Benefit of ^{18}F-FDG PET/CT in Treatment Naïve Nasopharyngeal Carcinoma

Shan-Shan Yang
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Yi-Shan Wu
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Wei-Chao Chen
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Jun Zhang
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Su-Ming Xiao
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Bao-Yu Zhang
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Zhi-Qiao Liu
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
En-Ni Chen
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Xu Zhang
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Pu-Yun OuYang
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center
Fang-Yun Xie (xiefy@sysucc.org.cn)
Sun Yat-Sen University Cancer Prevention and Treatment Center: Sun Yat-sen University Cancer Center https://orcid.org/0000-0003-4800-6025

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Abstract

Background

We aimed to testify the advantage of positron emission tomography and computed tomography(PET/CT) in diagnosing cervical lymph nodes and staging nasopharyngeal carcinoma, and investigate whether PET/CT could bring about benefit in survival and serve for individualized treatment.

Methods

A total of 2759 patients were enrolled in this study. 460 biopsied cervical lymph nodes were named cohort A. Cohort B consisted of 1093 T3N1M0 patients who received both PET/CT and magnetic resonance imaging(MRI), while Cohort C contained 1377 T3N1M0 patients who underwent MRI alone. Cohort D enrolled 838 patients receiving concurrent chemoradiotherapy(CCRT) with or without induction chemotherapy(IC) to develop radiologic score model to guide IC.

Results

In cohort A, the sensitivity, accuracy, and area under the curve of PET/CT were much higher than those of MRI (96.7%versus88.5%, $p < 0.001$; 88.0%versus81.1%,$p < 0.001$; 0.863versus0.796,$p < 0.05$) in diagnosing metastatic lymph nodes. In cohort B, MRI staged T3N0-3M0 patients showed non-different survival rates, as they were the same T3N1M0 if staged by PET/CT. Besides, patients staged by PET/CT + MRI showed higher survival rates than those staged by MRI alone($p < 0.05$), regardless of the Epstein–Barr virus DNA load. Interestingly, SUVmax-N, nodal necrosis and extranodal extension were highly predictive of survival. Radiologic score model based on these factors performed well(C-index = 0.72) in risk stratification. The identified high-risk patients undergoing IC + CCRT had higher 5-year failure-free survival than those receiving CCRT alone($p = 0.0064$).

Conclusion

PET/CT showed advantage in staging by accurate diagnosis of lymph nodes and contributed to survival benefit. PET/CT carried prognostic factor could identify high-risk patients and guide individualized treatment.

Introduction

Nasopharyngeal carcinoma is a specific head and neck cancer with unique geographical and ethnic distribution. Approximately 133354 new cases occurred in 2020 with the highest incidence in Southern China [1]. Radiotherapy is the main treatment modality for early-stage nasopharyngeal carcinoma, while concurrent chemoradiotherapy with or without induction chemotherapy is recommended for locoregionally advanced nasopharyngeal carcinoma.

The conventional work-up including head and neck magnetic resonance imaging (MRI), chest X-ray or computed tomography, abdominal sonography or computed tomography, and bone scan are recommended for tumor, node and metastasis (TNM) staging. As for patients with bilateral enlarged lymph nodes or palpable lymph nodes below the cricoid cartilage, ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography and computed tomography (PET/CT) is highly recommended, because of the high risk of occult distant metastasis [2, 3]. In terms of N0-1 patients with Epstein–Barr virus (EBV)-DNA lower than 4000 copies/mL, however, prior study [3] insisted the low risk of distant metastasis and the comparable value of conventional work-up to PET/CT at initial staging, and finally did not recommend PET/CT considering the economic effectiveness. Also, a recent study confirmed that there was no survival benefit of adding PET/CT to conventional work-up for stage I-II nasopharyngeal carcinoma [4]. We suppose that precise detection of metastatic cervical lymph nodes and correct N-stage perhaps more affect the prognosis of these patients, instead of focusing on the value of detecting occult distant metastasis. Staged T3 nasopharyngeal carcinoma without distant metastasis is the most typical representation. For example, patients with T3N0M0 can achieve comparable overall survival by intensity modulated radiotherapy alone to patients with stage II disease [5], whereas the risk of distant metastasis is as high as 18% at 3 years after radical chemoradiotherapy for T3N2-3M0 nasopharyngeal carcinoma, and induction chemotherapy followed by concurrent chemoradiotherapy is strongly recommended for these patients [6–8]. Therefore, we attempted to find if PET/CT can influence the prognosis of nasopharyngeal carcinoma by accurate diagnosis of metastatic lymph nodes.

Currently, the optimal treatment mode for the subgroup of T3N1M0 remains the most controversial [9, 10]. T3N1M0 patients belongs to locoregionally advanced disease, but clinical trials that justified the benefit of induction chemotherapy [8] did not include this sort of patients. A retrospective study found no survival benefit of the additional induction chemotherapy for these patients [9], whereas male patients staged with T3N1M0 and EBV DNA higher than 2000 copies/mL were the target population as suggested by another study [10]. Albeit EBV DNA showed prognostic value, it made little sense for the present in clinical practice due to the lack of unified test standard, robust serum level and accepted cutoff value. Considering the generality of PET/CT and MRI in different hospitals, we thus tried to find the way to serve for individualized treatment by developing a radiologic score in a cohort of T3N1M0 nasopharyngeal carcinoma.

Methods

Patients and study design

A total of 2759 patients who were pathologically diagnosed with nasopharyngeal carcinoma were obtained from May 2009 to May 2020 at Sun Yat-Sen University Cancer Center. 336 patients who underwent node fine-needle aspiration biopsy guided by ultrasonography or lymph node dissection, and examination of PET/CT and MRI before treatment constituted the Cohort A, to testify the accuracy of PET/CT in diagnosing metastatic lymph nodes. Cohort B consisted of 1093 T3N1M0 nasopharyngeal carcinoma patients who received both PET/CT and head and neck MRI, while Cohort C contained 1377 T3N1M0 patients who underwent MRI alone. Cohort B and Cohort C were compared to find the survival benefit of adding PET/CT to MRI. Specially, 838 patients in the cohort of B who received concurrent chemoradiotherapy with or without induction chemotherapy were identified as Cohort D to analyze the benefit of induction chemotherapy. The flowchart was presented in **Supplementary Fig. 1**. All the patients were restaged based on the 8th edition American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system. This study was approved by Sun Yat-sen University Cancer Center Institutional Review Board (No. B2021-059-01).

Imaging analysis

The protocols of PET/CT and MRI were deposited in **Supplementary Method**. MRI images were read by two experienced radiologists, and PET/CT by two experienced nuclear physicians who were blinded to MRI results. Any differences were resolved by consensus. The metastatic lymph nodes were diagnosed according to the radiologic criteria [11]: (1) retropharyngeal lymph node with a minimal axial diameter of 5mm or greater, and cervical lymph node with a minimal axial diameter of 10mm or greater, respectively; (2) minimal axial diameter of 8mm for clusters of 3 or more lymph nodes; (3) lymph nodes with necrosis or extranodal extension. Same as previous study [12], radiologic extranodal extension was categorized into 4 grades: Grade 0, no extranodal extension; Grade 1, invasion to surrounding fat; Grade 2, coalescent nodes; Grade 3, infiltrating adjacent structures. As reported [13], the diagnostic criteria for nodal necrosis based on MRI included: (1) focal area of low signal intensity on T1-weighted images with or without enhanced edges; (2) focal area of high signal intensity on T2-weighted images. In PET/CT, lymph node was considered as positive when ^{18}F-FDG uptake increased significantly compared with background [14]. In the final decision-making, PET/CT results were supplemented with MRI findings (Fig. 1**)**.

Treatment and follow-up

All patients received intensity-modulated radiotherapy. The prescribed doses were 66–72 Gy to gross tumor and lymph nodes. The treatment modality included concurrent chemoradiotherapy with or without induction chemotherapy, radiotherapy alone, and induction chemotherapy plus radiotherapy. After treatment, follow-up examinations were conducted at least every 3 months during the first 2 years, and then every 6 to 12 months thereafter. Examinations including EBV DNA testing, nasopharyngoscopy, head and neck MRI, chest X-ray or computed tomography, and abdominal sonography or computed tomography were performed regularly. PET/CT was recommended if necessary, and recurrence or metastasis was confirmed by biopsy if possible.

Statistical analysis

Failure-free survival (FFS, time from diagnosis to failure or death) was defined as the primary endpoint, and the second endpoints were distant metastasis-free survival (DMFS, time from diagnosis to distant metastasis or death), locoregional relapse-free survival (LRRFS, time from diagnosis to locoregional recurrence or death), and overall survival (OS, time from diagnosis to death).

Categorical variables were compared by Chi-square test. McNemar's paired-sample test or Chi-square test was used to compare PET/CT and MRI in terms of sensitivity, specificity, positive predictive value, and negative predictive value. And propensity score matching (PSM) method was applied to balance confounders between different groups at the ratio of 1:1. The cut-off values of continuous variables were determined by receiver operating characteristic curve (ROC) analysis. To confirm the benefit of PET/CT in N0-1 patients with EBV-DNA lower than 4000 copies/mL, the cut-off value of EBV-DNA was 4000 copies/mL in cohort B and cohort C [3], while the cut-off value was 2000 copies/mL in cohort D, in order to compared with the model reported in previous study [10].The survival rates were compared by Kaplan-Meier method. Univariate and multivariate Cox regression analysis were performed to determine independent factors. The model was evaluated by the concordance index (C-index). Statistical analysis was conducted by R 4.0.1 (http://www.r-project.org/) and SPSS 26.0. And a two-side $P < 0.05$ was considered to be statistically significant.

Results

Advantage of PET/CT vs. MRI in diagnosing cervical lymph nodes

In cohort A, 58.0% of patients (195/336) were diagnosed with stage III, and patients staged N1 accounted for 77.1% (259/336) **(Supplementary Table 1)**. Of the 460 biopsied cervical lymph nodes from 336 patients, 269 (58.5%) and 191 (41.5%) lymph nodes were pathologically positive and negative, respectively. Among them, 96.7% (260/269) of positive and 75.9% (145/191) of negative lymph nodes were correctly detected by PET/CT, while only 88.5% (238/269) of positive and 70.7% (135/191) of negative lymph nodes were correctly diagnosed by MRI. PET/CT was significantly more sensitive than MRI for detecting cervical lymph node metastasis ($p < 0.001$). As for specificity, no significant difference was observed between two imaging methods (75.9% vs. 70.7%, $p = 0.174$). The negative predictive value, positive predictive value, and accuracy of PET/CT and MRI were 94.2% vs. 81.3%, 85.0% vs. 81.0%, and 88.0% vs.81.1%, respectively (Table 1). And the area under the curve (AUC) of PET/CT was higher than that of MRI (0.863 vs. 0.796, $p < 0.05$). Notably, 14.4% (66/460) of lymph nodes had discrepancies between two imaging tests. Among them, PET/CT showed true positive in 22 lymph nodes which was diagnosed as negative lymph nodes by mistake in MRI, and true negative in 27 lymph nodes misdiagnosed as positive lymph nodes by MRI. Nonetheless, 17 lymph nodes were wrongly diagnosed as positive lymph nodes by PET/CT according to histopathology.

Table 1
Performance of PET/CT versus MRI in diagnosing 460 biopsied cervical lymph nodes of 336 patients

Imaging methods	TP	TN	FP	FN	Sensitivity (%)	*p*	Specificity (%)	*p*	PPV (%)	*p*	NPV (%)	*p*	Accuracy (%)	*p*
					95% CI		95% CI		95% CI		95% CI		95% CI	
PET/CT	260	145	46	9	96.7(93.5–98.4)		75.9 (69.1–81.7)		85.0(80.4–88.7)		94.2(88.9–97.1)		88.0(84.7–90.9)	
MRI	238	135	56	31	88.5(83.9–91.9)		70.7(63.6–76.9)		81.0 (75.9–85.2)		81.3 (74.4–86.8)		81.1(77.2–84.6)	
PET/CT vs. MRI						0.001		0.174		0.191		0.001		0.001

Abbreviations: FP, false positive; FN, false negative; NPV, negative predictive value; MRI, magnetic resonance imaging; PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; PPV, positive predictive value; TP, true positive; TN, true negative.

To evaluate whether the staging can be manipulated by PET/CT or MRI and subsequently affects the prognosis, the cohort B included 1093 patients who received pretreatment PET/CT and MRI. The median age was 45 (range,12–79) years, male accounted for 71.9%, and 819 (74.9%) patients had EBV-DNA lower than 4000 copies/ml (Table 2). With a median follow up time of 50 (range, 1-118) months, 48 (4.4%) patients died, 142 (13.9%) patients suffered from treatment failure, and 62 (5.7%) patients had distant metastasis. The 5-year OS, FFS, DMFS, and LRRFS were 96.0%, 85.6%, 93.6%, and 92.9%, respectively.

Table 2
Baseline characteristics of patients with T3N1M0 in primary Cohort B, Cohort C, and PSM cohort

	Primary cohort			PSM cohort		
	Cohort B: PET/CT + MRI (N = 1093)	Cohort C: MRI(N = 1377)	P	PET/CT + MRI (N = 954)	MRI(N = 954)	P
	N (%)	N (%)		N (%)	N (%)	
Age			0.021			0.911
Median(range)	45(12–79)	47(13–81)		46(12–79)	46(15–78)	
< 55	867(79.3)	1037(75.3)		747(78.3)	750(78.6)	
≥ 55	226 (20.7)	340 (24.7)		207 (21.7)	204 (21.4)	
Sex			0.362			0.754
Male	786 (71.9)	966 (70.2)		709 (74.3)	702 (73.6)	
Female	307(28.1)	411(29.8)		245(25.7)	252(26.4)	
ALB(g/L)			0.014			0.445
< 40	51(4.7)	98(7.1)		48(5.0)	40(4.2)	
≥ 40	1042 (95.3)	1279 (92.9)		906 (95.0)	914 (95.8)	
HB (g/L)			0.163			0.849
< 120	61(5.6)	97(7.0)		57(6.0)	60(6.3)	
≥ 120	1032 (94.4)	1280 (93.0)		897 (94.0)	894 (93.7)	
LDH(U/L)			0.949			0.904
< 250	1050(96.1)	1321(95.9)		919(96.3)	917(96.1)	
≥ 250	43 (3.9)	56 (4.1)		35 (3.7)	37 (3.9)	
EBV-DNA (copy/mL)			0.721			1
< 4000	819(74.9)	1022(74.2)		712(74.6)	711(74.5)	
≥ 4000	274 (25.1)	355 (25.8)		242 (25.4)	243 (25.5)	
Lymph Node			< 0.001			0.882
Retropharyngeal lymph node	299(27.4)	656(47.6)		295(30.9)	299(31.3)	
Cervical lymph node	794 (72.6)	721 (52.4)		659 (69.1)	655 (68.7)	
Treatment			0.162			0.578
CCRT	489 (44.7)	584 (42.4)		407 (42.7)	422 (44.2)	
IC + CCRT	349 (31.9)	418 (30.4)		311 (32.6)	297 (31.1)	
RT	116 (10.6)	163 (11.8)		106 (11.1)	93 (9.7)	
IC + RT	139 (12.7)	212 (15.4)		130 (13.6)	142 (14.9)	
Smoking			0.266			0.61
Yes	296 (27.1)	402 (29.2)		261 (27.4)	272 (28.5)	
No	797(72.9)	975(70.8)		693(72.6)	682(71.5)	
Drinking			0.387			0.749
Yes	175 (16.0)	202 (14.7)		141 (14.8)	147 (15.4)	
No	918(84.0)	1175(85.3)		813(85.2)	807(84.6)	
History			1			0.323
Yes	107 (9.8)	135 (9.8)		74 (7.8)	87 (9.1)	
No	986(90.2)	1242(90.2)		880(92.2)	867(90.9)	

Abbreviations: CCRT, concurrent radiochemotherapy; CI, confidence interval; EBV, EpsteinBarr virus; HB, hemoglobin; IC, induction chemotherapy; LDH, serum lactate dehydrogenase; MRI, magnetic resonance imaging; PSM: propensity scoring matching; PET/CT, 18F-fluorodeoxyglucose positron emission tomography/computed tomography; RT: radiotherapy

According to PET/CT alone, 633 of 1093 patients in the cohort B were staged with T3N1M0. All the patients were consistently staged with T3 by MRI, whereas 3.2% (20/633), 83.1% (526/633), 13.4% (85/633), and 5.2% (33/633) of patients were diagnosed with N0, N1, N2, and N3 if determined by MRI alone. But remarkably, no significant differences in OS, FFS, LRRFS or DMFS were observed among these N0, N1, N2, and N3 patients staged by MRI ($p = 0.68$, $p = 0.68$, $p = 0.61$, and $p = 0.96$, respectively; **Supplementary Fig. 2**).

Based on the MRI criteria alone, 599 of 1093 patients in the cohort B were diagnosed with T3N1M0. All these patients were also staged with N1 by PET/CT. Nonetheless, 12.2% (73/599) and 87.8% (526/599) of patients were classified as T2 and T3 retrospectively by PET/CT alone. Survival rates were not significant different between T2 and T3 patients staged by PET/CT ($p = 0.72$ for OS, $p = 0.85$ for FFS, $p = 0.93$ for LRRFS, and $p = 0.65$ for DMFS; **Supplementary Fig. 3**).

Prolonged survival rates of patients staged by PET/CT vs. MRI

To find if the advantage of PET/CT in diagnosis can contribute to the survival differences, the cohort C in which patients underwent MRI alone was compared with cohort B. As shown in Table 2, the baseline characteristics between PET/CT plus MRI and MRI alone were compared. However, the results showed there was an imbalance in age, lymph node location, and albumin between two groups ($p = 0.021$, $p = 0.014$, and $p < 0.001$, respectively). After PSM at the ratio of 1:1, no imbalance variable was observed between two groups. Of 1908 patients who were included in the PSM cohort, 485 (25.4%) patients had EBV-DNA higher than 4000 copies/ml. With a median follow-up period of 52 (1-151) months, 132(6.9%) patients died, 165 (6.5%) patients developed distant metastasis, and 211(11.1%) patients suffered from locoregional relapse. The 5-year OS, FFS, DMFS, and LRRFS were 93.0%, 78.6%, 90.9% and 87.2%, respectively.

In survival analysis, patients underwent both PET/CT and MRI had better OS than those underwent MRI alone (5-year OS, 95.7% vs. 90.4%, $p < 0.001$). In terms of FFS, DMFS, and LRRFS, patients received both PET/CT and MRI also had higher survival rates compared with those received MRI alone (5-year FFS, 85.7% vs. 71.7%, $p < 0.001$; 5-year DMFS, 93.9% vs. 87.9%, $p < 0.001$; and 5-year LRRFS, 93% vs. 81.4%, $p < 0.001$; Fig. 2). Univariate analysis was presented in **Supplementary Table 2**. As shown in **Supplementary Table 3**, multivariate analysis indicated that the application of PET/CT was an independent favorable prognostic factor for OS (hazard ratio [HR] = 0.49, 95% confidence interval [CI] 0.34–0.71, $p < 0.001$), FFS (HR = 0.5, 95% CI 0.40–0.61, p < 0.001), DMFS (HR = 0.44, 95% CI 0.32–0.61, p < 0.001), and LRRFS (HR = 0.38, 95% CI 0.28–0.51, p < 0.001), respectively.

Subgroup analysis was conducted in patients with EBV-DNA lower than 4000 copies/ml in the PSM cohort. In this subgroup, 1423 patients were eligible, of which 712 patients received both PET/CT and MRI. As shown in **Supplementary Fig. 4**, patients underwent both PET/CT and MRI had survival benefit in OS (5-year OS, 96.5% vs. 91.4%, p = 0.0012), FFS (5-year FFS, 86.1% vs. 75.4%, $p < 0.001$), DMFS (5-year DMFS, 93.7% vs. 90.9%, $p < 0.001$), and LRRFS (5-year LRRFS, 92.9% vs. 84.2%, p = 0.004) compared with those underwent MRI alone. Univariate analysis was deposited in **Supplementary Table 4**. In multivariable analysis (see **Supplementary Table 5**), addition of PET/CT was also an independent factor for OS (HR = 0.48, 95% CI 0.31–0.75, p = 0.0014), FFS (HR = 0.54, 95% CI 0.42–0.7, p < 0.001), DMFS (HR = 0.56, 95% CI 0.38–0.83, p = 0.0044), and LRRFS (HR = 0.45, 95% CI 0.31–0.64, p < 0.001), respectively.

Guiding individualized induction chemotherapy

In the Cohort B, 838 patients who received concurrent chemoradiotherapy with or without induction chemotherapy were selected to the Cohort D. However, there were significant differences in baseline characteristics between two treatment models (see Table 3). After PSM at 1:1 ratio, 698 patients were included in this well-balanced cohort. In the PSM cohort D, the median age were 46 years old (range, 13–73); 132(18.9%) patients had lymph node necrosis, and patients with grade 0, 1, 2, 3 radiologic extranodal extension accounted for 48.1% (336/698), 18.8% (131/698), 20.9% (146/698), 12.2% (85/698), respectively. With a median follow-up period of 50 (1-118) months, 117, 50, 45, 35 patients had treatment failure, locoregional relapse, distant metastasis, and died. The 5-year FFS, LRRFS, DMFS, and OS were 82.0%, 92.6%, 92.8% and 95.0%, respectively. Interestingly, univariate analysis (**Supplementary Table 6)** and multivariable analysis indicated that SUV-N higher than 9.35, in together with nodal necrosis and extranodal extension infiltrating adjacent structures, carried prognostic significance for FFS (p < 0.001, p = 0.002, and p = 0.002, respectively, **Supplementary Table 7**). Radiologic score was thus developed based on the number of the three factors. Patients with higher radiologic score had the lower FFS (p < 0.001, **Supplementary Fig. 5**). Thus, patients with one or more risk factors were classified into high-risk group (radiologic score > 0, n = 454), while patients with no risk factor were stratified into low-risk group (radiologic score = 0, n = 244). The survival curves showed patients in high-risk group had lower FFS, DMFS, LRRFS, and OS than those in lower-risk group (all p < 0.05, **Supplementary Fig. 6**). Radiologic score model had higher C-index than the model with gender and EBV-DNA (0.72 [95% CI:0.65–0.78] vs. 0.56 [95% CI: 0.49–0.63], p < 0.001).

Table 3
Baseline characteristics of patients in primary Cohort D and PSM cohort D

	Primary Cohort D			PSM Cohort D		
	CCRT (N = 489)	IC + CCRT(N = 349)	p	CCRT(n = 349)	IC + CCRT (n = 349)	p
	n (%)	n (%)		n (%)	n (%)	
Sex			0.617			0.511
Female	152(31.1)	102(29.2)		111(31.8)	102(29.2)	
Male	337 (68.9)	247 (70.8)		238 (68.2)	247 (70.8)	
Age			0.297			0.306
< 55	394(80.6)	270(77.4)		282(80.8)	270(77.4)	
≥ 55	95 (19.4)	79 (22.6)		67 (19.2)	79 (22.6)	
Albumin (g/L)			0.336			0.704
< 40	15(3.1)	16(4.9)		13(3.7)	16(4.9)	
≥ 40	474 (96.9)	333 (95.4)		336 (96.3)	333 (95.4)	
Hemoglobin (g/L)			0.786			0.658
< 120	14(2.9)	12(3.4)		9(2.6)	12(3.4)	
≥ 120	475 (97.1)	337 (96.6)		340 (97.4)	337 (96.6)	
LDH(U/L)			0.878			0.066
< 250	462(94.5)	328(94.0)		339(97.1)	328(94)	
≥ 250	27 (5.5)	21 (6.0)		10 (2.9)	21 (6.0)	
EBV-DNA (copy/mL)			0.001			0.073
< 2000	341(69.7)	203(58.2)		227(65.0)	203(58.2)	
≥ 2000	148 (30.3)	146 (41.8)		122 (35.0)	146 (41.8)	
Lymph Node			0.015			0.54
CLN	379(77.5)	295(84.5)		288(82.5)	295(84.5)	
RLN	110 (22.5)	54 (15.5)		61 (17.5)	54 (15.5)	
Smoking			0.431			0.729
Yes	135 (27.6)	87 (24.9)		92 (26.4)	87 (24.9)	
No	354(72.4)	262(75.1)		257(73.6)	262(75.1)	
Drinking			1			1
Yes	81 (16.6)	58 (16.6)		59 (16.9)	58 (16.6)	
No	408(83.4)	291(83.4)		290(83.1)	291(83.4)	
History			0.117			0.076
Yes	55 (11.2)	27 (7.7)		42 (12.0)	27 (7.7)	
No	434(88.8)	322(92.3)		307(88.0)	322(92.3)	
Nodal Necrosis			0.034			0.384
Yes	71 (14.5)	71 (20.3)		61 (17.5)	71 (20.3)	
No	418(85.5)	278(79.7)		217(82.5)	278(79.7)	
Minimal axial diameter(cm)			0.001			0.245
< 0.95	186(38.0)	95(27.2)		110(31.5)	95(27.2)	
≥ 0.95	303 (62.0)	254 (72.8)		239 (68.5)	254 (72.8)	
Maximal axial diameter(cm)			< 0.001			0.148

Abbreviations: CCRT, concurrent radiochemotherapy; CLN: Cervical lymph node; EBV, EpsteinBarr virus; IC, induction chemotherapy; LDH, serum lactate dehydrogenase; PSM: propensity scoring matching; rENE, radiologic extranodal extension; RLN: Retropharyngeal lymph node SUVmax-N, the maximal standardized uptake value of lymph node; SUVmax-T, the maximal standardized uptake value of primary tumor

	Primary Cohort D			PSM Cohort D		
< 1.35	208(42.5)	106(30.4)		125(35.8)	106(30.4)	
≥ 1.35	281 (57.5)	243 (69.6)		224 (64.2)	243 (69.6)	
SUVmax-T			0.318			0.929
< 9.25	131(26.8)	82(23.5)		80(22.9)	82(23.5)	
≥ 9.25	358 (73.2)	267 (76.5)		269 (77.1)	267 (76.5)	
SUVmax-N			< 0.001			0.59
< 9.35	286(58.5)	138(39.5)		146(41.8)	138(39.5)	
≥ 9.35	203 (41.5)	211 (60.5)		203 (58.2)	211 (60.5)	
rENE			0.02			0.24
Grade 0	261 (53.4)	164 (47.0)		172 (49.3)	164 (47.0)	
Grade 1	96 (19.6)	61 (17.5)		70 (20.1)	61 (17.5)	
Grade 2	91 (18.6)	73 (20.9)		73 (20.9)	73 (20.9)	
Grade 3	41 (8.4)	51 (14.6)		34 (9.7)	51 (14.6)	

Abbreviations: CCRT, concurrent radiochemotherapy; CLN: Cervical lymph node; EBV, EpsteinBarr virus; IC, induction chemotherapy; LDH, serum lactate dehydrogenase; PSM: propensity scoring matching; rENE, radiologic extranodal extension; RLN: Retropharyngeal lymph node SUVmax-N, the maximal standardized uptake value of lymph node; SUVmax-T, the maximal standardized uptake value of primary tumor

For all the patients, induction chemotherapy showed no survival benefit (p = 0.78, Fig. 3). But in the high-risk group stratified by radiologic score, patients receiving induction chemotherapy plus concurrent chemoradiotherapy had higher 5-year FFS than those receiving concurrent chemoradiotherapy alone (82.2% vs. 71.5%; p = 0.00642, Fig. 3). After adjusting for covariates, multivariate analysis also confirmed that the addition of induction chemotherapy was an independent factor for FFS (HR: 0.53, 95%CI: 0.35–0.8, p = 0.0026; **Supplementary Table 8 and Supplementary Table 9**). By contrast, no survival difference was observed between the two treatment modes in the low-risk group (p = 0.074, Fig. 3). The same conclusion was also reached for DMFS and RRFS. And the detailed results of DMFS, LRRFS and OS were deposited in supplementary Tables and Figures.

Discussion

In this large cohort study, PET/CT was proved to be more accurate than MRI in diagnosing cervical lymph nodes confirmed by histopathology. Accordingly, as accurate N-staging more precisely uncovered the true prognosis of patients, PET/CT plus MRI identified T3N1M0 patients showed higher survival outcomes than MRI staged T3N1M0 patients, even if EBV-DNA was lower than 4000 copies/ml. And PET/CT based SUVmax of lymph nodes in together with nodal necrosis and extranodal extension involved with adjacent structures could build a radiologic score model and identify high-risk T3N1M0 patients who can benefit from the addition of induction chemotherapy.

In fact, this was not the first report of advantage of PET/CT over MRI in diagnostic lymph nodes of nasopharyngeal carcinoma. But different from previous study [4, 15], the included 460 lymph nodes were pathologically confirmed in our study, instead of clinical follow up. The finding of PET/CT superior to MRI was also consistent with the results of studies in head and neck cancer [16]. Although the sensitivity of PET/CT we found in nasopharyngeal carcinoma (96.7%) was a bit higher than that of head and neck cancer (90.0%), the specificity of PET/CT was only 75.9% herein, lower than that of head neck cancer (94.0%) [17] but still better than MRI (70.8%). Perhaps, newly deep learning algorithm might be a good assistant to further improve the diagnostic performance. Notably, 18.6% (118/633) of PET/CT diagnosed T3N1M0 were up-staged with T3N2-3M0 by MRI, while only 3.2% (20/633) of patients were down-staged with T3N0M0 by MRI, without any discrepancy in T3 staging. This also indicated the high potential of over-diagnosis by MRI. The undifferentiated survival rates (**Supplementary Fig. 2**) across the misdiagnosed T3N0-3M0 patients by MRI but staged T3N1M0 by PET/CT testified again the higher possibility of getting closer to the true prognosis if staged by PET/CT, in terms of treatment outcomes. Certainly, MRI staged T3N1M0 patients were divided to T2N1M0 and T3N1M0 by PET/CT but no survival differences were observed between T2 and T3; as no gold standard to confirm T-stage of both examination equipment, we failed to draw a firm conclusion of PET/CT versus MRI in T-stage of nasopharyngeal carcinoma. Reviewing previous studies [15, 18], MRI seemed to be more accurate than PET/CT in diagnosing the involvement of local structures. Therefore, the combination of PET/CT and MRI may be the best recommendation for diagnosing and staging of treatment naïve nasopharyngeal carcinoma.

To testify if the diagnostic advantage of PET/CT can transfer to benefit in treatment outcomes, we directly compared two cohorts of T3N1M0 patients staged by PET/CT plus MRI or MRI alone. The significant higher survival rates of patients with PET/CT plus MRI, regardless of the EBV DNA load, finally supported our suppose. Obviously, PET/CT as an examination test cannot directly alter the final treatment outcomes by itself, but several prospective studies reported that adding PET/CT to conventional work-up could provide additional information and may change management approaches in 15.7%-33.8% of head and neck cancer patients [16, 19, 20]. Given the retrospective design of our study, the magnitude of actual changes in treatment modes before and after the application of PET/CT in these patients was not available. But on the other hand, we tried to investigate if PET/CT could predict the survival rate of patients and accordingly identify the high-risk patients to receive more intensive treatment. In a cohort of PET/CT and MRI staged T3N1M0 patients, induction chemotherapy showed no survival benefit for all the patients, as observed in prior studies [9]. Previous reported EBV DNA load and gender guided risk stratification [10] did not work here, possibly because of its poor specificity and generalization. By contrast, SUVmax-N, nodal necrosis and extranodal

extension involved with adjacent structures remained highly prognostic. In fact, these were not observed for the first time [12, 21, 22], which indicated the potential of good generalization. The radiologic score model based on the three characteristics showed a significantly ($p < 0.001$) higher C-index (0.72) than the model based on EBV DNA and gender [10] (C-index = 0.56) in risk stratification. Besides, the radiologic score model selected high-risk patients were just the target objectives who can benefit from the addition of induction chemotherapy. As shown in our study, the 5-year FFS rate of the high-risk T3N1M0 patients was similar to those more advanced patients included for clinical trials of induction chemotherapy [23]. Thus, it was not unreasonable that the high-risk T3N1M0 patients had significantly improved survival outcomes when receiving induction chemotherapy followed by concurrent chemoradiotherapy.

Based on 460 biopsied cervical lymph nodes, we firmly concluded the advantage of PET/CT in diagnosing lymph nodes. In a cohort of T3N1M0 patients, the interference of covariate factors including nodal size, nodal level, nodal laterality and T stage were totally excluded; we testified the survival benefit transferred from the accurate diagnosis by PET/CT and found the way to guide individualized induction chemotherapy for T3N1M0 patients by a radiologic score model based on PET/CT and MRI.

Declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Availability of data and material

The data and materials are available from the corresponding author on reasonable request.

Consent to participate

Informed consent was obtained from eligible patients.

Consent for publication

Not applicable.

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Code availability

Not applicable.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Sun Yat-sen University Cancer Center Institutional Review Board (No. B2021-059-01).

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Figures

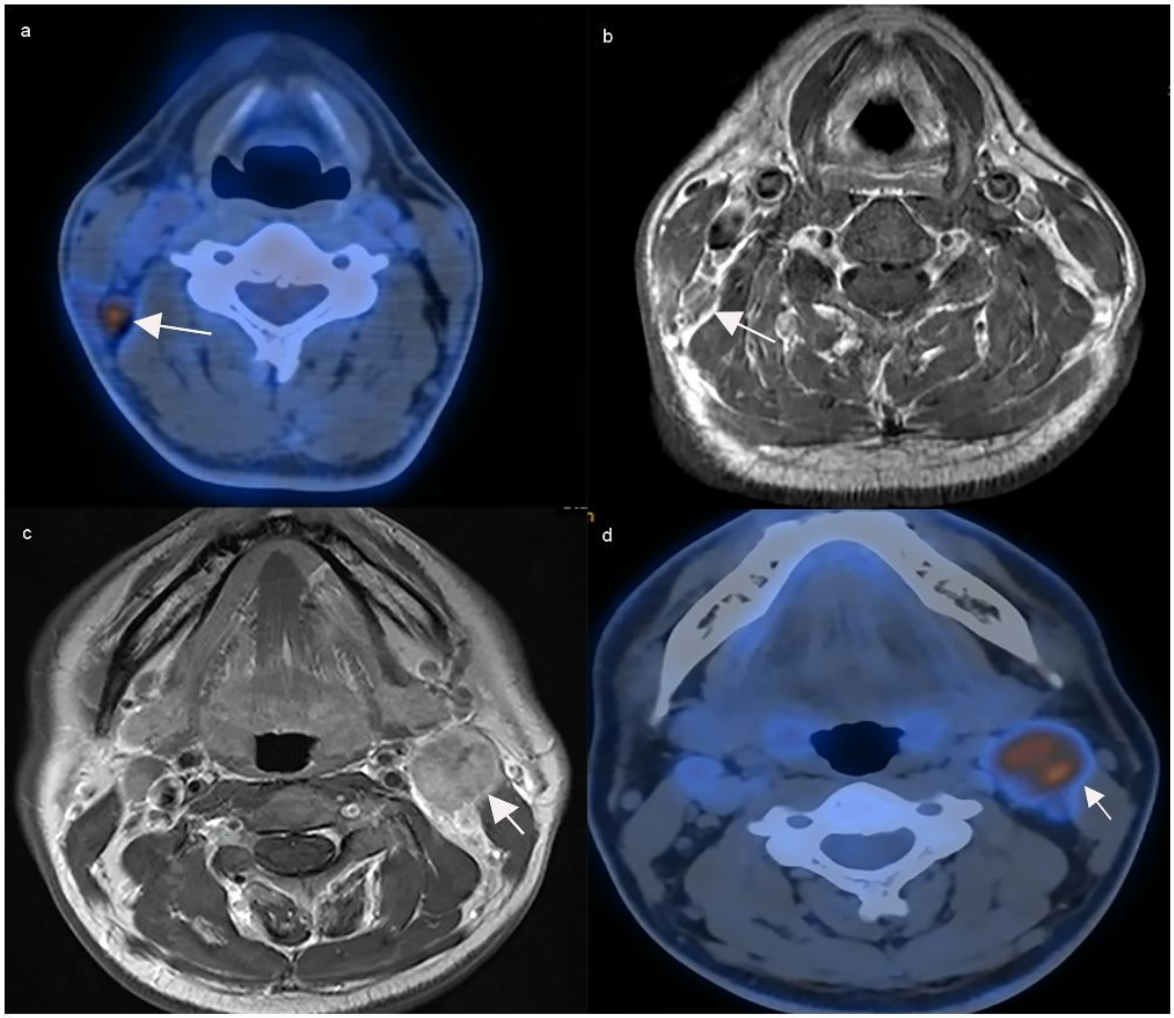

Figure 1

Cervical lymph nodes in PET/CT (left) and contrast-enhanced T1-weighted MRI (right), (a) PET/CT correctly diagnosed as positive lymph node, while MRI diagnosed as negative lymph node by mistake (b); Both PET/CT (c) and MRI (d) correctly detected metastatic lymph nodes. Abbreviations: MRI, magnetic resonance imaging; PET/CT, pretreatment positron emission tomography with computed tomography.

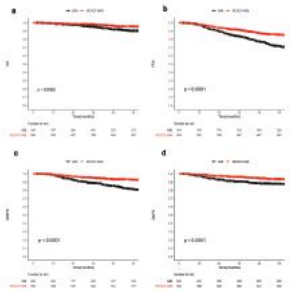

Figure 2

Survival curves compared PET/CT+MRI with MRI alone in PSM cohort: (a) OS, (b) FFS, (c) LRRFS, and (d) DMFS. Abbreviations: DMFS, distant metastasis-free survival; FFS, failure-free survival; LRRFS, locoregional relapse-free survival; MRI, magnetic resonance imaging; OS, overall survival; PET/CT, pretreatment positron emission tomography with computed tomography; PSM: propensity scoring matching.

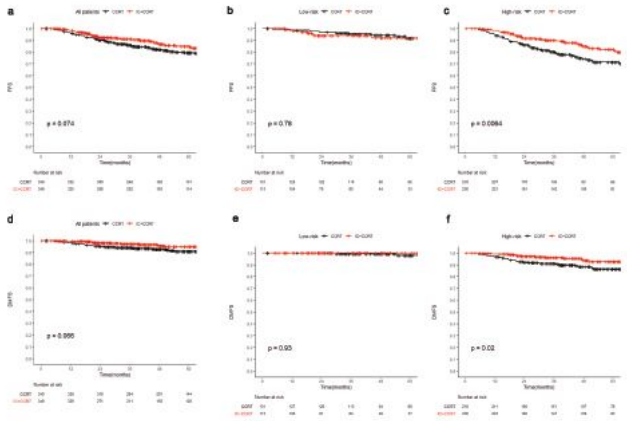

Figure 3

Kaplan–Meier FFS curves compared IC+CCRT and CCRT alone in the whole PSM cohort D(a), low-risk group(b) and high-risk group(c); and DMFS curves in in the whole PSM cohort D(d), low-risk group(e) and high-risk group(f) Abbreviations: CCRT, concurrent chemoradiotherapy; FFS, failure-free survival; IC, induction chemotherapy.

Supplementary Files

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- Supplementary.pdf