

# [<sup>18</sup>F] FDG PET/CT and Head and Neck MRI in the Diagnosis and Prognosis of Moroccan Patients With Nasopharyngeal Carcinoma

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## Research Article

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# Abstract

**Purpose:** While nasopharyngeal carcinoma (NPC) management in Morocco is still based on conventional work-ups: a head and neck computed tomography (HN-CT), thoracic and abdominal CT and bone scan, the combination of HN magnetic resonance imaging (HN-MRI) and 2-Deoxy-2-[<sup>18</sup>F] fluoro-D-glucose positron emission tomography/computed tomography ([<sup>18</sup>F] FDG PET/CT) is now widely used in the diagnostic and follow-up of this malignancy.

**Methods:** In this prospective study, [<sup>18</sup>F] FDG PET/CT and HN-MRI outcomes of 117 NPC patients diagnosed between January 2017 and December 2018 were investigated in order to assess their usefulness in routine management of Moroccan patients with NPC. The concordance between HN-MRI and [<sup>18</sup>F] FDG PET/CT in Tumor (T) and Nodal (N) classification was assessed and the association between [<sup>18</sup>F] FDG PET/CT metabolic parameters (Tumor- maximum standardized uptake value (T-SUV max), Nodal (N-SUV max), node-to-tumor SUV ratio (NTR) and distant metastasis (M-SUV max), TNM staging system, NPC stages and patient's survival outcomes was evaluated.

**Results:** Our results showed a moderate concordance between T-TEP and T-MRI categories with a Cohen kappa coefficient (k) at 0.45, and a mediocre concordance between N-TEP and N-MRI (k=0.3). Metabolic parameters of the [<sup>18</sup>F] FDG PET/CT were assessed; N-SUV max values were significantly higher in patients with advanced nodal involvement, with a mean of 7.4, 9.7 and 11.0 for patients with N1, N2 and N3 nodal categories, respectively (p<0.05). overall, N-SUV max, NTR were independent prognostic markers for overall survival and progression free survival in Moroccan NPC patients (p<0.05).

**Conclusion:** Our findings provide additional evidence into the complementary roles of HN-MRI and [<sup>18</sup>F] FDG PET/CT in TNM and overall staging of NPC. To the best of our knowledge, this is the first Moroccan study to highlight N-SUV max and NTR derived from [<sup>18</sup>F] FDG-PET/CT as promising metabolic biomarkers for NPC prognosis.

## Introduction

Nasopharyngeal carcinoma (NPC) is the second most common head and neck cancer and is characterized by a deep anatomy and a distinct geographical distribution (Chua et al. 2016). NPC is rare in most parts of the world with an annual incidence of < 1/100,000. However, in high endemic areas (southern China, Southeast Asia and Arctic region), the annual incidence of NPC varies between 30 and 80 cases per 100,000 per year (Bray et al. 2018). In Morocco, an intermediate incidence for NPC, the incidence of NPC is 4.2/100.000 in men and 1.2 /100.000 in women yearly (Benider et al. 2012). NPC clinical symptoms are extremely variable and typically non-specific in the early disease stages (I-II) (Lo et al. 2004). Therefore, it remains clinically silent for a long period of time, and more than 60% of NPC patients have advanced loco-regionally stage at diagnosis (III-IV) (Wang et al. 2017). Moreover, it has been widely assumed that early detection of NPC is associated with favorable treatment outcomes and a long survival rate; the 5-year survival rate for patients in early loco-regional stage (Tumor (T) 1, T2, Nodal (N) 0–1) being around 85%, while for patients with advanced loco-regional stages (T3, T4, N2 and N3), it's estimated at 65% (Lee et al. 2005).

Worldwide, NPC diagnosis is based on tripod: clinical examination with nasopharyngeal endoscopy, radiological imaging and histo-pathological confirmation. Head and neck magnetic resonance imaging (HN-MRI), HN computed tomography (CT), thoracic and abdominal CT and whole-body bone scan are the conventional work-ups (CWUs) currently used for NPC diagnosis and staging (Goh and Lim 2009). Despite their long clinical use, these conventional approaches have a number of limitations. Given that CWUs show limited contrast and can result in small metastatic lesions escape, this may considerably impact disease staging and treatment protocols (Brouwer et al. 2005). Thus, several studies recommended the use of 2-Deoxy-2-[<sup>18</sup>F] fluoro-D-glucose positron emission tomography/computed tomography ([<sup>18</sup>F] FDG PET/CT) and HN-MRI as new NPC diagnosis protocols and disease assessment (Brouwer et al. 2005; Liu et al. 2007; King et al. 2015). At diagnosis, [<sup>18</sup>F] FDG PET/CT derived imaging markers have improved the accuracy of staging (Chan et al. 2018), while they allowed a better assessment of NPC therapy effectiveness in NPC patients after treatment, by providing information on the residual scar mass and hence lowering the chances of treatment completely eradicating tumors (Wei et al. 2016). In this context, various [<sup>18</sup>F] FDG PET/CT metabolic parameters have been suggested as prognostic markers for NPC, including maximum standardized uptake value (SUV max), metabolic tumor volume (MTV), total lesion glycolysis (TLG) and node-to-tumor SUV ratio (NTR), that can reflect the tumor biologic characteristics and predict patient's survival (Chan et al. 2010; Moon et al. 2015; Wei et al. 2016). However, further studies are needed to deeply investigate the clinical application modality of [<sup>18</sup>F] FDG PET/CT metabolic parameters in the management of NPC.

In Morocco, a great attention was given to cancer management and substantial support was accorded to set up facilities with the most developed technologies for both diagnosis and therapy. In this field, two companies have been set up to produce [<sup>18</sup>F] FDG radioactive tracer by cyclotron technology and there are currently 7 medical centers using the [<sup>18</sup>F] FDG PET/CT technology, while, others are planned for the next years. This technology is often used in the management of the most prevalent cancers in Morocco, including, lymphoma, lung, breast etc..., but its use in NPC is still limited. The present study was designed to assess the usefulness of HN-MRI and [<sup>18</sup>F] FDG PET/CT in routine diagnosis and prognosis of NPC for a better management of this disease in Morocco. The concordance between HN-MRI and [<sup>18</sup>F] FDG PET/CT in Tumor and Nodal classification was assessed and the association between <sup>18</sup>F-FDG-PET/CT metabolic parameters (T-SUV max, N-SUV max, NTR and Metastatic (M-SUV max), TNM staging system, NPC stages and patient's survival outcomes (overall survival (OS), loco-regional recurrence-free survival (LRRFS) and progression free survival (PFS)) were evaluated.

## **Material And Methods**

### **Patients' recruitment and study design**

A total of 117 newly diagnosed patients with NPC, were prospectively recruited in Mohammed VI Center for Cancer Treatment in Casablanca-Morocco, between January 2017 and December 2018. Face-to-face interviews were conducted with all patients to collect information on epidemiological data. Clinical data were retrieved from medical records. All included patients underwent whole body [<sup>18</sup>F] FDG PET/CT or thoraco-abdominopelvic CT scan (TAP-CT) and HN-MRI scanning or HN-CT imaging before treatment. The study

protocol was approved by the Ethics Committee of Ibn Rochd University Hospital, Casablanca - Morocco and written informed consent was obtained from each recruited patient.

### Head & neck Magnetic Resonance Imaging (HN-MRI)

HN-MRI was performed in the Radiology Department of 20 August Hospital in Casablanca using the General Electric 1.5 Tesla machine. Axial and coronal T1-fast spin echo sequence, sagittal T2 cube and axial T2 fast spin echo sequence; without frequency selected fat suppression (in the neck for diagnosis of cervical adenopathy areas) and with frequency selected fat suppression (in the nasopharynx to determine local tumor extension); were obtained before injection of the contrast material. Intravenous administration of gadopentetate dimeglumine (Gd-DTPA) (Magnevist; Schering, Berlin, Germany) was done with a dose of 0.1 mmol/kg body weight, and contrast-enhanced fat-suppressed T1 spin echo sequences in axial and coronal planes were performed. All MRI imaging were captured with a section thickness of 4 mm and imaging matrix of 256 × 256. Interpretation and stratification of MRI results were recorded by an expert radiologist and performed from MRI images and reports.

### [<sup>18</sup>F] FDG PET/CT imaging

[<sup>18</sup>F] FDG PET/CT was conducted in the Nuclear Medicine Department of Ibn Rochd University Hospital, Casablanca. [<sup>18</sup>F] FDG PET/CT imaging was performed with a PET/CT scanner (Siemens Biograph 6). All patients fasted for at least 6h before the PET/CT. The capillary blood glucose level was < 7mmol/l. [<sup>18</sup>F] FDG activities ranging from 3.7 to 5.5 MBq/Kg were injected intravenously and images were acquired 60 to 80 minutes later. CT was realized from the head to the proximal mid-thighs before PET acquisition. The hepatic SUV was further used to compare [<sup>18</sup>F] FDG uptake in lesions using the expected normal liver as a reference; hepatic SUV of 2.5 was used communally as a cut-off for tumor contouring. SUV max values of liver, nasopharynx tumor (T- SUV max), nodes (N- SUV max), metastasis (M- SUV max), and the MTV were calculated using Siemens software's. The NTR was defined as N-SUV max/ T-SUV max. The interpretation of [<sup>18</sup>F] FDG PET/CT finding was performed directly from PET images, non-contrast-enhanced CT and fused images. Interpretation and stratification of results was performed by two senior nuclear medicine physicians.

### Disease staging

Based on radiological and functional imaging, pathological staging was performed according to the 7th edition of the International Union against Cancer / American Joint Committee on Cancer (UICC/AJCC) system. To evaluate [<sup>18</sup>F] FDG PET/CT and HN-MRI in T and N staging of NPC patients, we used results of 77 patients who paired these two exams. The HN-MRI was considered as the gold standard for Tumor staging and the [<sup>18</sup>F] FDG PET/CT for nodal staging and distant metastasis.

### Post-treatment follow-up and clinical endpoints

All patients received post-treatment follow-up every 3 months during the first year, every 6 months during the second and third years, and annually thereafter. Clinical examinations, nasopharyngeal endoscopy and imaging follow-up were performed routinely according to the clinical evolution of each patient. Overall survival was defined as the interval from the date of diagnosis to the last follow-up or date of death from any

cause. Locoregional recurrence -free survival (LRRFS) was defined as the interval from the date of diagnosis to the first evidence of radiological or histological loco-regional recurrence, death from any cause or last follow-up. Progression free survival (PFS) was defined as the time from the diagnosis to progression of disease, death or last follow-up (whichever occurred first).

## Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive analysis was carried out to characterize patients' socio-demographic and clinical variables. The concordance between T and N categories was performed using the Cohen kappa coefficient. The kappa coefficient ( $\kappa$ ) was used as a descriptive indicator of concordance and varies between 0 and 1 ( $\leq 0.2$ : poor concordance; 0.21–0.4: fair concordance; 0.41–0.6: moderate concordance; 0.61–0.8: good concordance and  $\geq 0.81$  very good concordance). The association between TNM staging system, NPC stages and [ $^{18}\text{F}$ ] FDG PET/CT metabolic parameters (T-SUV max, N-SUV max, NTR and M-SUV max) was analyzed using the ANOVA test. The optimal cut-offs of T-SUV max, N-SUV max, and NTR were obtained using the receiver operating characteristic (ROC) curve analysis. OS, LRRFS, and PFS curves were plotted with the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression models to identify the radiological prognostic factors influencing OS, LRRFS, and PFS. Results were expressed as hazard ratios (HRs) with their 95% confidence intervals (CIs). The following variables were entered as covariates into the model: tumor size, nodal classes, metastatic status and overall stages. Statistical significance was assumed at a  $p$  value less than 0.05. Only significant factors ( $p$ -value < 0.05) on univariate analysis were included in multivariate models.

## Results

### Patients' characteristics

The socio-economical and clinical characteristics of the 117 studied patients are presented in Table 1. The mean age of patients was 43.2 with extreme ages of 12 and 80 years old. NPC was more prevalent in men (64.1%) than women (35.9%), with a sex ratio of 1.7. The main symptoms reported by patients at disease onset showed that most patients presented with lymph node syndromes (82.1%) and headache (79.5%) as early-onset symptoms. The other common presenting symptoms were otologic issues and nasal obstruction reported in 70.9% (83/117) and 61.5% (72/117) of patients, respectively. The non-keratinizing undifferentiated carcinoma prevails and was found in 95.7% of patients (112/117). According to the 7th edition of the AJCC/UICC staging system, 23.9% of patients with NPC were classified in group III (28/117) and 65.0% in group IV (76/117). Imaging outcomes showed that most patients had tumor stages T3 (38/117) and T4 (50/117) and nodal stages N1 (30/117) and N2 (52/117). Furthermore, 31.6% (37/117) of patients have already developed metastasis at time of diagnostic. Evaluation of the local extension of nasopharyngeal tumors by HN-MRI showed that out of the 93 patients, 12 patients (12.9%) presented a limited tumor to the nasopharynx area and 81 patients (87.1%) have parapharyngeal tumor extension. Moreover, the tumor involved the bony structure of skull base in 53 patients (57.0%), and neurologic structures in 35 patients (37.6%).

Table 1  
Patient's characteristics

	<b>Characteristics</b>	<b>Number of cases</b>	<b>%</b>
<b>Gender</b>	Female	42/117	35.9
	Male	75/117	64.1
<b>Age</b>	≤ 32 years old	32/117	27.4
	< 32 years old	85/117	72.6
<b>Smoking status</b>	No	100/117	85.5
	Yes	17/117	14.5
<b>Drinking status</b>	No	100/117	85.5
	Yes	17/117	14.5
<b>Clinical presentations</b>	Headache	93/117	79.5
	Lymph node syndromes	96/117	82.1
	Unilateral	53/117	45.3
	Bilateral	43/117	36.8
	Otologic issues	83/117	70.9
	Nasal obstruction	72/117	61.5
	Epistaxis	63/117	53.8
	Neck swelling	28/117	23.9
	Trismus	34/117	29.1
	Neurologic Syndrome	12/117	10.3
<b>Histopathology</b>	Non-keratinizing undifferentiated carcinoma	112/117	95.7
	Non-keratinizing differentiated carcinoma	2/117	1.7
	Keratinizing squamous cell carcinoma	1/117	0.9
	Others	2/117	1.7
<b>Tumor stage</b>	T1	12/117	10.3
	T2	17/117	14.5
	T3	38/117	32.5
	T4	50/117	43.7

	Characteristics	Number of cases	%
<b>Nodal stage</b>	N0	10/117	8.5
	N1	30/117	25.6
	N2	52/117	44.4
	N3	25/117	21.4
<b>Metastatic status</b>	M0	80/117	68.4
	M1	37/117	31.6
<b>Stage of the disease (NPC stage)</b>	I	2/117	1.7
	II	11/117	9.4
	III	28/117	23.9
	IV	76/117	65.0
<b>Local extension of nasopharyngeal tumors by HN-MRI</b>	Limited tumor to the nasopharynx area	12/93	12.9
	Parapharyngeal involvement	81/93	87.1
	Skull base bone invasion	53/93	57.0
	Neurologic involvement	35/93	37.6

#### Concordance between HN-MRI and [<sup>18</sup>F] FDG PET/CT in T and N staging

Among the 117 included patients, 77 patients underwent both HN-MRI and <sup>18</sup>F-FDG-PET/CT, and were therefore used to evaluate imaging results in order to assess these two techniques in T and N staging accordingly. Tumor staging by HN-MRI showed that 34 patients were classified T4 (44.2%), 25 were classified T3 (32.5%), 12 were classified T2 (15.6%) and 6 were classified T1 (7.8%). T disease staging using the [<sup>18</sup>F] FDG PET/CT was as follows: 25 patients were classified T4 (33.8%), 29 were T3 (37.7%), 15 were T2 (18.2%) and 8 were classified T1 (10.4%). The [<sup>18</sup>F] FDG PET/CT correctly classified 59 patients (76%), underestimated 9 patients (11.6%) and overestimated 9 patients (11.6%), which makes a total of 18 misclassified patients (23%). Overall, a moderate concordance was observed between T-TEP and T-MRI categories with a Cohen kappa coefficient at 0.45. Regarding nodal staging, HN-MRI and [<sup>18</sup>F] FDG PET/CT showed a perfect concordance for N2 class, with 35 patients staged N2 (45.5%), while HN-MRI and [<sup>18</sup>F] FDG PET/CT did not detect nodal invasion in 10 (13%) and 8 patients (10.4%), respectively. Moreover, HN-MRI detected unilateral nodal involvement (N1) in 18 patients (23.4%) and N3 in 14 patients (18.2%), while [<sup>18</sup>F] FDG PET/CT detect N1 nodal involvement in 21 patients (27.3%) and N3 in 13 patients (16.9%). This difference between [<sup>18</sup>F] FDG PET/CT and HN-MRI in N staging was significant with a mediocre degree of concordance (k = 0.3). HN-MRI correctly classified nodal involvement of 71 patients (92%), underestimated nodal involvement of three patients (3.8%), and overestimated nodal involvement of three patients (3.8%), which makes a total of six (7.7 %) misclassified patients (Table 2).

Table 2  
Concordance between HN-MRI and [<sup>18</sup>F] FDG PET/CT in T and N staging

Tumor stage	T MRI	T TEP		Nodal stage	N MRI	N TEP	
T1	6 (7.8%)	8 (10.4%)		N0	10 (13.0%)	8 (10.4%)	
T2	12 (15.6%)	15 (18.2%)	K = 0.459 <i>p</i> = 0.00	N1	18 (23.4%)	21 (27.3%)	K = 0,30 <i>p</i> = 0.00
T3	25 (32.5%)	29 (37.7%)		N2	35 (45.5%)	35 (45.5%)	
T4	34 (44.2%)	25 (33.8%)		N3	14 (18.2%)	13 (16.9%)	

Association analysis between metabolic [<sup>18</sup>F] FDG PET/CT parameters, TNM classes and NPC stage

Overall, the mean T-SUV max of the studied patients was 11.8 (3.30–36.10), the mean N-SUV max was 9.2 (1.50–19.8) and the mean M-SUV max was 7.4 (1.60–21.50). The NTR was also calculated, and showed a mean of 0.82 (0.16 to 1.9). The best cutoffs values for T-SUV max, N-SUV max and NTR were 10.5, 7.9 and 0.82, respectively (Fig. 1). Association analysis between metabolic [<sup>18</sup>F] FDG PET/CT parameters, TNM classes and NPC stage was further performed (Table 3). Our data showed that N-SUV max values were significantly higher in patients with advanced nodal involvement, with a mean of 7.4, 9.7 and 11 for patients with N1, N2, and N3 nodal classes, respectively (*p* = 0.01). However, no significant difference was observed between N-SUV max, tumor size, metastatic status and NPC stage (*p* > 0.05). Similarly, no significant associations were found between [<sup>18</sup>F] FDG PET/CT metabolic parameters (T-SUV max, M-SUV max, NTR), TNM classes and NPC stage (*p* > 0.05).

Table 3

Association analysis between metabolic [<sup>18</sup>F] FDG PET/CT parameters, TNM classes and NPC stage

	T-SUV max			N-SUV max			NTR			M-SUV max		
	N	Mean (range)	p	N	Mean (range)	p	N	Mean (range)	p	N	Mean (range)	p
<b>Tumor extension</b>												
<b>T1</b>	11	10.0(4.2–14.3)	0.03	9	8.6 (4.3–11.7)	0.6	9	0.96 (0.5–1.9)	0.3	4	6.7 (3.0–12.2)	0.1
<b>T2</b>	15	9.4 (5.0–18.1)		14	8.6 (2.9–15.2)		14	0.90 (0.3–1.6)		3	6.5 (4.9–8.6)	
<b>T3</b>	32	11.5 (3.3–25.4)		29	9.1 (1.5–17.8)		29	0.81 (0.1–1.9)		10	5.2 (1.6–13.4)	
<b>T4</b>	41	13.5 (5.8–36.1)		39	10.0 (3.4–32.0)		39	0.76 (0.2–1.7)		14	9.4 (3.8–21.5)	
<b>Nodal involvement</b>												
<b>N0</b>	8	10.9(5.8–13.5)	0.6	-	-	<b>0.01</b>	-	-	0.1	-	-	0.2
<b>N1</b>	26	11.0 (3.3–25.4)		26	7.4 (1.5–16.5)		26	0.75 (0.16–1.91)		4	5.1(1.6–7.8)	
<b>N2</b>	41	12.3(4.3–19.8)		41	9.7 (1.6–15.2)		41	0.82(0.26–1.97)		13	6.8(4.9–12.6)	
<b>N3</b>	24	12.5 (5.1–36.1)		24	11.0 (4.2–32.0)		24	0.91 (0.52–1.47)		14	8.6(1.6–21.5)	
<b>Metastatic status</b>												
<b>M0</b>	63	12.1 (4.2–36.1)	0.5	55	9.1 (1.6–32.0)	0.5	55	0.78(0.26–1.91)	0.1			
<b>M1</b>	36	11.4 (3.3–20.3)		36	9.7 (1.5–19.8)		36	0.88 (0.16–1.97)				
<b>Stage of the disease (NPC stage)</b>												
<b>I</b>	2	11.1(8.7–13.5)	0.2	-	-	0.4	-	-	0.1			

		<b>T-SUV max</b>		<b>N-SUV max</b>		<b>NTR</b>		<b>M-SUV max</b>
<b>II</b>	9	8.3 (4.2– 13.2)	8	7.4 (2.9– 14.2)	8	1.06 (0.32– 1.91)		
<b>III</b>	23	12.3 (4.3– 25.4)	20	9.7 (1.6– 16.5)	20	0.78(0.26– 1.18)		
<b>IV</b>	65	12.2 (3.3– 36.1)	63	9.4 (1.5– 32.0)	63	0.81 (0.16– 1.97)		

#### Radiological prognostic factors related to OS of NPC patients

After a mean follow-up time of 37 months (20–54 mo), 66.3% of patients were alive with mean 4-year OS of 22.7 months. In the present study, the evaluation of radiological and metabolic prognostic factors influencing OS was performed. Our results showed that OS was better in patients with N-SUV max < 7.9 versus  $\geq$  7.9 (mean 38.4 vs. 31.4 mo, respectively; HR, 0.70; 95% CI, 0.48–1.01;  $p = 0.05$ ) and NTR < 0.81 versus  $\geq$  0.81 (mean 40.4 vs. 26.5 mo, respectively; HR, 0.55; 95% CI, 0.38–0.78;  $p = 0.001$ ); suggesting higher N-SUV max and NTR as an independent poor prognostic factors for NPC. However, no association between T-SUV max, parapharyngeal tumor extension, skull base bone tumor invasion, neurologic involvement and OS was observed among NPC patients ( $p > 0.05$ ) (Table 4).

Table 4  
Radiological factors related to OS of NPC patients

OS				Univariate analysis		Multivariate analysis	
		4-year rate (%)	Mean (months)	HR (95% CI)	p	HR (95% CI)	p
<b>T-SUV max</b>	<b>99</b>						
< 10.5	45	59,8%	33.8	1.11 (0.58–2.15)	0.74	-	-
≥ 10.5	54	61.5%	37.1				
<b>N-SUV max</b>	<b>91</b>						
< 7.9	35	70.0%	38.4	0.70 (0.48–1.01)	<b>0.05</b>	0.39 (0.17–0.89)	<b>0.02</b>
≥ 7.9	56	48.9%	31.4				
<b>NTR</b>	<b>91</b>						
< 0.81	47	73.8%	40.4	0.55 (0.38–0.78)	<b>0.001</b>	0.41 (0.18–0.94)	<b>0.03</b>
≥ 0.81	44	38.8%	26.5				
<b>Parapharyngeal involvement</b>	<b>93</b>						
No	12	82.5%	43.8%	0.76 (0.36–1.56)	0.4	-	-
Yes	81	67.0%	40.0%				
<b>Skull base bone invasion</b>	<b>93</b>						
No	40	71.4%	42.3	0.88 (0.59–1.30)	0.5	-	-
Yes	53	67.1%	38.9				
<b>Neurologic involvement</b>	<b>93</b>						
No	58	67.5%	40.9	0.96 (0.65–1.43)	0.8	-	-
Yes	35	70.6%	39.5				

Radiological prognostic factors related to LRRFS of NPC patients

Univariate analysis showed that LRRFS was not significantly affected by T-SUV max, N-SUV max, NTR and neurologic involvement with HRs of 0.97 (95% CI: 0.42–2.26;  $p = 0.9$ ), 0.45 (95% CI: 0.17–1.18;  $p = 0.1$ ), and 0.71 (95% CI: 0.30–1.70;  $p = 0.4$ ), respectively. Similarly, our results revealed that patients without parapharyngeal tumor extension, skull base bone tumor invasion and neurologic involvement have better LRRFS with a trend of significance, compared to those with parapharyngeal tumor extension, bone tumor

invasion and neurologic involvement: mean 43.4 vs. 40.5 mo, and an HR of 0.60 (95% CI, 0.13–2.61;  $p = 0.4$ ), mean 44.6 vs. 38.6 mo and an HR of 0.51 (95% CI, 0.20–1.28;  $p = 0.1$ ) and mean 41.4 vs. 40.6 mo and an HR of 0.95 (95% CI: 0.39–2.31;  $p = 0.9$ ), respectively (Table 5).

Table 5  
Radiological factors related to LRRFS of NPC patients

	LRRFS				
	N	4-year rate (%)	Mean (months)	Univariate Analysis	
				HR(95% CI)	p
<b>T-SUV max</b>	<b>99</b>				
< 10.5	45	67.4%	39.1	0.97 (0.42–2.26)	0.9
≥ 10.5	54	54.8%	40.7		
<b>N-SUV max</b>	<b>91</b>				
< 7.9	35	75.9%	42.7	0.45 (0.17–1.18)	0.1
≥7.9	56	51.0%	37.3		
<b>NTR</b>	<b>91</b>				
< 0.81	47	69.0%	39.8	0.71 (0.30–1.70)	0.4
≥ 0.81	44	51.1%	38.6		
<b>Parapharyngeal involvement</b>	<b>93</b>				
No	12	76.2%	43.4	0.60 (0.13–2.61)	0.4
Yes	81	56.5%	40.5		
<b>Skull base bone invasion</b>	<b>93</b>				
No	40	68.5%	44.6	0.51 (0.20–1.28)	0.1
Yes	53	59.8%	38.6		
<b>Neurologic involvement</b>	<b>93</b>				
No	58	68.3%	41.4	0.95 (0.39–2.31)	0.9
Yes	35	47.1%	40.6		

#### Radiological prognostic factors related to PFS of NPC patients

Univariate analysis showed that PFS was significantly shorter among patients with high N-SUVmax (mean 31.0 vs. 21.4 mo; HR, 0.52; 95% CI, 0.29–0.93;  $p = 0.02$ ) and high NTR (mean 30.4 vs. 18.7 mo; HR, 0.46; 95% CI, 0.27–0.79;  $p = 0.003$ ). T- SUVmax, parapharyngeal tumor extension and neurologic involvement were not found to represent a significant prognostic factor for PFS in NPC ( $p = 0.7$ ,  $p = 0.3$  and  $p = 0.2$ , respectively). Of note, a trend of decreased PFS time and rates was observed in patients with skull base bone tumor invasion

compared to patients with limited tumor (38.0% vs. 51.7%; 27.6 vs 36.3 mo; HR, 0.54; 95% CI, 0.29–1.02;  $p=0.05$ ) (Table 6).

Table 6  
Radiological factors related to PFS of NPC patients

PFS							
	N	4-year rate (%)	Mean (months)	Univariate analysis		Multivariate analysis	
				HR (95% CI)	p	HR (95% CI)	p
<b>T-SUV max</b>	<b>99</b>						
< 10.5	45	39.8%	26.6	0.93 (0.55–1.57)	0.7	-	-
≥ 10.5	54	29.9%	26.4				
<b>N-SUV max</b>	<b>91</b>						
< 7.9	35	47.8%	31.0	0.52 (0.29–0.93)	<b>0.02</b>	0.46 (0.23–0.90)	<b>0.04</b>
≥ 7.9	56	23.2%	21.4				
<b>NTR</b>	<b>91</b>						
< 0.81	47	46.0%	30.4	0.46 (0.27–0.79)	<b>0.003</b>	0.50 (0.28–0.89)	<b>0.01</b>
≥ 0.81	44	18.1%	18.7				
<b>Parapharyngeal involvement</b>	<b>93</b>						
No	12	63.5%	36.6	0.60 (0.21–1.68)	0.3	-	-
Yes	81	37.6%	30.2				
<b>Skull base bone invasion</b>	<b>93</b>						
No	40	51.7%	36.3	0.54 (0.29–1.02)	<b>0.05</b>	0.18 (0.07–0.50)	<b>0.001</b>
Yes	53	38.0%	27.6				
<b>Neurologic involvement</b>	<b>93</b>						
No	58	49.3%	33.2	0.69 (0.38–1.25)	0.2	-	-
Yes	35	29.3%	27.6				

#### Multivariate Analysis for PFS and OS

Only significant prognostic factors identified in univariate analysis for OS and PFS were assessed in the multivariate analysis (Tables 4 and 5). Among all the radiological and metabolic factors studied, we identified

N-SUV max and NTR as independent prognostic factors for both OS and PFS ( $p < 0.05$ ), and skull base bone invasion as independent prognostic factor for PFS in patients with NPC ( $p = 0.001$ ).

## Discussion

International recommendation demonstrates that when MRI and [ $^{18}\text{F}$ ] FDG PET/CT are available, the other imaging modalities are optional in NPC staging (Ng et al. 2009; Hung et al. 2020). However, in view of the limited access to HN-MRI and [ $^{18}\text{F}$ ] FDG PET/CT, the conventional imaging diagnosis workup remains widely used in the clinical management of Moroccan patients with NPC. A diagnostic strategy based on the combination of HN-MRI and [ $^{18}\text{F}$ ] FDG PET/CT was employed for NPC patients recruited between January 2017 and December 2018 in Mohammed VI Center for Cancer Treatment of Casablanca, and features extracted from these both imaging modalities were investigated to highlight the overall diagnostic and prognostic values of metabolic and radiological combination.

Epidemiologic and clinical characteristics of the 117 NPC patients enrolled in the present study clearly highlight the urgent need of an effective diagnostic and therapeutic strategy. In fact, our results showed that 82.1% of patients were diagnosed with positive lymph nodal, including 52 patients with N2 (44.4%) and 25.6 patients with N3 (21.4%) involvement, suggesting a high risk of distant metastasis and probable low survival rates among these patients. In fact, a significant association has been reported between N2 and N3 involvement and a higher risk of distant failure after treatment ( $p < 0.001$ ) (Mak et al. 2015; Pastor et al. 2018). Moreover, Lee and al. have demonstrated that patients at advanced stage of NPC (T3, T4 and N2, N3) have less than 5 years' survival rate (65%), as compared to patients at an early stage of the disease (85%) (Lee et al. 2005). In NPC, management of distant metastasis is always a challenge. In a meta-analysis enrolling 1774 patients with NPC, [ $^{18}\text{F}$ ] FDG PET/CT was found to be more efficient than the conventional workup for the detection of distant metastases in patients with NPC (Xu et al. 2017). In the present study, the use of [ $^{18}\text{F}$ ] FDG PET/CT in the definition of patients with distant metastasis showed that 31.6% of patients present distant metastasis at diagnosis. Furthermore, despite the aggressive regimen used for the treatment of these patients diagnosed with distant metastasis, the mean survival time didn't exceed 14.4 months (Li et al. 2015). To limit cancer progression and metastasis development, there's an urgent need to set up an early diagnosis and therapeutic strategy to allow a better loco-regional control, prevent the extent of distant metastasis and improve survival rate of NPC patients.

Findings agreed that HN-MRI is preferred over CT and [ $^{18}\text{F}$ ] FDG PET/CT in the evaluation of loco-regional extension of NPC (T), before and during treatment, and in post-treatment surveillance (Mohandas et al. 2014; Li et al. 2015; Hung et al. 2020). Recently, NPC management was improved by the implementation of [ $^{18}\text{F}$ ] FDG PET/CT and derived biological parameters, which were of great help in the initial diagnosis of NPC, the evaluation of clinical response and especially the monitoring of NPC metastasis disease (Wu et al. 2016; Meng et al. 2020). Accordingly, we have tried in this study to highlight the diagnostic and prognostic values of HN-MRI and [ $^{18}\text{F}$ ] FDG PET/CT in Moroccan patients with NPC.

Our data showed significant discrepancies between [ $^{18}\text{F}$ ] FDG PET/CT and HN-MRI findings in the staging of both tumor extension and nodal involvement. Even both [ $^{18}\text{F}$ ] FDG PET/CT and HN-MRI detect the presence of

primary tumors in all patients, considering the HN-MRI as the gold standard for T classification; [<sup>18</sup>F] FDG PET/CT correctly classified 59 patients (76%), underestimated 9 patients (11.6 %) and overestimated 9 patients (11.6%), making a total of 23% of misclassified patients. Hence, the Cohen kappa coefficient showed moderate concordance between [<sup>18</sup>F] FDG PET/CT and HN-MRI in T staging ( $r = 0.45$ ). These results are in agreement with previously reported data indicating that HN-MRI is more sensitive and specific than CT and [<sup>18</sup>F] FDG PET/CT in mapping the parapharyngeal space involvement, bone marrow involvement, paranasal sinuses and intracranial extension (King et al. 2008; Li et al. 2019). In this study, a low Cohen kappa coefficient ( $k = 0.3$ ) was obtained for nodal staging, suggesting a mediocre concordance between [<sup>18</sup>F] FDG PET/CT and HN-MRI in nodal assessment. However, no discordance was seen between HN-MRI and [<sup>18</sup>F] FDG PET/CT for N2 staging; and HN-MRI didn't detect cervical nodal metastasis in 2 patients and downstage 3 patients (N1 category). These results are consistent with previous studies reporting that both techniques present high specificity (73–97%), but [<sup>18</sup>F] FDG PET/CT has a higher sensitivity (97–100%) in the detection of nodes involvement compared to HN-MRI (84–92%) (Mohandas et al. 2014). Nevertheless, Ou et al. reported that retropharyngeal lymph nodes are identified more easily by HN-MRI compared to [<sup>18</sup>F] FDG PET/CT, due to the effect of blooming artifact in [<sup>18</sup>F] FDG PET/CT that may result in difficulties in differentiating a primary nasopharyngeal tumor burden from a retropharyngeal node. More precaution in the analysis of retropharyngeal nodes areas by the [<sup>18</sup>F] FDG PET/CT is therefore required (Ou et al. 2014). Globally, our data suggest a good complementarity between HN-MRI and [<sup>18</sup>F] FDG PET/CT for better management of NPC. In this field, it has been established that the use of HN-MRI and [<sup>18</sup>F] FDG PET/CT in initial NPC diagnostic allows a more precise clinical staging of patients, which could improve treatment strategies and contribute to increase significantly patient survival (Ou et al. 2014; Meng et al. 2020).

Accumulating data indicate the promising role of metabolic parameters derived from pre-treatment [<sup>18</sup>F] FDG PET/CT as a useful prognostic radiological biomarker. In the present prospective study, pretreatment [<sup>18</sup>F] FDG PET/CT metabolic parameters (T-SUV max, N- SUV max, and NTR) and HN-MRI tumor invasion were evaluated as predictor biomarkers of OS, LRRFS and PFS.

Scientific evidence suggested that bone invasion and intracranial involvement are strongly related to distant metastasis occurrence and poor survival in NPC (Cheng et al. 2005; Fei et al. 2019). Moreover, the relationship between parapharyngeal space involvement and the occurrence of metastasis is still controversial (Cheng et al. 2005; Mo et al. 2012). Our results with regards to the relationship between nasopharyngeal tumor invasion defined by HN-MRI (Parapharyngeal involvement, bone invasion and intracranial involvement) and survival outcomes showed that skull base bone invasion are an independent prognostic factor for PFS in patients with NPC ( $p = 0.001$ ). Homogenizing the definition of the parapharyngeal space and including a large cohort of patients are needed to confirm this finding.

Overall, the mean T-SUV max, N-SUV max, M-SUV max, and NTR were 11.8, 9.2, 7.4 and 0.82, respectively. Assessing the association between metabolic [<sup>18</sup>F] FDG PET/CT parameters, TNM classes and NPC stage, our results revealed that T-SUV max, M-SUV max and NTR were not associated to TNM classes and stage of NPC ( $p > 0.05$ ). These findings are contrary to previous studies, reporting a strong link between metabolic [<sup>18</sup>F] FDG

PET/CT parameters, tumor aggressiveness and patient's survival outcomes (Teo et al. 1996; Schulte et al. 1999; Allal et al. 2002; Xie et al. 2010). Thus, a study on a larger cohort is needed to confirm this finding.

Moreover, our finding showed no significant differences in 4-years OS, LRRFS and PFS of patients with low or high T-SUV max ( $p > 0.05$ ). According to our results univariate analysis demonstrated that T-SUV max can't be a prognostic metabolic marker for NPC. Though Xie et al. showed that patients with lower T-SUV max, have a significantly better 5-year OS and DFS (Xie et al. 2010). This could be due to the short follow-up period. Several studies suggest that N-SUV max is more important than T-SUV max for prediction of DMFS in NPC patients (Lin et al. 2016) (Türkölmez et al. 2017; Jeong et al. 2017). In another study, Chen et al. reported that a high N-SUV max on pretreatment [ $^{18}\text{F}$ ] FDG PET/CT ( $> 7.75$ ) was an independent prognostic factor for worse DMFS in NPC patients (Chen et al. 2015). Furthermore, Türkölmez et al. demonstrated that high T-SUV max and N-SUV max were related to death risk (Türkölmez et al. 2017). Similarly, our results reported that high N-SUV max ( $> 9.4$ ) was significantly associated with poor OS and PFS, with HR of 0.7 (95% CI, 0.48–1.01;  $p = 0.05$ ) and 0.52 (95% CI, 0.29–0.93;  $p = 0.02$ ) for OS and PFS, respectively. In addition, recent evidences have demonstrated that the NTR has a strong correlation with clinical outcomes for lung, esophageal and cervical cancers (Cirak 2011; Chen et al. 2015; Chung et al. 2017). For NPC, the only published study investigating the prognostic value of NTR found that high NTR ( $> 0.9181$ ) could help in risk stratification of patients to identify those at higher risk of distant metastasis ( $p < 0.001$ ) (Hung et al. 2020). In the same line, we observed that NTR was high in patients with distant metastasis (0.90) compared to those without distant metastasis (0.78). Interestingly, multivariate analysis highlights NTR as a strong predictor of 4-years OS and PFS, with HR of 0.41 (95% CI, 0.18–0.94;  $p = 0.03$ ) for OS, and 0.5 (95% CI, 0.28–0.89;  $p = 0.01$ ) for PFS. Further research is however needed to investigate the clinical application modality of [ $^{18}\text{F}$ ] FDG PET/CT metabolic parameters in the management of NPC. Currently, the clinical usefulness of hybrid PET/MRI in clinical practice is debated. This modality seems to be a promising tool in terms of increasing the resilience of the radiological images and reducing the diagnostic time of head and neck cancers and many other cancers (Becker and Zaidi 2014; Chen et al. 2020).

## Conclusions

Our findings clearly provide additional evidence on the complementary roles of HN-MRI and [ $^{18}\text{F}$ ] FDG PET/CT in TNM and overall staging of NPC. To the best of our knowledge, this is the first Moroccan study to highlight N-SUV max and NTR derived from [ $^{18}\text{F}$ ] FDG PET/CT and Skull base bone invasion defined by HN-MRI as promising metabolic and radiologic biomarkers for NPC prognosis. The present results could be a good basis for future studies confirming the need to introduce these two imaging modalities in the standard management of NPC and the others cancer in Morocco.

## Declarations

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### **Ethical Approval**

The study protocol was approved by the Ethics Committee of Ibn Rochd Hospital of Casablanca, Morocco and written informed consent was obtained from each patient. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee on human experimentation and with the Helsinki declaration of 1975, as revised in 1983.

## Informed Consent

Informed consent was obtained from all individual participants included in the study

## Availability of data and material

The prospective data that support the findings of this study are available from the corresponding author upon reasonable request.

## Conflict of interest statement

The authors declare that they have no competing interests.

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## Figures

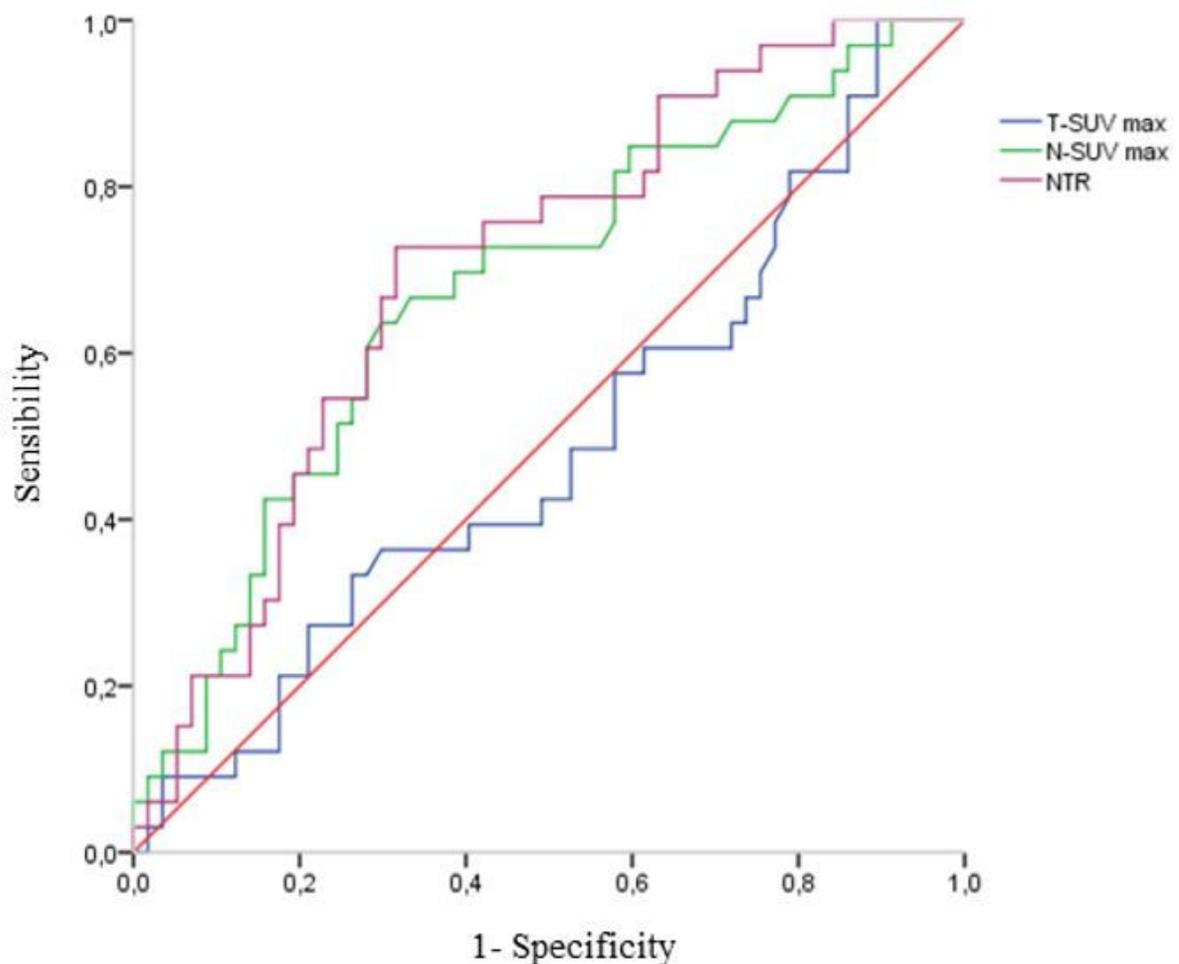


Figure 1

Time-dependent receiver operating characteristic curve analysis of OS prediction based on the T-SUV max, N-SUV max and NTR in patients with NPC. The area under the curve was 0.48 ( $p < 0.36$ , 95% CI 0.36–0.61), and 10.5 was determined as the best T-SUV max cutoff value for survival prediction. The area under the curve was 0.67 ( $p < 0.05$ , 95% CI 0.56–0.79), and 7.9 was determined as the best N-SUV max cutoff value for survival prediction. The area under the curve was 0.70 ( $p < 0.001$ , 95% CI 0.59–0.81), and 0.82 was determined as the best NTR cutoff value for survival prediction.