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Original Article

Clinical features and survival outcomes between ascending and descending types of nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: A big-data intelligence platform-based analysis

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ABSTRACT

Purpose: To compare clinical features and survival outcomes in patients with ascending type (type A) and descending type (type D) nasopharyngeal carcinoma (NPC) in the intensity-modulated radiotherapy (IMRT) era.

Materials and methods: A total of 5194 patients with type A and type D NPC treated at Sun Yat-sen University Cancer Center were randomly selected. Tumors that were mainly advanced local disease (T3-4 stage) with early stage cervical lymph node involvement (N0-1 stage) were determined as type A, while tumors with advanced lymph node disease (N2-3 stage) but early stage local invasion (T1-2 stage) were classified as type D NPC. Kaplan–Meier's analysis was used to evaluate survival rates, and log-rank test survival curves were used for comparison. In the multivariate analysis Cox proportional hazard models were developed.

Results: There was a larger proportion of type A tumors (82%) than type D tumors (18%). Compared to patients with type A tumors, those with type D tumors had increased likelihood of distant metastasis, regional recurrence, disease recurrence, and death ($P < 0.001$ for all), however, not for local recurrence ($P < 0.001$). The HR (hazard ratio) for death following recurrence of disease for type D tumors were 1.6 compared to type A tumors. Multivariate analysis revealed that elevated EBV DNA, elevated lactate dehydrogenase, alcohol consumption, and no family history of cancer attributed to the development of type D tumors. Annual hazard rate in type A patients increased, peaking at 12–18 months after initial treatment and downward thereafter. Similar trend also occurred in type D during the first 5 years following treatment. Notably, a minor peak was also observed 7–8 years post treatment.

Conclusions: In the IMRT era, recurrence patterns differed across tumor types. Type D NPC had a more aggressive clinical course and worse outcomes compared with type A NPC.

Abbreviations: NPC, nasopharyngeal carcinoma; RT, Radiotherapy; type A, ascending type; type D, descending type; SYSUCC, Sun Yat-Sen University Cancer Centre; CT, computed tomography; LDH, lactate dehydrogenase, AJCC, American joint committee on cancer; IMRT, intensity-modulated radiotherapy; MRI, magnetic resonance imaging; ECT, whole body bone scan; PET, positron emission tomography; OS, overall survival; RRFS, regional relapse-free survival; LRFS, local relapse-free survival; DMFS, distant metastasis-free survival; DFS, disease-free survival; AC, adjuvant chemotherapy; IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; NCCN, National Comprehensive Cancer Network; CI, confidence interval; ART, adaptive radiotherapy; HBO, hyperbaric oxygen.

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Nasopharyngeal carcinoma (NPC) disproportionately burdens southeast Asia, where the highest incidence is in Southern China [1]. Annually, there are 87,000 new NPC diagnosis, and approximately 70% of patients are classified as locoregionally advanced disease [2]. Radiotherapy (RT) is the primary treatment modality for locoregionally advanced NPC [3], which can be categorized by characteristics of natural disease progression as follows: 1) predominantly advanced local disease with early stage cervical lymph node involvement as ascending type (type A, T3-4N0-1); 2) advanced lymph node disease but early stage local invasion as descending type (type D, T1-2N2-3); and 3) predominantly advanced local disease along with advanced lymph node disease (type AD, T3-4N2-3) [4,5].

The clinical biologic behaviors can vary significantly among the three subtypes of locoregionally advanced NPC, although type A and type D NPC were both classified as locoregionally advanced disease and had the same pathologic type. For instance, Xie et al. [4] found that patients with type A disease generally suffered local failure compared to those with type D disease, where distant failure often occurs. The available data in the above study provided us with detailed information on the clinical biologic behavior of type A and type D NPC. However, the risk factors associated with these two subtypes remain unclear. Moreover, current advances in radiation technology and imaging techniques, as well as the introduction of chemotherapy potentially provides great value to reinvestigate clinical features and survival outcomes in patients with different NPC subtypes.

Based on the above premise, we directly compared the clinical features, patterns of recurrence, and survival outcomes between patients with type A and type D NPC undergoing modern RT treatment. We also performed univariate analysis followed by multivariable logistic regression models to recognize factors associated with the development of NPC subtypes. As Epstein–Barr virus (EBV) serology plays a significant role in NPC development [6,7], we also investigated whether the clinical typing system correlated with EBV DNA.

Materials and methods

Study patients

The cohort included NPC patients diagnosed from April 2009 to December 2015 at Sun Yat-Sen University Cancer Centre (SYSUCC). A novel 'big data' research system was utilized allowing for organizing, integrating, restructuring, and updating data in real-time from numerous clinical business systems based on well-designed models and algorithms. Details on the intelligence platform at SYSUCC was previously published [8]. All medical records and pathology reports were reviewed. Patient information was obtained at the accrual and included details on age at diagnosis (years), histology, gender, disease stage, plasma EBV DNA, lactate dehydrogenase (LDH) treatment (chemotherapy and radiation treatment), and other characteristics. We identified eligible patients using the following inclusion criteria: pathologically diagnosed undifferentiated non-keratinizing carcinoma of the nasopharynx (World Health Organization [WHO] Type III); stages T3-4N0-1 or T1-2N2-3; no evidence of distant metastasis; and receiving radical intensity-modulated RT at initial diagnosis.

Diagnosis and treatment

Patients underwent complete pretreatment evaluations comprising of physical examination, hematology and biochemistry profiling, fiberoptic nasopharyngoscopy, magnetic resonance imaging (MRI) scanning of the suprasellar cistern to the collarbone, and computed tomography (CT). Additionally, patients also received abdominal ultrasonography, whole body bone scan (ECT), or ^{18}F-Fluorodeoxyglucose positron emission tomography and computed tomography (PET-CT). Real-time quantitative polymerase chain reaction (PCR) was used to measure plasma EBV DNA as previously described [9–11]. All patients were restaged based on the 8th edition of the American joint committee on cancer (AJCC) staging system [12] and treated in accordance with principles of treatment for NPC patients at SYSUCC. More detailed information on treatment is available in Supplementary Materials (available online).

The definition of NPC subtypes

In the present study, ascending-type (type A) NPC was defined as patients with mainly advanced local disease (stage T3-4) but early stage cervical lymph node invasion (stage N0-1). Descending-type (type D) NPC was defined as advanced lymph node disease (stage N2-3) but early stage local involvement (stage T1-2).

Data sharing

Key raw data were uploaded onto the Research Data Deposit public platform (RDD), with the approval number of RDDA2019001019.

Follow-up and outcome

Following treatment, we evaluated patients once every three months in the first 3 years, once every 6 months for the next two years, and once afterward. During visits, clinical examinations, nasopharyngoscopy, and EBV DNA were routinely performed. Patients with clinical suspicion of recurrence or metastasis were recommended for MRI, CT, ECT, or even PET-CT, followed by confirmatory cytological biopsies if possible. The median time of follow-up was 51.6 months (ranging 2.2–103.9 months) in the type A group, which did not differ significantly ($P = 0.437$) in comparison with type D patients of 51.9 months (range 4.8–102.1 months). The primary endpoint was overall survival (OS), and secondary endpoints were regional relapse-free survival (RRFS), local relapse-free survival (LRFS), distant metastasis-free survival (DMFS), and disease-free survival (DFS). OS was calculated from the date of initial treatment to date of death from any cause; RRFS was calculated from the date of first regional relapse; LRFS to date of first regional relapse; DMFS was calculated from the date of first distant relapse; DFS was calculated from the first relapse at any site, death from any cause, or date of last follow-up visit, whichever first occurred.

Statistical analysis

Categorical variables were classified according to clinical findings, and continuous variables were transformed into categorical variables based on routine cutoff points in clinical application [13–15]. Clinicopathologic characteristics were compared between type A and type D tumors using χ^2 test or Fisher's Exact Test for frequencies. Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression to estimate risk of death for causes in both type A and type D tumors, while adjusting for known prognostic variables (e.g. age, gender, histology, cigarette smoking status, alcohol consumption, family history of cancer, T stage, N stage, EBV DNA, LDH, hemoglobin [HGB], and treatment strategy).

Survival curves were depicted using the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazards regression models were used to test the independent significance

of different factors. Additionally, forest plots were generated using Microsoft Excel (Microsoft Inc., Redmond, WA, USA) utilizing the Neyeloff method [16] to summarize the adjusted HRs and 95% CIs of the predictors for the development of NPC subtypes. All statistical analyses and figures were generated using SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA) or the rms package in R version 3.3.2 (http://www.r-project.org/), unless otherwise specified. All tests were two-tailed and P values < 0.05 were considered statistically significant.

Results

Comparison of clinical features between type A and type D tumors

Table 1 presents patient characteristics stratified by type A and type D tumor groups. The rate of male patients were significantly higher in the type D group compared with type A group (76.4% vs 72.7%, respectively; $P = 0.021$). In the type D group, patients were more likely to smoke cigarettes (38.3% vs. 34.8%, $P = 0.047$), consume alcohol (18.2% vs. 12.7%, $P < 0.001$), have an elevated EBV DNA ($P < 0.001$), increased LDH levels ($P < 0.001$), and stage IVA disease (39.9% vs. 31.1%, $P < 0.001$) compared with type A group. Less than 1% of type D tumors had cranial nerve syndrome (CNS), whereas almost one-tenth of the type A tumors had CNS (0.8% vs. 8.3%, respectively; $P < 0.001$). With respect to treatment strategy, patients with type D NPC were more likely to receive induction chemotherapy (IC) plus concurrent chemoradiotherapy (CCRT). There were no observed statistical associated differences regarding age ($P = 0.149$), hemoglobin (HGB, $P = 0.803$), and high-sensitivity C-reactive protein (hs-CRP, $P = 0.240$) between type A and type D NPC.

Patterns of recurrence in type A and type D NPC patients

Among patients with type A tumors, the 5-year OS rate (88.5%) was significantly higher compared to the rate in type D tumor patients (85.1%; $P < 0.001$; Fig. 1A). Compared with type A group, type D tumors had an elevated probability of regional recurrence within five years following diagnosis (HR, 2.60, 95% CI, 1.91–3.54; $P < 0.001$; Fig. 1B). In contrast, decreased proportion of patients with type D tumor experienced local recurrence compared with patients with type A cancer (5-year LRFS, 93.1% vs 96.7%, respectively; $P < 0.001$; Fig. 1C). Type D tumors were significantly associated with worse DMFS in comparison to type A tumors (5-year DMFS, 85.4% vs 90.5%, respectively; $P < 0.001$; Fig. 1D). Furthermore, patients with type D NPC were more likely to suffer disease recurrence than patients with type A NPC (5-year DFS, 78.2% vs 82.3%, respectively; $P < 0.001$; Fig. 1E). Overall, as compared with patients of type D tumor, those with type A had significantly better OS, RRFS, DMFS, and DFS ($P < 0.001$ for all), though was not observed for LRFS (HR, 0.41; 95% CI, 0.26–0.63; $P < 0.001$).

Prognostic factors for patients with type A and type D NPC

The 3- and 5-year OS, RRFS, LRFS, DMFS, and DFS rates for type A NPC were 93.7% and 88.5%, 97.7% and 96.6%, 95.1% and 93.1%, 92.3% and 90.5%, and 86.4% and 82.3%, respectively. Univariate analysis for the prognostic factors for type A NPC is listed in Table S1. In the multivariable analyses, we continued to observe that gender, age, T stage, EBV DNA, and LDH were independent risk factors for OS; gender, EBV DNA, hs-CRP, and LDH were significantly associated with RRFS; T stage and family history of cancer were independent risk factors for LRFS; gender, T stage, N stage, EBV DNA, and LDH were independent risk factors for DMFS. Moreover, gender, age, T stage, EBV DNA, and LDH were associated with DFS ($P < 0.05$ for all; Table 2).

Table 1
Characteristics of patients with type A versus type D NPC.

Characteristic	Type A (n = 4252) No. (%)	Type D (n = 942) No. (%)	P value
Gender			0.021
Male	3091 (72.7)	720 (76.4)	
Female	1161 (27.3)	222 (23.6)	
Age, year			0.149
≤29	334 (7.9)	68 (7.2)	
30–39	907 (21.3)	226 (24)	
40–49	1486 (34.9)	332 (35.2)	
50–59	997 (23.4)	222 (23.6)	
≥60	528 (12.4)	94 (10.0)	
Overall stage (8th edition)			<0.001
III	2928 (68.9)	566 (60.1)	
IVA	1324 (31.1)	376 (39.9)	
Cigarette consumption			0.047
No	2771 (65.2)	581 (61.7)	
Yes	1481 (34.8)	361 (38.3)	
Alcohol consumption			<0.001
No	3711 (87.3)	771 (81.8)	
Yes	541 (12.7)	171 (18.2)	
Family of cancer history			0.014
No	3118 (73.3)	728 (77.3)	
Yes	1134 (26.7)	214 (22.7)	
Cranial nerve symptoms			<0.001
No	3897 (91.7)	934 (99.2)	
Yes	355 (8.3)	8 (0.8)	
Clinical stage			<0.001
III	2928 (68.9)	566 (60.1)	
IVA	1324 (31.1)	376 (39.9)	
EBV DNA, copy/mL			<0.001
$<10^3$	1829 (43.0)	289 (30.7)	
10^3-10^4	1037 (24.4)	225 (23.9)	
10^4-10^5	826 (19.4)	241 (25.6)	
$\geq10^5$	250 (5.9)	128 (13.6)	
Unknown	310 (7.3)	59 (6.3)	
HGB, g/L			0.803
<113	143 (3.4)	30 (3.2)	
113–151	2715 (63.9)	608 (64.5)	
≥151	1215 (28.6)	284 (30.1)	
Unknown	179 (4.2)	20 (2.1)	
hs-CRP, g/mL			0.240
<1.0	1277 (30.0)	310 (32.9)	
1.0–3.0	1589 (37.4)	351 (37.3)	
≥3.0	1301 (30.6)	271 (28.8)	
Unknown	85 (2.0)	10 (1.1)	
LDH, U/L			<0.001
<245	3920 (92.2)	840 (89.2)	
≥245	257 (6.0)	92 (9.8)	
Unknown	75 (1.8)	10 (1.1)	
Treatment modality			<0.001
RT alone	221 (5.2)	25 (2.7)	
CCRT alone	1712 (40.3)	322 (34.2)	
IC plus CCRT	1799 (42.3)	474 (50.3)	
CCRT plus AC	109 (2.6)	17 (1.8)	
IC plus RT	411 (9.7)	104 (11.0)	

Abbreviation: NPC, nasopharyngeal carcinoma; WHO, EBV, Epstein–Barr virus; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase. RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; AC, adjuvant chemotherapy.

The 3- and 5-year OS, RRFS, LRFS, DMFS, and DFS rates for type D NPC were 90.4% and 85.1%, 94.2% and 92.2%, 98.1% and 96.7%, 87.7% and 85.4%, and 82.2% and 78.2%, respectively. Univariate analysis of prognostic factors for type D NPC is shown in Table S2. To adjust for various prognostic factors, multivariate analysis was conducted. Consistent with univariate analysis, N stage, EBV DNA, and LDH were independent risk factors for OS; only EBV DNA was associated with RRFS; T stage and treatment strategy were independent risk factors for LRFS; gender, N stage, EBV DNA, HGB, hs-CRP, and LDH had a significantly strong correlation with DMFS; and gender, N stage, EBV DNA and LDH were associated with DFS ($P < 0.05$ for all; Table 3).

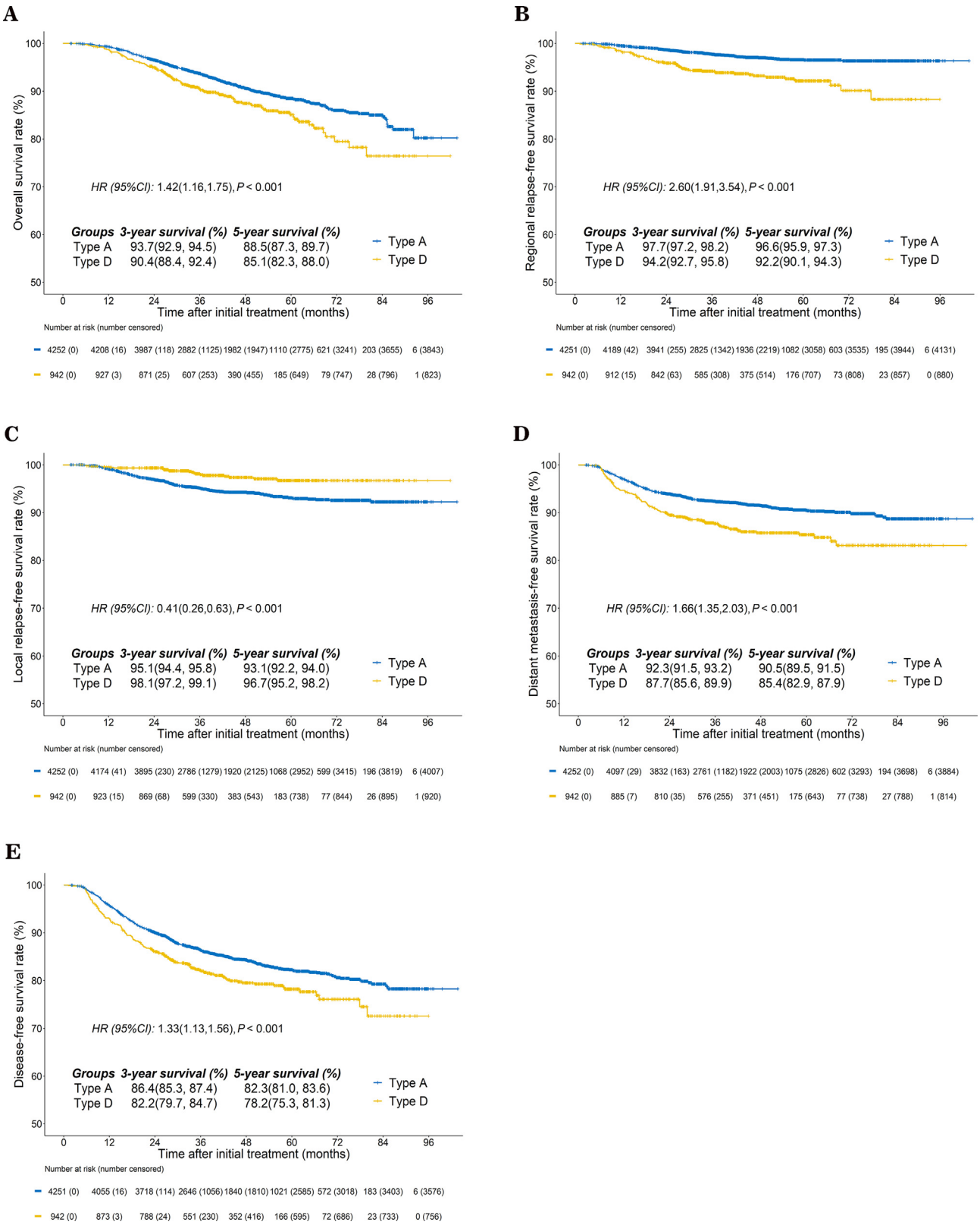

Fig. 1. Kaplan–Meier's survival curves are shown for (A) overall survival, (B) regional relapse-free survival, (C) local relapse-free survival, (D) distant metastasis-free survival, and (E) disease-free survival in patients with type A versus type D NPC.

Time of recurrence between type A and type D tumors

Generally, recurrence rates are presented with cumulative incidence curves. However, the annual hazard rate at six-month intervals were more precise in assessing the timing of tumor recurrence (Fig. 2). The recurrence pattern differed across tumor types. Among the type A patients, the annual hazard rate increased notably and

Table 2
Multivariate analysis of prognostic factors for patients with type A NPC (n = 4252).

Endpoint	Variable	P[a]	HR	95% CI for HR
OS				
	Gender	0.007	1.48	1.11–1.97
	Age	<0.001	1.67	1.35–2.07
	T stage	<0.001	2.37	1.92–2.92
	EBV DNA	<0.001	1.47	1.19–1.81
	hs-CRP	0.090	1.20	0.97–1.48
	LDH	0.001	1.75	1.27–2.42
	Cigarette consumption	0.848	1.02	0.81–1.28
	Family of cancer history	0.095	0.81	0.64–1.04
RRFS				
	Gender	0.049	1.64	1.00–2.67
	EBV DNA	0.012	1.67	1.12–2.48
	hs-CRP	0.001	0.44	0.27–0.73
	LDH	0.010	2.16	1.20–3.89
LRFS				
	T stage	<0.001	2.21	1.71–2.86
	LDH	0.082	1.49	0.95–2.33
	Family of cancer history	0.041	0.72	0.52–0.99
DMFS				
	Gender	0.044	1.34	1.01–1.78
	T stage	<0.001	1.79	1.44–2.23
	N stage	0.011	1.60	1.11–2.29
	EBV DNA	<0.001	1.82	1.45–2.28
	hs-CRP	0.502	1.08	0.86–1.35
	LDH	0.001	1.74	1.25–2.44
	Cigarette consumption	0.950	0.99	0.78–1.26
DFS				
	Gender	0.043	1.24	1.01–1.53
	Age	0.013	1.23	1.04–1.44
	T stage	<0.001	1.85	1.57–2.17
	N stage	0.064	1.25	0.99–1.58
	EBV DNA	<0.001	1.43	1.21–1.68
	hs-CRP	0.643	1.04	0.88–1.23
	LDH	0.001	1.60	1.23–2.09
	Cigarette consumption	0.538	1.06	0.88–1.27
	Family of cancer history	0.066	0.84	0.70–1.01

Abbreviation: NPC, nasopharyngeal carcinoma; HR, hazard ratio; CI, confidence interval; EBV, Epstein–Barr virus; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; OS, overall survival; LRFS, local relapse-free survival; RRFS, regional relapse-free survival; DMFS, distant metastasis-free survival; DFS, disease failure-free survival.

[a] P values were calculated using an adjusted Cox proportional hazards model.

peaked 12–18 months after initial treatment, followed by a long-term continuously decreasing trend. Similar patterns were observed among type D patients within the first five years after initial treatment. However, another hazard rate minor peak was observed 7–8 years post treatment. Additionally, time from disease recurrence to death also interests us. Median survival time from recurrence of disease to death was 29.9 months (IQR, 19.5–42.6; 95% CI, 29.3–30.5). Compared to patients with type A, the interval was shorter for patients with type D tumor (27.3 months; IQR, 17.1–40.5; 95% CI, 25.5–28.7; $P = 0.025$ for difference).

Factors associated with the development of type A and type D NPC

In the univariate analysis, male patients ($P = 0.018$), cigarette smokers ($P = 0.044$), alcohol consumption ($P < 0.001$), no family history of cancer ($P = 0.011$), elevated EBV DNA levels ($P < 0.001$), and increased serum LDH ($P < 0.001$) were independently statistically associated with greater risk of type D tumors (Table S3). Type D group comprised of 56% tumors with EBV DNA $\geq$ 4000 copies/mL compared to 40% for type A tumors with EBV DNA $\geq$ 4000 copies/mL ($P < 0.001$). When the above prognostic factors were added to the logistic regression models, elevated EBV DNA (HR, 1.79; 95% CI, 1.54–2.08; $P < 0.001$), elevated LDH (HR, 1.51; 95% CI, 1.15–1.95; $P = 0.002$), and alcohol consumption (HR, 1.47; 95% CI, 1.18–1.83; $P = 0.001$) remained statistically associated with development of type D tumors. While family history of cancer had a significantly strong correlation with the development of type A tumors (HR, 0.81; 95% CI, 0.68–0.97; $P = 0.020$; Fig. 3).

Discussion

This is the largest study comparing clinical features, patterns of recurrence, and survival outcomes between type A and type D NPC patients treated with radical IMRT and chemotherapy. Our findings indicate that patients with type D NPC had more aggressive clinical course and worse outcomes compared with type A NPC. The HR for death following recurrence of disease among type D tumors was 1.6 compared to type A tumors. Multivariate analysis revealed that alcohol consumption, absence of family history of cancer, elevated EBV DNA, and elevated LDH were attributed to the development of type D tumors.

Our study included more than 4000 patients with type A NPC and approximately 1000 type D NPC patients. For this reason, we can more accurately evaluate the different distribution in clinical features between type A and type D NPC. Our results showed that type A NPC was more common than type D NPC, which is in line with previous publications [5]. Currently, it is widely accepted that plasma EBV DNA load can potentially reflect tumor burden [7,17]. In the present study, type D NPC patients had a greater plasma EBV DNA load compared to type A disease, which suggest that type D NPC had a higher tumor load in comparison with type A disease. Further analyses revealed that raised EBV DNA, elevated LDH,

Table 3
Multivariate analysis of prognostic factors for patients with type D NPC (n = 942).

Endpoint	Variable	P[a]	HR	95% CI for HR
OS				
	N stage	0.001	2.00	1.34–2.99
	EBV DNA	<0.001	2.38	1.51–3.77
	HGB	0.138	0.56	0.26–1.21
	hs-CRP	0.172	1.31	0.89–1.94
	LDH	0.038	1.66	1.03–2.69
RRFS				
	N stage	0.138	1.49	0.88–2.52
	EBV DNA	0.043	1.80	1.02–3.18
LRFS				
	T stage	0.008	7.17	1.67–30.82
	Treatment strategy	0.032	0.06	0.06–0.88
DMFS				
	Gender	0.015	1.90	1.13–3.19
	N stage	0.026	1.54	1.05–2.26
	EBV DNA	<0.001	2.45	1.58–3.78
	HGB	0.034	0.41	0.18–0.94
	hs-CRP	0.043	1.47	1.01–2.13
	LDH	0.004	1.93	1.23–3.04
DFS				
	Gender	0.026	1.57	1.06–2.32
	T stage	0.159	1.25	0.92–1.71
	N stage	0.003	1.61	1.18–2.21
	EBV DNA	<0.001	1.94	1.39–2.73
	hs-CRP	0.153	1.26	0.92–1.72
	LDH	0.021	1.60	1.07–2.40

Abbreviation: NPC, nasopharyngeal carcinoma; HR, hazard ratio; CI, confidence interval; EBV, Epstein–Barr virus; HGB, hemoglobin; hs-CRP, high sensitivity C-reactive protein; LDH, lactate dehydrogenase; OS, overall survival; LRFS, local relapse-free survival; RRFS, regional relapse-free survival; DMFS, distant metastasis-free survival; DFS, disease failure-free survival.

[a] P values were calculated using an adjusted Cox proportional hazards model.

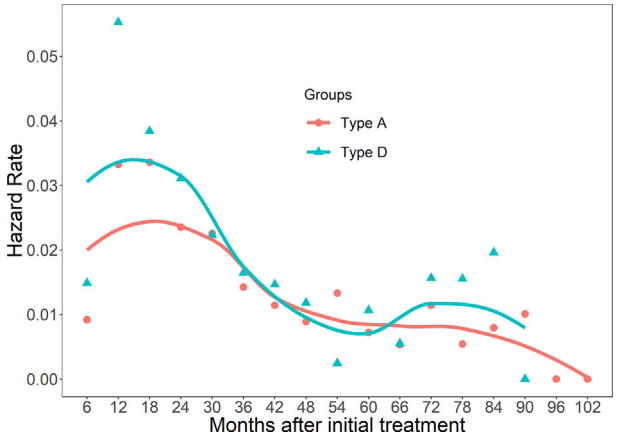

Fig. 2. Rates of disease recurrence in type A and type D NPC.

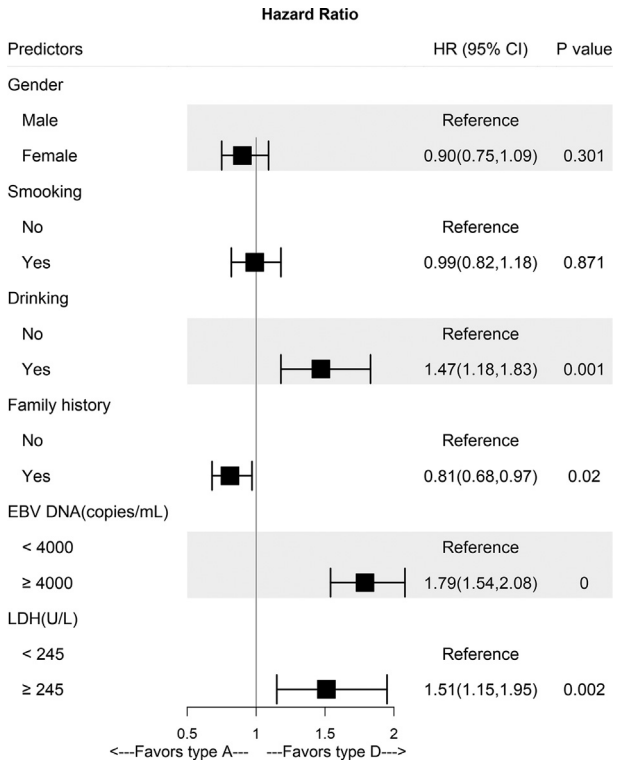

Fig. 3. Forest plots depicting the adjusted HRs and 95% CIs for the factors associated with the development of NPC subtypes.

alcohol consumption, and no family history of cancer was attributed to the development of type D NPC. Though we were unable to identify a specific mechanism, our findings support the importance of evaluating these clinical risk factors in patients with NPC by tumor subtype.

Our results indicated that type D NPC patients were more likely to suffer distant metastases, regional recurrence, and death in comparison to type A NPC, which is in line with previous publications [18,19]. However, whether the above-mentioned recurrence patterns have an impact on survival cannot be answered by our study. Our inability to determine whether recurrence patterns have an impact on survival is due to potential bias in retrospective chart analysis, and differences in administered chemotherapeutic regimen might distort analysis. Nevertheless, we must mention that the risk of disease recurrence was higher relative to type D tumors, particularly in the first two years after treatment. We also found that the median time to death was 47 months in type A and 25 months in type D NPC patients following disease recurrence. These findings suggest that type D NPC had a more aggressive tumor biology and improving the intensity of surveillance modalities for type D NPC in the first two years after treatment might be necessary.

Local recurrence is a key factor inhibiting the improvement of the curative effect for type A NPC. Once local recurrence occurred, the 5-year survival rate was only 37%–41%, and the incidence of radiation damage, such as nasopharynx necrosis, and hemorrhage was as high as 51%, which seriously affected patients' quality of life [20,21]. Therefore, the improvement of local control for patients with type A disease is an important way to improve survival. Retrospective analyses has indicated that adaptive radiotherapy (ART) can provide an improved local control, particularly for locally advanced NPC. However, relative randomized clinical trial is still needed in the future. Conversely, hypoxia has long been known to play a crucial role in radiotherapy resistance [22]. Therapeutic attempts to restore tumor oxygenation before or during radiotherapy have included red blood cell transfusion, erythropoietin administration, and hyperbaric oxygen (HBO) treatment [23]. Despite HBO treatment having a therapeutic benefit in patients with head and neck cancer [22], inconsistent clinical trial data for other cancer types and huge logistical hurdles have impeded widespread uptake of this approach. Overall, hypoxia is the main cause of local recurrence for NPC after RT, and improving hypoxia of tumor cells is an important method to improve local control, however, further research is needed.

Distant metastasis is the main cause of treatment failure in patients with type D NPC. Studies [24,25] have confirmed that patients with high pretreatment (Pre-H) EBV DNA are significantly associated with higher risk of distant metastasis. Some studies even indicated that patients with Pre-H EBV DNA may have micro-metastases at other sites before treatment [26]. As the main advantage of IC is to eradicate subclinical micro-metastasis, IC of sufficient intensity, such as 4 cycles might be a reasonable approach to reduce distant metastasis of type D NPC, particularly for those with Pre-H EBV DNA. However, this hypothesis should be further explored through prospective clinical trials. Also, detectable post-RT plasma EBV DNA is a high-risk factor for NPC distant metastasis [27,28], and adjuvant chemotherapy (AC) may be helpful for patients with detectable post-RT plasma EBV DNA [29]. However, toxicity and tolerance should be considered when AC is indicated [30]. In addition, both the optimal testing point in time for post-RT plasma EBV DNA levels for risk classification [31] and AC regimens require further research [26].

During the study period, CCRT ± IC/AC is recommended by the National Comprehensive Cancer Network (NCCN) for locoregionally advanced NPC. Although both type A and type D NPC belongs to locoregionally advanced NPC, the majority of these two types display with distinct survival patterns [4–5,18]. Therefore, it may be inferred that optimizing the treatment of NPC requires further reference to the biological characteristics of the tumors. Due to the study design, we were unable to analyze treatment preferences for patients or their physicians' recommendations. However, our results indicated that type A NPC patients received significantly less IC than type D patients, and physicians tended to select the treatment regimen of combined IC with CCRT for type D disease. Given the main advantage of IC is to eradicate distant micrometastases and improve distant control, the choice of IC plus CCRT for treatment of type D NPC is not surprising [32]. To support our previous findings, we compared the outcomes of CCRT, IC plus RT, or IC plus CCRT in the treatment of type D NPC, and confirmed that IC plus CCRT is potentially a more appropriate strategy for type D NPC [19].

The present study confirmed that type D tumors are more likely to be associated with elevated levels of EBV DNA and LDH than type A tumors. Prior studies have confirmed that elevated levels of EBV DNA are strongly associated with impaired survival for NPC [6–7,24–25]. In line with previous studies, our results found that type D NPC had higher levels of EBV DNA load, and its prognosis was significantly worse than that of type A NPC. Apart from EBV DNA, elevated LDH levels also demonstrated negative prognostic indicators in patients with NPC [13]. However, it remains unknown the mechanism underlying this phenomenon. Prior publications [33] suggested that serum LDH levels typically indicate presence of a hypoxic environment associated with large tumor burden, and tumor hypoxic status has shown to be an important determinant of clinical outcomes in patients that receive chemotherapy and radiotherapy [34]. Other studies [35] suggested LDH levels are potentially related to host factors. For instance, cellular turnover, cachexia, and inflammation because of progressive tumor growth.

There are some limitations that must be noted. A major concern in the present study was the retrospective analysis from a single center among a southeastern Asian population and no external validation was performed. Therefore, our findings may not be generalizable to other Asian groups. External validation was not performed mainly due to a lack of data availability from other centers. Secondly, we did not design this study to assess which treatment strategy is most suitable for treatment of both type A and type D NPC but to evaluate survival outcomes and identify risk factors associated with NPC subtype development. However, the use of a large database provides greater understanding on the clinical biologic behavior of NPC subtypes. Finally, since the intelligence platform of our center failed to collect the date for acute and late toxicities, treatment-related toxicities were lacking in information.

In conclusion, recurrence patterns are significantly different between type A and type D tumors. Type D NPC is a more aggressive disease subtype and had worse outcomes compared with type A NPC. HR for death following disease recurrence in patients with type D NPC were 1.6 compared with type A NPC. However, further clinical trials are needed to improve patient outcomes based on these recurrence patterns of NPC subtypes. Additionally, alcohol consumption, no family history of cancer, elevated EBV DNA, and elevated LDH were attributed to the development of type D tumors. This study would provide greater knowledge on the clinical–biological behavior of NPC subtypes and contributes to basic research in NPC.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.025.

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