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Should all nasopharyngeal carcinoma with masticator space involvement be staged as T4?

Henry Sze [a,*], Lucy L.K. Chan [b,1], W.T. Ng [b,1], Albert W.M. Hung [b,1], Michael C.H. Lee [b,1], Amy T.Y. Chang [b,1], Oscar S.H. Chan [b,1], F.Y. Cheung [b,1], Rebecca M.W. Yeung [b,1], Anne W.M. Lee [c,2]

[a] Department of Clinical Oncology, Faculty of Medicine, The University of Hong Kong, China
[b] Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Hong Kong, China
[c] Clinical Oncology Center, The University of Hong Kong – Shenzhen Hospital, Shenzhen, China

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SUMMARY

Introduction: The prognostic significance of the involvement of anatomical masticator space (MS) in nasopharyngeal carcinoma (NPC) was retrospectively reviewed.
Material and methods: 1104 Patients with non-metastatic NPC treated with radical radiotherapy between 1998 and 2010 were re-staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system; tumors with medial pterygoid muscle (MP) and/or lateral pterygoid muscle (LP) involvement but did not fulfill the criteria for T3 or T4 were staged as TX. The tumor volume data, dosimetric data and survival endpoints of different T stage diseases were analyzed and compared to study the significance of MS involvement.
Results: The overall MS involvement rate was 61.0%. The median volumes of the primary gross tumor volume were 9.6 ml, 15.2 ml, 19.9 ml, 32.6 ml and 77.3 ml for T1, T2, TX, T3 and T4, respectively ($p < 0.001$). T1, T2 and TX tumors received higher minimum dose to the gross tumor volume and planning target volume than T3 and T4. Multivariate analysis showed that age, gender, T-/N-classification and the use of chemotherapy were significant prognostic factors for various survival end-points. Patients with TX disease had similar survival rates as with T1–T2; and had a significantly better 5-year overall survival rate (86.6% vs. 76.6%; $p = 0.013$) and a trend of higher 5-year distant failure-free survival rate (91.5% vs. 81.3%; $p = 0.09$) than patients with T3 disease.
Conclusion: NPC with the involvement of MP and/or LP alone should be classified as T2 disease.

Introduction

Classification of nasopharyngeal carcinoma (NPC) provides clinicians with important information for the formulation of treatment plan and estimation of survival. The T-classification for NPC is largely based on the extent of involvement of the anatomical structures surrounding the nasopharynx. In particular, the involvement of pharyngobasilar fascia, parapharyngeal space and muscles of mastication are important landmarks of local tumor extension along the lateral direction.

According to anatomical criteria, the masticator space (MS) is a deep fascial space outlined by a superficial layer of the deep cervical fascia and contains the masticatory muscles, posterior mandible, and mandibular nerve. In the definition widely adopted in diagnostic radiology, the four masticatory muscles include the medial pterygoid (MP), lateral pterygoid (LP), temporalis and masseter muscles [1]. On the other hand, the infratemporal fossa (ITF) is a nonfascial lined space containing much of the MS (except masseter), the retroantral buccal fat and the medial part of prestyloid parapharyngeal space, but its exact boundaries vary in different definitions [2,3].

In the 5th edition of the American Joint Committee on Cancer (AJCC) TNM staging system published in 1997, involvement of the ITF was one of the staging criteria for T4 disease [4]. Here ITF was defined as the space beyond the anterior surface of the LP, or lateral extension beyond the postero-lateral wall of the

* Corresponding author at: Department of Clinical Oncology, 1/F Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. Tel.: +852 2255 4352.
E-mail address: hcksze@hku.hk (H. Sze).
[1] Postal address: Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong, China.
[2] Postal address: Clinical Oncology Center, The University of Hong Kong – Shenzhen Hospital, The University of Hong Kong - Shenzhen Hospital, 1 Haiyuan 1st Road, Futian District, Shenzhen, China.

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maxillary antrum and the pterygo-maxillary fissure. With this definition, the involvement of MP and/or LP alone was not considered a T4 criterion, though it was also not involved for other T-classifications. In the AJCC 6th edition published in 2002, "MS" was added, but only as a synonym for ITF with the same definition [5], the significance of the involvement of MP and/or LP alone therefore remained undefined.

In the latest AJCC 7th edition published in 2010, there was a change in definition of MS to include all four masticatory muscles, and the disease with MS involvement was classified as T4 [6]. This was consistent with the definition adopted in diagnostic radiology. On the other hand, tumors with involvement of MP and/or LP alone, where their significance was not specified in previous editions, were all up-staged to T4 disease. The immediate impact on the overall group staging, estimation of prognosis and management strategy especially the use of aggressive treatment with combination chemo-irradiation cannot be overemphasized.

In Southern China where the incidence of NPC is significantly higher than other parts of the world, the China 2008 staging system is also commonly used. In this staging system, diseases with involvement of MP are classified as T3 while those with invasion to the rest of the anatomical MS are classified as T4 [7].

The MS involvements that define T4 disease according to the different classification systems are depicted in Fig. 1. There is clearly a lack of universal consensus on the significance of the different degrees of involvement of the masticatory muscles in the prognostification of NPC.

In this retrospective study, we aim to determine the prognostic significance of the involvement of anatomical MS in NPC with a focus on defining the role of MP and/or LP involvement in the T-classification of NPC staging. The definition of ITF is the same as that in the AJCC 5th edition in the rest of this article and it contains the temporalis, masseter and the posterior mandible.

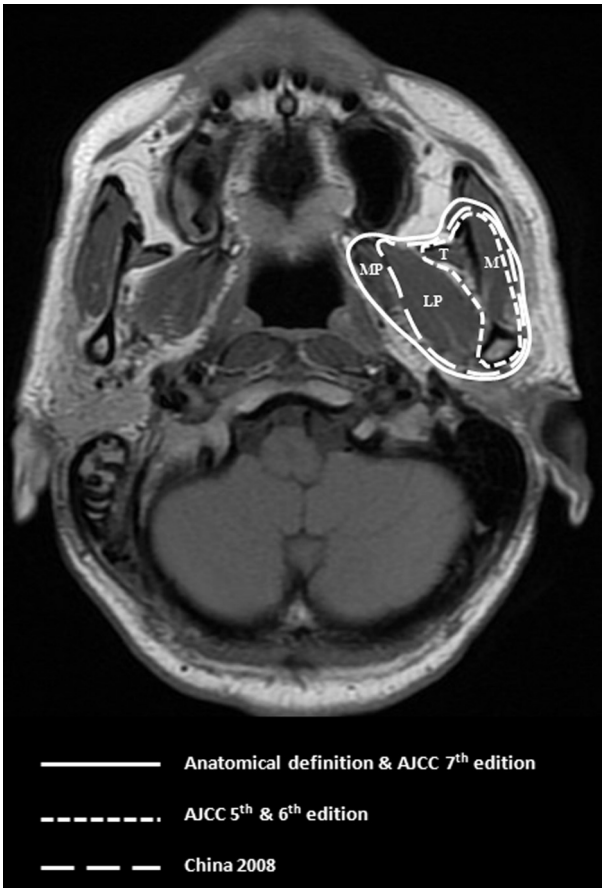

Fig. 1. The masticator space that defines T4 disease according to different classification systems. *Abbreviations:* AJCC = American Joint Committee on Cancer, LP = lateral pterygoid, M = masseter, MP = medial pterygoid, and T = temporalis.

Materials and methods

Patient selection

1104 Consecutive patients with newly diagnosed non-disseminated NPC referred to the Pamela Youde Nethersole Eastern Hospital (Hong Kong) from January 1998 to December 2010 were included in this study. Fibreoptic nasoendoscopy, chest radiograph and magnetic resonance imaging (MRI) (or computed tomography (CT) if MRI was contraindicated) of the nasopharynx and neck region were performed for staging. Positron emission tomography (PET) was an optional investigation. Patients were originally staged according to the AJCC 5th edition. The AJCC 6th edition was basically the same as the 5th edition with the addition of MS as a synonym for ITF. Tumors extending into the ITF were managed as T4 diseases, while those involving the MP and/or LP alone were staged and treated as T2 diseases. All the images for tumor staging were evaluated independently by a radiologist and a clinical oncologist and disagreements were resolved by consensus.

Treatment

Radical radiotherapy delivering 70 Gy to the primary tumor in 2 Gy per fraction at 5–6 fractions per week using 3D conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT)

Table 1
Patient characteristics, tumor and treatment factors.

Factor	Value
Age	
Median	49
Range	17–89
Male gender	814 (73.7%)
Histology	
Keratinizing squamous carcinoma	9 (0.8%)
Non-keratinizing squamous carcinoma	71 (6.4%)
Undifferentiated carcinoma	1024 (92.8%)
Imaging used for staging	
MRI	1103 (99.9%)
CT	73 (6.6%)
PET CT	105 (9.5%)
N-stage	
N0	75 (6.8%)
N1	270 (24.5%)
N2	559 (50.6%)
N3	200 (18.1%)
Radiotherapy technique	
IMRT	407 (36.9%)
3D CRT	697 (63.1%)
Radiotherapy fractionation	
5 fractions per week	468 (42.4%)
Additional boost	
Brachytherapy	32 (2.9%)
SRT	41 (3.7%)
SRT for residual disease	38 (3.4%)
Combination chemotherapy	
Concurrent/adjuvant	268 (24.3%)
Neoadjuvant/concurrent	368 (33.3%)
Concurrent alone	26 (2.4%)
Induction alone	28 (2.5%)

Abbreviations: CRT: conformal radiotherapy; CT: computed tomography; IMRT: intensity-modulated radiotherapy; MRI: magnetic resonance imaging; PET CT: positron emission tomography computed tomography; SRT: stereotactic radiotherapy.

with 6MV photon beam, with or without chemotherapy, were prescribed to all the patients. Details of the radiotherapy techniques have been published previously [8,9]. Patients with stage I–II diseases were treated with radiotherapy alone. For patients with stage III–IVB diseases chemotherapy was also given except for patient refusal, participation in clinical trial [10], age exceeding 75, or the presence of other medical conditions that were contra-indicative. Various regimens of concurrent cisplatin based chemotherapy (together with either induction or adjuvant chemotherapy) had been used because prospective trials were being conducted during the study period to assess the benefit of different sequences of chemotherapy for stage III and IV diseases [11–13].

The patients were followed up at least once every 3 months during the first 2 years, every 6 months for the next three years and annually thereafter until death.

Re-grouping according to the modified T-classification

All patients were re-staged according to the AJCC 7th edition with the exclusion of the masticatory muscles involvement as a staging criterion. Patients with tumor involving the MP and/or LP alone but not reaching the other criteria of T3 and T4 diseases were staged as TX. The subsequent dosimetric and survival analysis were performed based on the re-staged T-classification groupings to determine the clinical behavior of patients with TX disease without the confounding effects from the involvement of other structures that could up-stage the tumor regardless of the involvement of the masticatory muscles.

Tumor volumes and dosimetric data

The definitions of different target volumes can be found in our previous publications on our radiotherapy techniques [8,9]. The gross tumor volume of the primary tumor (GTV_P), the mean and minimum dose to the GTV_P (denoted as GTV_P D_{mean} and GTV_P D_{min}, respectively) and to the planning target volume receiving 70 Gy (denoted as PTV_70 D_{mean} and PTV_70 D_{min}, respectively) were analyzed and compared between T1, T2, T3, T4 and TX diseases. Games–Howell test was used because of the non-uniform sample size and heterogenous variance.

Survival outcomes

The rates of local failure free survival (LFFS – persistence/recurrence at local site), distant failure free survival (DFFS – disease recurrence at distant sites) and overall survival (OS – death from any cause) of different disease groups were analyzed and compared. The actuarial rates were calculated with the Kaplan Meier method, and the times were measured from the date of commencement of radiotherapy. Log rank test was used to compare survival outcomes and Cox's proportional hazards model was used to analyze the significance of the potential prognostic factors. The Statistical Package for Social Sciences computer program, version 18.0 (SPSS, Chicago, IL) was used for all the statistical analyses.

Results

The median follow-up time was 7.0 years (range: 0.2–15.2 years). Table 1 lists the patient characteristics, tumor factors and treatment factors. The prevalence of the masticatory muscles involvement was 61.0%. The rates of involvement of (i) MP alone, (ii) MP and LP only, and (iii) MP, LP and ITF, were 43.8%, 12.0% and 5.2%, respectively. The distribution of masticatory muscles involvement among T-classifications, staged according to the AJCC 7th edition with the exclusion of masticatory muscles involvement as a staging criterion, is shown in Table 2.

Re-grouping according to the modified T-classification

All patients were re-staged according to the AJCC 7th edition with the exclusion of the masticatory muscles involvement as a staging criterion. With this modified system 122 patients who had involvement of the MP and/or LP but without tumor invasion into other defining structures for T3 or T4 diseases were classified as TX. Table 3 shows the result of re-grouping of T-classification.

Table 2
Distribution of masticatory muscles involvement in each T-classification according to the AJCC 7th edition with the exclusion of the involvement of the masticatory muscles as a staging criterion.

T-classification	MP/LP/ITF: –	MP: + LP/ITF: –	MP/LP: + ITF: –	MP/LP/ITF: +
T1	168	0	0	0
T2	112	118*	4*	1
T3	119	273	42	10
T4	32	93	86	46

Abbreviations: ITF = infratemporal fossa, MP = medial pterygoid, LP = lateral pterygoid, '+' = involved, '–' = not involved.
* Patients with stage TX after re-grouping of T-classification.

Table 3
Re-grouping according to the modified T-classification.

T-classification and definition	Number of patients
T1: tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension	168
T2: tumor with parapharyngeal extension	112
T3: tumor involves bony structures of skull base and/or paranasal sinuses	434
T4: tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the ITF	268
TX: tumor with involvement of the MP and/or LP (but not fulfilling the definition for T3 or T4)	122

Abbreviations: ITF = infratemporal fossa, LP = lateral pterygoid, MP = medial pterygoid.

Table 4a
Dosimetric outcome according to T-classifications.

Median value	T1 (n = 163)	T2 (n = 110)	T3 (n = 431)	T4 (n = 261)	TX (n = 120)
GTV_P D_{mean} (Gy)	72.0 (70.5–73.8)	72.1 (70.7–76.3)	72.2 (70.7–76.4)	71.7 (68.6–74.9)	72.2 (71.1–74.3)
GTV_P D_{min} (Gy)	70.3 (68.5–71.8)	70.1 (67.3–72.6)	69.0 (47.7–72.3)	57.6 (29.9–70.3)	70.0 (67.0–72.1)
PTV_70 D_{mean} (Gy)	71.9 (70.9–73.4)	72.1 (71.0–74.0)	72.0 (70.2–74.1)	71.4 (68.6–74.0)	72.1 (70.9–73.6)
PTV_70 D_{min} (Gy)	67.3 (61.7–69.8)	67.1 (54.5–69.1)	64.0 (29.9–69.3)	48.5 (23.4–68.7)	66.9 (55.4–69.3)

Abbreviations: D_{mean} = mean dose, D_{min} = minimum dose, GTV_P = gross tumor volume of the primary tumor, PTV_70 = planning target volume receiving 70 Gy.

Table 4b
p-values for Games–Howell test on comparing dosimetric outcomes between T-classifications.

	T1	T2	T3	T4
T2	GTV_P D_{mean}: 0.20 GTV_P D_{min}: 0.008* PTV_70 D_{mean}: 0.027* PTV_70 D_{min}: 0.13	–	–	–
T3	GTV_P D_{mean}: <0.001* GTV_P D_{min}: <0.001* PTV_70 D_{mean}: 0.009* PTV_70 D_{min}: 0.009*	GTV_P D_{mean}: 0.57 GTV_P D_{min}: <0.001* PTV_70 D_{mean}: 0.98 PTV_70 D_{min}: <0.001*	–	–
T4	GTV_P D_{mean}: <0.001* GTV_P D_{min}: <0.001* PTV_70 D_{mean}: <0.001* PTV_70 D_{min}: <0.001*	GTV_P D_{mean}: <0.001* GTV_P D_{min}: <0.001* PTV_70 D_{mean}: <0.001* PTV_70 D_{min}: <0.001*	GTV_P D_{mean}: <0.001* GTV_P D_{min}: <0.001* PTV_70 D_{mean}: <0.001* PTV_70 D_{min}: <0.001*	–
TX	GTV_P D_{mean}: 0.10 GTV_P D_{min}: <0.001* PTV_70 D_{mean}: 0.054 PTV_70 D_{min}: 0.024*	GTV_P D_{mean}: 1.00 GTV_P D_{min}: 0.55 PTV_70 D_{mean}: 1.00 PTV_70 D_{min}: 1.00	GTV_P D_{mean}: 0.41 GTV_P D_{min}: <0.001* PTV_70 D_{mean}: 1.00 PTV_70 D_{min}: <0.001*	GTV_P D_{mean}: <0.001* GTV_P D_{min}: <0.001* PTV_70 D_{mean}: <0.001* PTV_70 D_{min}: <0.001*

Abbreviations: D_{mean} = mean dose, D_{min} = minimum dose, GTV_P = gross tumor volume of the primary tumor, GTV_P vol. = volume of the gross tumor volume of the primary tumor, PTV = planning target volume, '*' = statistically significant.

Tumor volume and dosimetric data

Details of the tumor volume and dosimetric data could not be retrieved in 19 patients. The median GTV_P volumes (range) of T1, T2, T3, T4 and TX were (unit in ml) 9.6 (0.7–40.6), 15.2 (4.6–43.3), 32.6 (3.4–288.4), 77.3 (11.6–279.9) and 19.9 (2.9–74.3), respectively. This volume increased in the order of T1, T2, TX, T3 and T4 with a significant difference among them ($p < 0.001$). Tables 4a and 4b summarize respectively the dosimetric data and the *p*-values for their comparison between T-classifications. Tumors with T4 disease had the lowest GTV_P D_{mean}, GTV_P D_{min}, PTV_70 D_{mean} and PTV_70 D_{min} ($p < 0.001$). TX tumors had significantly lower GTV_P D_{min} ($p < 0.001$) and PTV_70 D_{min} ($p = 0.024$) than T1 tumors and higher GTV_P D_{min} ($p < 0.001$) and PTV_70 D_{min} ($p < 0.001$) than T3 tumors. The dosimetric data of TX and T2 were very similar with no significant difference between them.

Survival outcomes

The 5-year LFFS, DFFS and OS of the entire cohort were 87.3%, 83.1% and 75.9%, respectively. On univariate analysis, the involvement of any masticatory muscles was a significant factor in predicting the rates of LFFS ($p = 0.004$), DFFS ($p < 0.001$) and OS ($p < 0.001$). However, its predictive value was lost in multivariate analysis when other factors including age, gender, T-/N-classification and the use of chemotherapy were also taken into account (Table 5).

The 5-year LFFS for patients with T1, T2, TX, T3 and T4 were 93.7%, 91.2%, 93.7%, 88.5%, and 75.9% respectively. The 5-year DFFS for T1, T2, TX, T3 and T4 were 92.2%, 92.8%, 91.5%, 81.3% and 70.9% respectively, and the 5-year OS were 86.8%, 90.8%, 86.6%, 76.6% and 56.7% respectively. Patients with T4 disease had the worst 5-year LFFS, DFFS and OS (Table 6). On the other hand, there is no significant difference in 5-year LFFS, DFFS and OS between patients with TX disease and those with T1 or T2 disease. The TX group had a significantly better 5-year OS ($p = 0.013$) and, though not statistically significant, demonstrated a trend of higher 5-year DFFS ($p = 0.09$) than patients with T3 disease. The survival curves were shown in Fig. 2.

Role of involvement of MP vs. LP

As seen from Table 2, among 122 patients with TX disease, 118 of them had MP involvement while only 4 had LP involved. The small sample size of patients with LP involvement made it impossible for accurate statistical testing. Patients with T3 disease were therefore used in order to explore the impact of the involvement of MP versus that of LP on the survival outcomes in the absence of the other defining features of the more advanced T4 dis-

Table 5
Multivariate analyses on treatment outcome.

	Hazard ratio (95% CI)	*p*
Local failure		
Age, per year increase	1.01 (1.00–1.02)	0.18
Gender (female vs. male)	0.72 (0.49–1.07)	0.11
T stage		<0.001
T2 vs. T1	1.05 (0.49–2.26)	0.91
T3 vs. T1	1.22 (0.61–2.43)	0.58
T4 vs. T1	2.73 (1.32–5.67)	0.007
Tx vs. T1	0.95 (0.39–2.33)	0.91
Involvement of masticatory muscles (yes vs. no)	1.15 (0.71–1.86)	0.58
Brachytherapy (yes vs. no)	0.24 (0.03–1.85)	0.17
SRT (yes vs. no)	1.70 (0.83–3.48)	0.15
Chemotherapy (yes vs. no)	0.91 (0.63–1.32)	0.64
Distant failure		
Age, per year increase	1.01 (1.00–1.02)	0.12
Gender (F vs. M)	0.67 (0.46–0.96)	0.030
T stage		0.001
T2 vs. T1	1.19 (0.53–2.69)	0.67
T3 vs. T1	2.14 (1.09–4.22)	0.028
T4 vs. T1	3.29 (1.60–6.75)	0.001
Tx vs. T1	1.37 (0.59–3.19)	0.47
Involvement of masticatory muscles (yes vs. no)	1.16 (0.76–1.76)	0.49
N stage		<0.001
N1 vs. N0	2.28 (0.80–6.49)	0.12
N2 vs. N0	3.32 (1.19–9.28)	0.022
N3 vs. N0	6.77 (2.40–19.09)	<0.001
Brachytherapy (yes vs. no)	0.98 (0.22–4.37)	0.97
SRT (yes vs. no)	0.17 (0.023–1.18)	0.073
Chemotherapy (yes vs. no)	0.75 (0.53–1.07)	0.11
Overall survival		
Age, per year increase	1.04 (1.03–1.05)	<0.001
Gender (F vs. M)	0.68 (0.52–0.89)	0.005
T stage		<0.001
T2 vs. T1	1.19 (0.68–2.07)	0.54
T3 vs. T1	1.72 (1.07–2.76)	0.025
T4 vs. T1	3.17 (1.92–5.22)	<0.001
Tx vs. T1	1.09 (0.59–2.00)	0.79
Involvement of masticatory muscles (yes vs. no)	1.14 (0.84–1.55)	0.39
N stage		<0.001
N1 vs. N0	1.10 (0.66–1.83)	0.73
N2 vs. N0	1.49 (0.91–2.45)	0.12
N3 vs. N0	2.35 (1.40–3.93)	0.001
Brachytherapy (yes vs. no)	0.90 (0.39–2.07)	0.80
SRT (yes vs. no)	1.41 (0.82–2.43)	0.21
Chemotherapy (yes vs. no)	0.76 (0.59–0.98)	0.037

Table 6
p-values for log rank test on 5-year rates of survival between T-classifications.

	T1	T2	T3	T4
T2	LFFS: 0.60 DFFS: 0.67 OS: 0.62	–	–	–
T3	LFFS: 0.09 DFFS: 0.001* OS: <0.001*	LFFS: 0.37 DFFS: 0.016* OS: 0.010*	–	–
T4	LFFS: <0.001* DFFS: <0.001* OS: <0.001*	LFFS: <0.001* DFFS: <0.001* OS: <0.001*	LFFS: <0.001* DFFS: 0.003* OS: <0.001*	–
TX	LFFS: 0.56 DFFS: 0.18 OS: 0.54	LFFS: 0.98 DFFS: 0.48 OS: 0.91	LFFS: 0.32 DFFS: 0.09 OS: 0.013*	LFFS: <0.001* DFFS: <0.001* OS: <0.001*

Abbreviations: DFFS = distant failure-free survival, LFFS = local failure-free survival, OS = overall survival, '*' = statistically significant.

ease. Then T3 patients were grouped into 4 subgroups: group 1 were those without any involvement of the masticatory muscles, group 2 were those with involvement of MP, group 3 and group 4 were those with extension to LP and ITF respectively. Their survival curves are shown in Fig. 3. No statistically significant difference was detected in the 5-year LFFS and DFFS among the 4 groups. Group 4 had the lowest rate of 5-year OS ($p = 0.011$) while no difference was found among groups 1–3.

Discussion

A robust staging system is critical for determining prognosis, appropriate treatment options and treatment outcomes. Because the T-classification for NPC relies so heavily on the exact involvement of anatomical structures, clear terminology with well-defined and universally agreed nomenclature should be used. The use of MS has created confusion as there is a lack of consistent definition not only between diagnostic radiologists and oncologists but also in different versions of AJCC staging system. Thus, the prognostic significance of the involvement of MS in NPC has been a matter of debate.

Since the publication of the AJCC 7th edition, studies have been performed to investigate whether tumors with the involvement of anatomical MS should be regarded as T4 disease. Tang et al. reported a series of 924 MRI-staged NPC patients with more than 80% of the patients underwent two-dimensional conventional

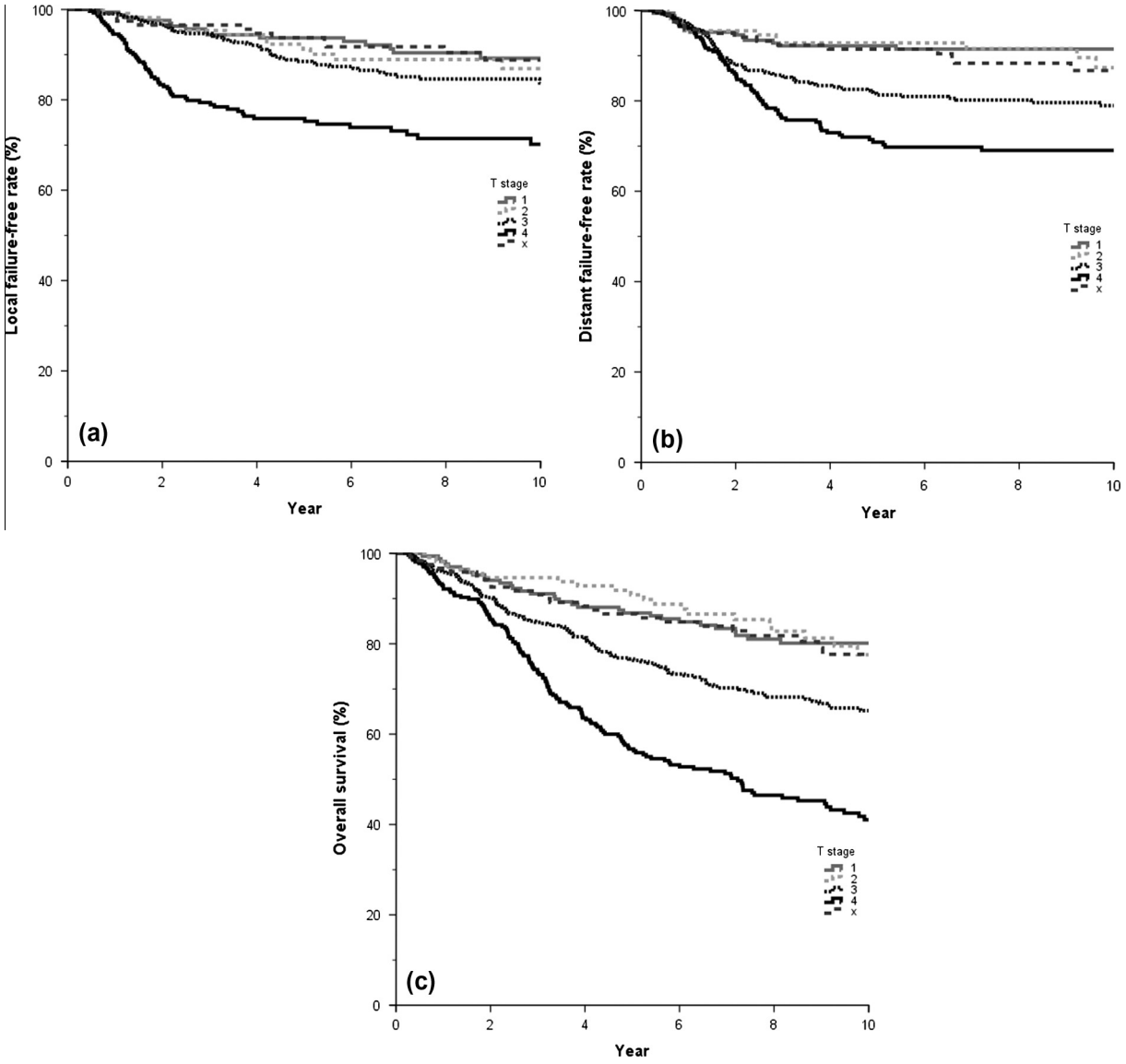

Fig. 2. Survival outcome for stages T1–T4 and TX. (a) Local failure-free survival, (b) distant failure-free survival, and (c) overall survival.

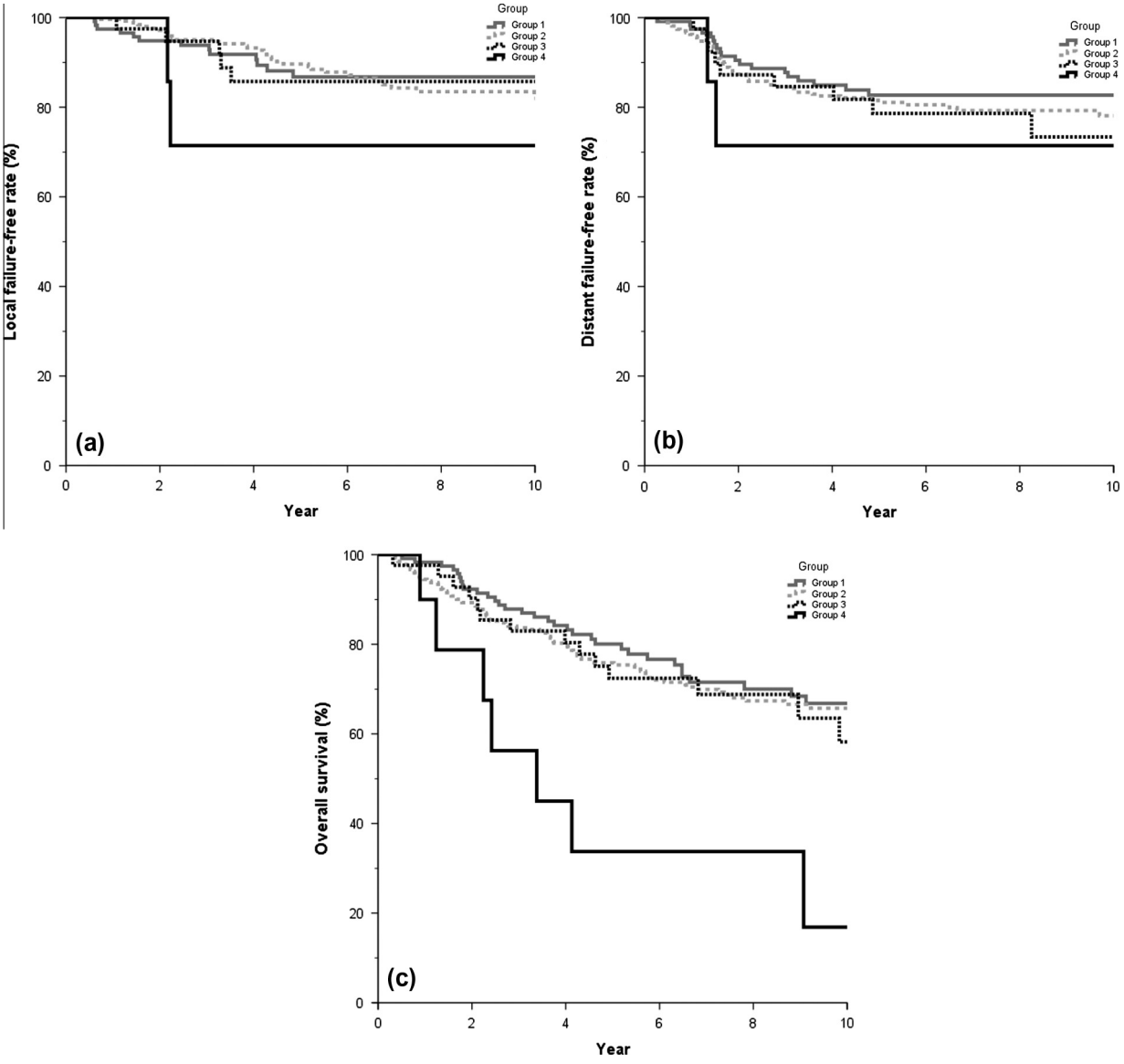

Fig. 3. Survival outcome for groups 1–4 among patients with T3 disease. (a) Local failure-free survival, (b) distant failure-free survival, and (c) overall survival.

radiotherapy (2D RT) [14]. Of the 182 patients with anatomical MS involvement, 97.8% had T3 or T4 diseases. Involvement of the anatomical MS was found to be an independent prognostic factor for local control and OS by multivariate analyses. In addition, T3 tumors with anatomical MS involvement had survival outcome similar to T4 diseases but significantly poorer than T3 tumors without anatomical MS involvement. They therefore concluded that tumors with anatomical MS involvement should be regarded as T4 disease. In another study from the same group, the treatment outcomes of 140 patients with T4 NPC treated with IMRT were reported [15]. Patients who were staged as T4 disease due to the involvement of anatomical MS alone had significantly better distant control and OS than those who had involvement of the intracranial region, cranial nerves and/or orbit (5-year rates of DFFS 87.0% vs. 66.8% and OS 82.5% vs. 62.6%, respectively). The authors thus proposed subclassification of T4 into two subgroups with different prognosis. However, this study did not include patients with T1–T3 diseases to more accurately define the prognostic importance of anatomical MS involvement.

Another important question about the prognostic significance of anatomical MS involvement is whether the degree of involvement as defined by invasion into different individual masticatory muscle should affect the T-classification. Sun et al. reported the results of 903 NPC patients with 84.1% of them treated with 2D RT [16]. Significant difference in OS was observed between patients with involvement of the MP alone versus those with extension into the ITF. This gave a strong hint that different degree of anatomic MS involvement did play a role in risk categorization. However, in the series by Tang et al., the comparison between 29 patients with ITF involvement and 153 patients with MP and/or LP involvement only did not show any significant difference in the survival outcomes [14].

In contrast to previous studies, the current study reported the treatment outcomes of patients with all the T-classifications treated with modern RT techniques with either 3DCRT or IMRT. We isolated the patients with the involvement of MP and/or LP without any defining features of more advanced T3 and T4 disease and staged them as TX in order to minimize the confounding effect by T-classification. Our study demonstrated that NPC involving the MP and/or LP had survival outcome comparable to T1–T2 diseases and superior to the more advanced T3–T4 diseases. Taking into account the tumor size and the dosimetric data, NPC with MP

and/or LP involvement should be staged and managed as T2 disease in modern era using advanced RT techniques.

Previous studies have demonstrated a predictive role of tumor volume in the treatment outcome regardless of the radiotherapy techniques [17–22]. It was estimated that the local failure increased by 1% for every 1 cm^3 increase in tumor volume [18]. So the tumor volume could be one of the intrinsic factors for TX to have a more favorable outcome than more advance disease besides sparing of other high risk structures. In a report by Ng et al. on the patterns of failure after IMRT, it was found that the minimum dose to the GTV_P was a significant factor in predicting local failure with patients receiving at least 66.5 Gy to the primary tumor having better local control [9]. Tumors of TX was shown to have better radiotherapy coverage than T3 tumors in terms of the minimum dose to primary tumor and the planning target volume and this could be an important extrinsic factor that could explain the more favorable outcome than the more advanced disease.

Recently, Zhang et al. reported a series of 808 patients with NPC treated with IMRT. It was shown that the involvement of the anatomical MS with various degree of invasion carried different prognostic significance. Patients with involvement of the LP and beyond had significantly poorer DFFS and OS than those with involvement of the MP, and also poorer LFFS, DFFS and OS when compared with patients with stage T2 or T3 disease. Their survivals are however similar to patients with stage T4 disease [23]. It was proposed that tumors involving LP should be staged as T4 and those involving MP should be regarded as T2. On the other hand, the study by Sun et al. showed no difference in survival between tumors with MP and LP involvement [16]. From our current study, the involvement of LP is highly associated with advance T-classification i.e., T3–T4 diseases. It is likely that the pterygoid plates were already involved when there was tumor extension to the LP. Analysis of the patients with T3 disease does not support upstaging tumors with LP involvement to T4 because the survival outcomes of groups 1–3 were similar for all end-points.

For the prevalence of the anatomical MS involvement, the rate of 61% in the current cohort appeared much higher than that in other reported series, which were 19.7–20.2% [14,23]. Instead of a genuine imbalance in patient composition among these large cohorts, it is more likely that the difference is due to variation in the criteria of MS involvement used by different radiologists. While there should be minimal discrepancy for the diagnosis of gross MS involvement, subtle involvement of the MP is not uncommonly encountered especially when the tumor is spreading antero-laterally and it could pose both a diagnostic challenge and a source of variation among different centers or individual radiologists. Further effort should be spent for its unification.

Some limitations of this study merit discussion. First, the role of isolated ITF involvement could not be adequately addressed because of the fact that majority of them had co-existing features of T4 disease and only one patient had tumor involving the ITF without features of the advanced stage disease. This also concurred with the previous editions of the AJCC staging system as its involvement was regarded as T4 disease. Second, there were only a limited number of patients with extension to the LP among the TX subgroup. It is not possible to investigate the prognostic difference in tumors involving MP versus those with further extension to LP, in the absence of other high risk features. Further study is warranted to confirm the difference in prognosis between tumors with MP and LP involvement.

To improve the staging system in the future, it is important to adopt nomenclature of anatomical sites with clear and unambiguous definition. For the terms like MS and ITF, it appears that there is a lack of unequivocal agreement in their definition not only among different versions of the staging systems but also between the specialties of diagnostic radiology and radiation oncology. The use of individual masticatory muscle names could be considered, or else a clear definition of the anatomical spaces agreed by both specialties should be used. Clinical data should be taken into account during the consideration of inclusion of stage-defining structures to reflect the treatment outcome and the prognosis in modern era using more sophisticated imaging and radiotherapy techniques.

Conclusion

A clear nomenclature system is of paramount importance for the staging of NPC. The definitions of MS and ITF are inconsistent and ambiguous and should be revised in future staging systems. We have demonstrated that NPC with extension to the MP and/or LP alone without fulfilling the other criteria for T3 and T4 should be staged as T2 disease. Further study is warranted to define the prognostic significance of the involvement of individual masticatory muscle.

Conflict of interest statement

None declared.

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