcinoma, patients with NP invasion alone had better clinical outcomes than the other T4b patients. Thus, for these patients, nasopharynx invasion alone should not be reconsidered to be an independent criterion of T4b classification in the next version of cancer staging.

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