Radiotherapy and Oncology 134 (2019) 37–43

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Subclassification of skull-base invasion for nasopharyngeal carcinoma using cluster, network and survival analyses: A double-center retrospective investigation

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A R T I C L E I N F O

Article history:
Received 18 November 2018
Received in revised form 15 January 2019
Accepted 17 January 2019
Available online 1 February 2019

Keywords:
Nasopharyngeal carcinoma
Skull-base invasion
Subclassification
Cluster analysis
Network analysis
Survival analysis

A B S T R A C T

Purpose: To investigate the prognostic value of skull-base invasion (SBI) for nasopharyngeal carcinoma (NPC), propose a subclassification of SBI.

Methods: 792 and 433 patients with pathologically proven NPC and complete clinical and magnetic resonance imaging records at Sun Yat-sen University Cancer Center and Foshan Hospital were enrolled, and investigated using heat map/cluster, network and survival analyses.

Results: The results of heat map/cluster analyses and network analysis showed that T3 patients with pterygoid process and/or base of the sphenoid bone invasion (T3 slight) had better treatment outcomes than those with other SBIs (T3 severe). Significant differences were observed between T3-slight and T3-severe groups with regard to 5-year overall survival (OS) (93.0% vs. 83.5%, $p = 0.014$) and progression-free survival (PFS) (82.5% vs. 74.1%, $p = 0.044$) rates. No significant difference was observed between T3-slight group and T2 patients with regard to 5-year OS (93.0% vs. 84.7%, $p = 0.062$) and PFS (82.5% vs. 78.9%, $p = 0.459$) rates. Therefore, we downgraded patients with T3 slight to T2, yielding a new T classification sample. The survival curves of the 5-year OS and PFS rates of T2 and T3 were more reasonable after sample redistribution than those before sample redistribution. The differences in the 5-year OS and PFS rates between T2 and T3 patients after sample redistribution approached significance ($p = 0.075$ and 0.051, respectively).

Conclusions: Different types of SBIs had different effects on the prognosis for NPC. We recommend patients with T3 slight not be defined as T3 but, rather, as T2.

Nasopharyngeal carcinoma (NPC) is a malignant head and neck cancer with a distinct ethnic and geographic pattern of distribution; the highest annual incidences of NPC (approximately 30 cases per 100,000 persons) are observed in southern China [1]. The TNM staging system for malignant tumors is intended to evaluate prognosis, aid in treatment planning, facilitate the stratification of treatment, and coordinate clinical studies among different treatment centers [2,3]. Skull-base invasion (SBI) is generally considered a major factor contributing to the poor prognosis of NPC [4–6] and has been consistently classified into the T3 category from the 5th to the prevailing 8th edition of the American Joint Committee on Cancer (AJCC) staging system [7,8]. However, according to the AJCC classification, any SBI site and single or multiple SBIs are all defined as T3.

In recent decades, the efficacy of NPC treatment has greatly increased with the popularization of magnetic resonance imaging (MRI) and the implementation of intensity-modulated radiotherapy (IMRT) as well as combined chemotherapy [9]. Based on these achievements, researchers have performed a series of investigations on the prognostic value of SBI for NPC patients and have proposed that different SBI types have different effects on the treatment outcomes of NPC patients [10–13], leading to the recommendation that SBI classification be refined. The fact is that there is a wide range and complex anatomic structure in the skull base area, and patients with different SBIs have poor prognostic consistency. Therefore, the subclassification of NPC SBIs is necessary.

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https://doi.org/10.1016/j.radonc.2019.01.021
0167-8140/

A heat map is a graphical representation of the experimental data and analytic results in which the individual values contained in a matrix are represented as colors; it is one of the most popular methods to present gene expression data [14]. Cluster analysis is another prevailing method in the field of gene expression that can be used to classify sample subtypes [15]. In addition, network analysis is a powerful tool to discover connection(s) among respective variables, such as genes, plants and drugs [16]. To date, these three methods have been widely used in biology and medicine. However, their application in the investigation of SBI of NPC patients has not yet been reported.

The present study aimed to investigate the prognostic value of SBI for NPC patients treated with IMRT and, if possible, to propose a subclassification of SBI. First, we assessed the posttreatment outcomes of T3-classified NPC patients with different SBIs using heat map and cluster analyses [14,15] to determine whether a subclassification of SBI exists and then strengthened the findings with the results of network analysis [16] to present a hypothesis for the subclassification of SBI. Next, we used survival analysis to verify our hypothesis and, consequently, redistribute those T2- and T3-classified patients to yield new T2 and T3 samples according to different SBIs. Finally, we compared the prognoses of those T2- and T3-classified patients before and after the redistribution. We expected that the subclassification of SBI would provide evidence for a new T classification of NPC in the future.

Patients and methods

Participants

We enrolled 792 NPC cases from Sun Yat-sen University Cancer Center between January 2010 and January 2013. The inclusion criteria were as follows: (i) pathologically confirmed NPC; (ii) complete pretreatment clinical information and laboratory data; (iii) complete data of MRI images for nasopharynx and neck regions; and (iv) treated with IMRT. The exclusion criteria included the following: (i) NPC with disseminated disease before treatment; (ii) patients with other tumors concurrently.

In addition, a total of 433 NPC patients who were treated at First People's Hospital of Foshan between April 2010 and March 2014 were included. The inclusion and exclusion criteria for those patients were the same as those for patients in the Cancer Center.

This study was approved by the committees of the Institutional Review Boards at Sun Yat-sen University Cancer Center and the First People's Hospital of Foshan. All data have been deposited at Sun Yat-sen University Cancer Center for future reference (www.researchdata.org.cn), with the Research Data Deposit (RDD) number as RDDA2018000928.

Imaging protocol

A detailed description of the imaging protocol is presented in the *supplementary material*.

Imaging assessment

A detailed description of the imaging assessment is presented in the *supplementary material*.

Treatment

A detailed description of the treatment protocol is presented in the *supplementary material*.

Follow-up

We followed the enrolled patients every 3 months in the first two years and every 6 months thereafter; the entire follow-up time was 5 years. The endpoint of our study was overall survival (OS), which was calculated from the date of the initial diagnosis until the date of death due to any cause, and progression-free survival (PFS), which was calculated from the date of the initial diagnosis until the date of failure or death from any cause, whichever occurred first.

Statistical analyses

First, we used heat map and cluster analyses to visually display the posttreatment outcomes of T3-stage patients with different SBIs treated in Cancer Center and Foshan Hospital to determine whether different SBIs have different effects on the prognosis of NPC patients. Next, we performed network analysis to observe the survival outcome of T3-classified patients with different SBIs, further strengthening our hypothesis concerning the subclassification of SBI. Based on the abovementioned analysis, the SBIs were subjected to univariate and multivariate analyses to verify the SBI subclassification. For univariate analysis, we investigated the hazard ratio (HR) of each SBI site using the T1 and T2 classifications as reference groups. For multivariate analysis, we ranked all SBI sites in terms of their HR after eliminating confounding factors, with the T1 and T2 classifications set as reference groups. Additionally, we analyzed the treatment outcomes of T3 patients with only pterygoid process and/or base of the sphenoid bone invasion (named T3 slight) and T1 and T2 patients. Based on the results, we attempted to classify patients with T3 slight and patients with T3 classification and other SBIs into different T classifications, yielding new T classification samples. Finally, we investigated the differences in the 5-year OS and PFS rates for T-classified patients before and after the redistribution of T-classified patients with SBIs. All analyses were performed using R software (version 3.4.3; stats, survival, Hmisc, rms, ggplot2, survminer; ClustOfVar; network, sna, GGally). All tests were two-sided, and a p value less than 0.05 was considered significant.

Results

Characteristics of patients in Cancer Center and the Foshan Hospital cohorts

The sociodemographic and clinical characteristics of the patients in Cancer Center and the Foshan Hospital cohorts are shown in Table 1.

Preliminary heat map/cluster analysis and network analysis concerning the subclassification of SBI

There were 442 cases of T3-classified patients in total (442/1225, 36.1%).

The posttreatment outcomes of T3-classified patients according to heat map and cluster analysis are shown in Fig. 1. Patients with only pterygoid process and/or base of the sphenoid bone invasion (T3 slight) clustered with surviving patients, while patients with other SBIs clustered with deceased patients. Therefore, we suspected that, to some extent, patients with T3 slight might have a different treatment outcome from those with other SBIs.

The results of network analysis are shown in Fig. 2. The variables (representing different SBIs) and patients were clearly divided into two groups. Patients with T3 slight exhibited a superior treatment outcome to that of patients with other SBIs.

Table 1
Sociodemographic and clinical characteristics of the participants.

Variables	Hospital 1 (N = 792)	Hospital 2 (N = 433)	Chisqure p-Value	Total data (N = 1225)	OS:Univariate Cox regression p-value
Sex			0.212		
Male	576 (72.7%)	329 (76.0%)		905(73.9%)	Reference
Female	216 (27.3%)	104 (24.0%)		320 (26.1%)	0.031
Age			0.002		
≥45 years old	397 (50.1%)	257 (59.4%)		654 (53.4%)	Reference
<45 years old	395 (49.9%)	176 (40.6%)		571 (46.6%)	<0.001
Histologic type			<0.001		
WHO type 1	5 (0.6%)	–		5 (0.4%)	Reference
WHO type 2	41 (5.2%)	–		41 (3.3%)	0.684
WHO type 3	746 (94.2%)	433 (100%)		1179 (96.2%)	0.455
T classification			0.547		
T1	204 (25.8%)	121 (27.9%)		325 (26.5%)	Reference
T2	97 (12.2%)	60 (13.9%)		157 (12.8%)	0.002
T3	296 (37.4%)	146 (33.7%)		442 (36.1%)	0.001
T4	195 (24.6%)	106 (24.5%)		301 (24.6%)	<0.001
N classification			0.031		
N0	182 (23.0%)	75 (17.3%)		257 (21.0%)	Reference
N1	438 (55.3%)	241 (55.7%)		679 (55.4%)	0.051
N2	113 (14.3%)	84 (19.4%)		197 (16.1%)	<0.001
N3	59 (7.4%)	33 (7.6%)		92 (7.5%)	<0.001
Stage			0.940		
I	73 (9.2%)	37 (8.5%)		110 (9.0%)	Reference
II	175 (22.1%)	100 (23.1%)		275 (22.4%)	0.223
III	303 (38.3%)	161 (37.2%)		464 (37.9%)	0.007
IV	241 (20.4%)	135 (31.2%)		376 (30.7%)	<0.001
Chemotherapy			0.224		
No	107 (13.5%)	70 (16.2%)		177 (14.4%)	Reference
Yes	685 (86.5%)	363 (83.8%)		1048 (85.6%)	0.146
OS			<0.001		
No	705 (89%)	349 (80.6%)		1054 (86.0%)	
Yes	87 (11%)	84 (19.4%)		171 (14.0%)	
PFS			0.237		
No	629 (79.4%)	331 (76.4%)		960 (78.4%)	
Yes	163 (20.6%)	102 (23.6%)		265 (21.6%)	

The prognostic value of SBI for NPC patients – survival analyses

T3 patients were classified into two groups: patients with T3 slight (named the T3-slight group), and patients with other SBIs (named the T3-severe group). A total of 176 and 266 patients belonged to T3-slight and T3-severe groups, respectively.

The results of univariate analysis demonstrated that the HR for death of T3-slight group was slightly higher (HR = 1.418, 95% CI = 0.711–2.829), but the difference from that of T1 patients was not significant ($p = 0.321$). Compared with that of patients in the T2-classification group, the HR for death of the T3-slight group was slightly lower (HR = 0.534, 95%CI = 0.273–1.044), although the difference between the groups was not significant ($p = 0.067$). In the Cox multivariate analysis, based on the results of univariate analysis for OS in the Table 1, the following variables were included as confounding factors: age (<45 years, ≥45 years), sex, and N classification. The T1 and T2 classification were taken as references, each factor was ranked according to the increased HR for death, and the *HRs* of the T3-slight group were larger than and less than 1, but always had the lowest ranking. The detailed ranking is shown in Table 2.

The survival curves of the 5-year OS rates and PFS rates for T1, T2, T3-slight and T3-severe groups are shown in Fig. 1 of the *supplementary material (Fig. S1)*. Significant differences were observed between T3-slight and T3-severe groups with regard to the 5-year OS rate (93.0% vs. 83.5%, $p = 0.014$) and the 5-year PFS rate (82.5% vs. 74.1%, $p = 0.044$). However, no significant difference was observed between T3-slight and T2 groups with regard to the 5-year OS rate (93.0% vs. 84.7%, $p = 0.062$) and the 5-year PFS rate (82.5% vs. 78.9%, $p = 0.459$). Furthermore, the 5-year OS and PFS rates for the T3-slight group were not significantly different from those for the T1 group (93.0% vs. 94.5%, $p = 0.319$; 82.5% vs. 87.2%, $p = 0.145$, respectively).

Based on the abovementioned analysis, T3-slight patients had a better prognosis than T3-severe patients. In addition, the HR for death of T3-slight patients was higher than that for T1 patients and lower than that for T2 patients.

Among the 176 cases of T3-slight patients, 129 (129/176, 73.3%) had invasion in the parapharyngeal space, longus capitis muscle, tensor veli palatini muscle, medial pterygoid, and lateral pterygoid, which belong to the anatomical structures of T2 classification, while the other 47 cases exhibited only pterygoid process and/or base of the sphenoid bone invasion, without invasion of those anatomical structures of T2 classification. We categorized these patients as group 1 and group 2, respectively. The survival curves of the 5-year OS rates and PFS rates for both groups are shown in Fig. 2 of the *supplementary material (Fig. S2)*. No significant differences between the groups in terms of the 5-year OS rate (91.3% vs. 93.7%, $p = 0.848$) and the 5-year PFS rate (87.1% vs. 80.9%, $p = 0.411$) were observed.

Therefore, we downgraded those patients with T3-slight to the T2 classification. Thus, patients in the previous T2 and T3 classifications were redistributed.

Comparison between the prognoses of patients with T2 and T3 classifications before and after classification redistribution

According to the above results, 176 (176/1225, 14.4%) T3-classified cases were downgraded to the T2 classification, yielding new samples containing 333 and 266T2 and T3 patients, respec-

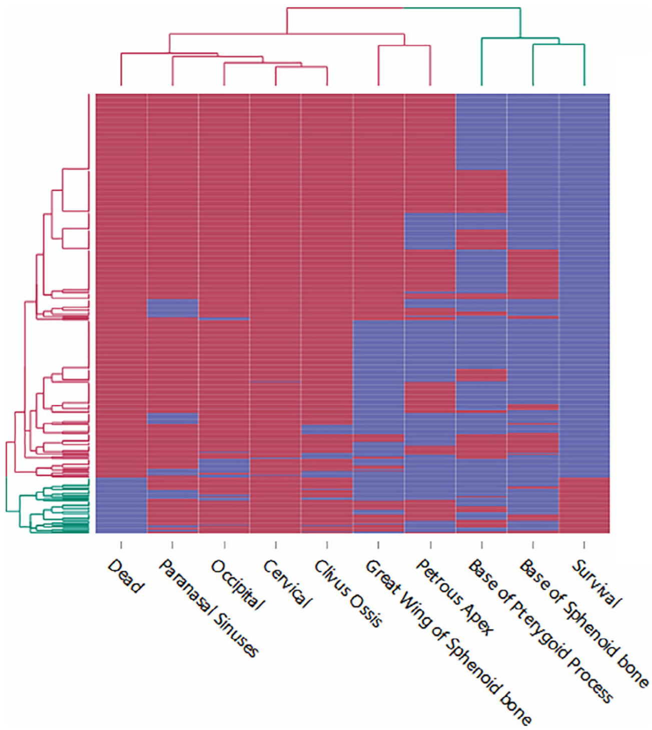

Fig. 1. Heat map and cluster analyses for T3-classified patients. The red line groups meant close to "dead" while the blue line groups meant close to "survival", respectively. The results showed T3 patients with only pterygoid process and/or base of the sphenoid bone invasion (T3 slight) clustered with surviving patients, while patients with other SBIs (T3 severe) clustered with deceased patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

tively. The median follow-up period for the merged dataset was 60.3 months (range, 1.4–83.4 months), the 5-year OS rates for T2 and T3 patients, before and after sample redistribution, were as follows: 84.7% versus 89.1% (T2), 87.3% versus 83.5%, respectively. The 5-year PFS rates for T2 and T3 patients, before and after sample redistribution, were as follows: 78.9% versus 80.9% (T2), 77.5% versus 74.1%, respectively. (Table 1 in the *supplementary material, Table S1*).

The survival curves of the 5-year OS rates and PFS rates for all the T classification patients before and after the redistribution of T2- and T3-classified patients are shown in Fig. 3. In terms of the 8th AJCC staging system (before sample redistribution), the survival curve of T2 classification patients almost completely overlapped that of T3 patients, suggesting that the treatment outcome of T2 patients might be approximately the same as that of T3 patients. The difference in the survival rates for both groups of patients was not significant ($p = 0.595$, 0.671 for 5-year OS and PFS rates, respectively). However, in terms of the new T2/3 classification sample (after sample redistribution), the survival curve of T2 patients was higher than that of T3 patients, suggesting that the treatment outcome of T2 patients was better than that of T3 patients. In addition, the difference in the survival rates for both groups of patients approached significance ($p = 0.075$, 0.051 for 5-year OS and PFS rates, respectively).

Discussion

In our study, 36.1% of cases were T3-classified patients. For those patients, we first used heat map and cluster analyses [14,15] to visually display their survival likelihood. The results illustrated that patients with T3 slight tended to experience "survival", while patients with T3 severe were more likely to experience "death." Next, the results of network analysis [16]

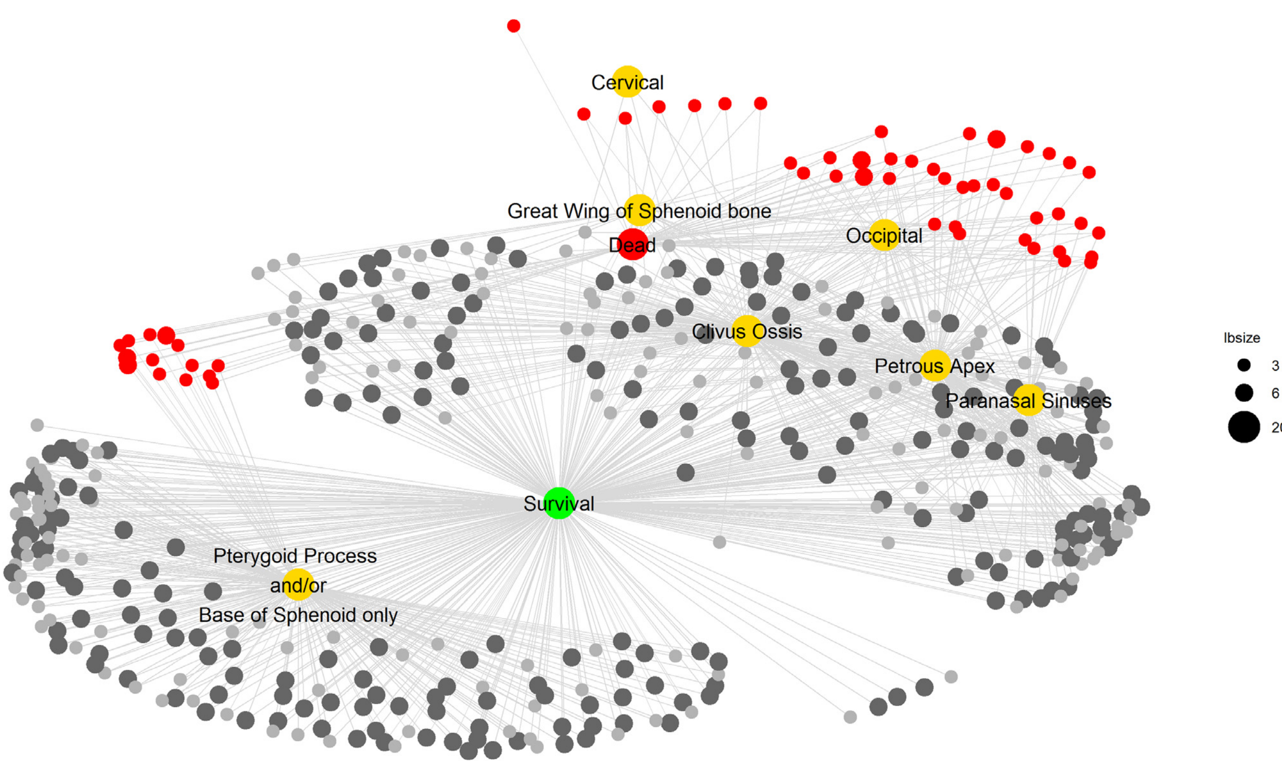

Fig. 2. Network analysis for T3-classified patients. The results revealed that the variables (representing different SBIs) and patients were all clearly divided into two groups: patients with T3 slight were more likely to experience "survival," while those patients with T3 severe were more likely to experience "death" (note: in the figure, the larger black dots and smaller gray dots represent patients who survived for more than 5 years and less than 5 years, respectively, while the red dots represent patients who died during follow-up). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Survival analysis of skull-base invasion (SBI) for T3 patients with NPC.

T3 structures	Num	Univariate Cox regression		Multivariate Cox regression*		Rank
		HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	
T1 as Reference	325	T1 as Reference		T1 as Reference		
only pterygoid process and/or base of sphenoid bone invasion	176	1.418 (0.711,2.829)	0.321	1.117 (0.557,2.241)	0.755	1
pterygoid process	312	2.310 (1.334,3.998)	0.003	1.929 (1.111,3.35)	0.020	5
base of sphenoid bone	348	2.397 (1.402,4.099)	0.001	1.871 (1.088,3.217)	0.024	4
clivus	201	3.202 (1.826,5.616)	0.000	2.611 (1.473,4.626)	0.001	6
petrous apex	175	3.354 (1.893,5.942)	0.000	2.701 (1.505,4.845)	0.001	7
great wing of sphenoid bone	29	4.013 (1.600,10.065)	0.003	2.798 (1.095,7.146)	0.032	8
condyles occipitalis	27	3.379 (1.254,9.102)	0.016	2.987 (1.096,8.139)	0.032	9
cervical spine	3	0.000 (0.000,Inf)	0.998	0.000 (0.000,Inf)	0.998	0
skull-base except paranasal sinus	393	2.027 (1.181,3.479)	0.010	1.605 (0.932,2.766)	0.088	2
paranasal sinus	49	5.135 (2.534,10.406)	0.000	3.767 (1.8,7.882)	0.000	10
T3	442	2.353 (1.398,3.960)	0.001	1.865 (1.104,3.152)	0.020	3
T2 as Reference	157	T2 as Reference		T2 as Reference		
only pterygoid process and/or base of sphenoid bone invasion	176	0.534 (0.273,1.044)	0.067	0.582 (0.294,1.153)	0.121	1
pterygoid process	312	0.856 (0.507,1.444)	0.560	0.943 (0.555,1.604)	0.829	5
base of sphenoid bone	348	0.901 (0.541,1.501)	0.690	0.926 (0.554,1.549)	0.770	4
clivus	201	1.195 (0.699,2.044)	0.514	1.217 (0.709,2.087)	0.476	6
petrous apex	175	1.242 (0.719,2.145)	0.437	1.273 (0.735,2.205)	0.389	7
great wing of sphenoid bone	28	1.516 (0.615,3.739)	0.366	1.409 (0.569,3.487)	0.459	9
condyles occipitalis	27	1.204 (0.456,3.182)	0.708	1.395 (0.523,3.722)	0.506	8
cervical spine	3	0.000 (0.000,Inf)	0.997	0.000 (0.000,Inf)	0.997	0
skull-base except paranasal sinus	393	0.750 (0.449,1.254)	0.272	0.784 (0.466,1.317)	0.357	2
paranasal sinus	49	1.946 (0.980,3.863)	0.057	1.875 (0.93,3.783)	0.079	10
T3	442	0.875 (0.534,1.433)	0.595	0.908 (0.552,1.493)	0.704	3

* According to the univariate analysis for overall survival in Table 1, the following variables were included as the confounding factors: age (<45 years, ≥45 years), sex and *N* classification.

demonstrated that those patients with T3 slight were clearly separate from patients with T3 severe, with better living rates. Heat map, cluster and network analyses are methods for statistical analysis that are widely used in the field of gene expression. In our study, we demonstrated the treatment outcomes and distribution trends of patients with different SBIs using these three tools. Additionally, both preliminary experiments shed substantial light on the existence of the subclassification of SBI.

However, objectively, the most convincing evidence that patients with different SBIs indeed have different treatment outcomes is survival analysis. Then, we performed the survival analysis; the results revealed that, on one hand, the 5-year OS and PFS rates for the T3-slight group were significantly different from those for the T3-severe group, while were not significantly different from those for the T1- and T2-classification groups. On the other hand, the results of univariate analysis showed that the HR for death of the T3-slight group was slightly higher than that of the T1-classification group and lower than that of the T2-classification group. However, there were no significant differences between the HRs for death between the T3-slight group and the T1- and T2-classification groups. For the multivariate analysis, after eliminating confounding factors, the HR for death of the T3-slight patients was always ranked as lowest, whether the T1 or T2 classification group was set as the reference.

Furthermore, when those T3-slight patients were divided into 2 groups according to the presence or absence of invasion of those anatomical structures belonged to the T2 classification, no significant difference was found between the groups with respect to the 5-year OS and PFS rates. Therefore, a subclassification of SBI is warranted. Allocating those patients with T3 slight into the T2 classification might be more suitable. Thus, we redistributed the T2- and T3-classified patients and consequently yielded new T2 and T3 classification samples. To our knowledge, this study is the first to classify T3 patients with SBI into two subgroups based on relatively rigorous and scientific steps, which included making assumptions through preliminary experiments and verifying them using univariate and multivariate analyses. Therefore, we believe our results could be well substantiated and applied to evidence-based practice.

For our dataset, according to the 8th AJCC staging system (before sample redistribution), the survival curves of the 5-year OS and PFS rates of T2-classification patients almost overlapped with those of T3 patients, suggesting that the treatment outcomes of T2 patients were not dramatically different from those of T3 patients. However, in terms of the new T classification (after sample redistribution), the separation trends of the survival curves of the 5-year OS and PFS rates between T2 and T3 classification were more obvious. In addition, the differences in the 5-year OS and PFS rates between T2 and T3 patients all approached statistical significance in the new T classification, which were obviously superior to the results obtained according to the 8th AJCC staging system (before sample redistribution). Thus, patients with T3 slight showed improved 5-year OS and PFS rates among T3-classification patients. Several causes might be responsible for this improved survival. On one hand, the pterygoid process and the base of the sphenoid bone are adjacent to the nasopharynx and are prone to be infiltrated by the primary lesion of the nasopharynx when the primary tumor volume is still small. According to the studies of Guo et al. [17] and Liang et al. [18], a small primary tumor volume of NPC represents a positive significant prognostic factor for local control. On the other hand, as the tumor is contiguous to the nasopharynx, the accurate delivery of an increased dose to the affected pterygoid process and base of the sphenoid bone can provide better local control in the era of IMRT [10]. In addition, a total of 393 cases in our T3-classification sample invaded skull-base sites except paranasal sinus, and some of them contained neural foramina. Liu et al [19]. suggested that tumor invasion of these anatomical sites was frequently associated with MRI-detected cranial nerve involvement. Other researchers have also proposed that perineural tumor spread in the head and neck could result in a higher incidence of distant metastases [20,21]. By contrast, tumor invasion of only the pterygoid process and/or the base of the sphenoid bone, which did not include the neural foramina, showed an obviously lower risk for distant metastases. The above

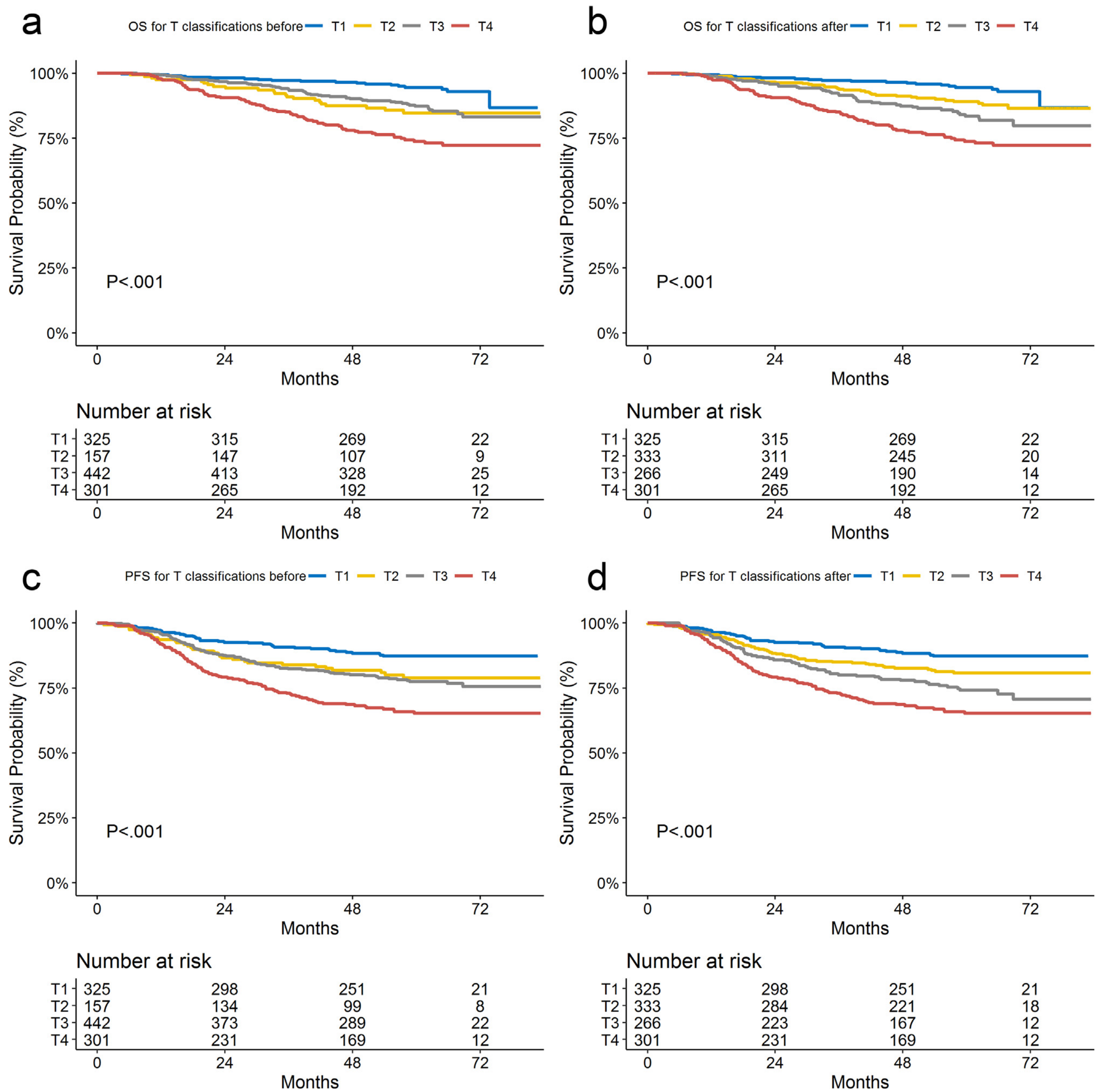

Fig. 3. Kaplan–Meier's curves of the 5-year overall survival and progression-free survival for NPC patients with T1–4 classifications before (a, c) and after (b, d) the sample redistribution of T2- and T3-classified samples. (a, c) According to the 8th AJCC staging system (before sample redistribution), the survival curve of T2 classification patients was almost completely overlapped with that of T3 patients. (b, d) In terms of the new T classification samples (after sample redistribution), the separation trends of the survival curves of the 5-year OS and PFS rates between T2 and T3 classification were more obvious. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

situations can explain the better OS and PFS of patients with only pterygoid process and/or base of the sphenoid bone invasion.

Subclassification of SBI has important clinical significance. Firstly, it can predict the prognosis in T3 patients with nasopharyngeal carcinoma receiving IMRT. Our results revealed that patients with T3 slight had better outcomes in terms of OS and PFS, when compared to patients with T3 severe. Secondly, according to the National Comprehensive Cancer Network (NCCN) in 2017, NPC patients with SBI should receive concurrent chemoradiotherapy plus induction chemotherapy. However, we found in this study that the hazard ratio for death of patients with T3 slight was not significantly different from that of patients with T1 classification. Therefore, whether patients with T3 slight should be treated with induction chemotherapy concurrently with chemoradiotherapy, merits further investigation, which, further emphasized the necessity of subclassification of conventional T3.

This study has two limitations. First, NPC is a unique disease that is almost never resected for treatment; thus, pathological confirmation of SBI is unrealistic. This situation is a common and difficult problem encountered in imaging studies of skull-base lesions. Additionally, the sample size was a bit small, possibly resulting in the nonsignificant conclusions regarding the differences in the 5-year OS and PFS rates between T2 and T3 patients according to the new T classification (after sample redistribution). Thus, we look forward to increasing our sample size and further improving the results.

In conclusion, different types of SBIs had different effects on the prognosis for the NPC patients. We recommend that patients with T3 slight not be defined as T3 but, rather, T2. We consider that the subclassification of SBIs would provide evidence for the adjustment of T classification of NPC in the future.

Funding

This work was supported by the Natural Science Foundation of Guangdong Province, China (No. 2016A030310464); the Medical Science and Technology Research Foundation of Guangdong Province (No. A2016328); the National Natural Science Foundation of China (No. 81572652); Health & Medical Collaborative Innovation Project of Guangzhou City, China (No. 201604020003); the Science and Technology Planning Project of Guangdong Province (No. 2017B020226004); the Health & Medical Collaborative Innovation Project of Guangzhou City (201803010021); and the Guangdong Medical Research Fund Project (No. A2016320).

Ethical considerations

Institutional Review Board approval was obtained.

Conflict of interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.021.

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