RESEARCH ARTICLE

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Predictors for Disease-Free and Progression-Free Survivals in Metabolic Responders and Non-Responder on Follow-Up ^{18}FDG PET/CT after Chemoradiation in Patients With Nasopharyngeal Cancer

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Abstract

Objective: To determine disease free survival (DFS) and progression free survival (PFS) and their predictors in patients with nasopharyngeal cancer (NPC) having achieved complete (CMR) and partial metabolic response (PMR) on post-chemoradiation (CRT) ^{18}FDG PET/CT. **Materials and Methods:** Retro-prospective study conducted at PET/CT Section of JCIA accredited healthcare facility of Pakistan. Total 73 patients of NPC patients who had baseline and post-CRT ^{18}FDG PET/CT were included and prospectively followed till predefined study end points of recurrence or disease progression or death from April-2016 till January 2024. Based on CMR on post-CRT ^{18}FDG PET/CT, 45 patients labelled as responders while 28 with PMR as non-responders. Using logistic regression and ROC analysis, the predictors of recurrence and disease progression were analyzed in both groups. Kaplan Meier's survival plots were analyzed to measure DFS in responders and PFS in non-responders respectively. **Results:** Body mass index (BMI), SUV_{max} and Stage-IV disease were found significantly higher in non-responder group. DFS in responders was significantly higher than PFS in non-responder (60.157 month ± 8.047 Vs 8.145 months ± 1.851). DFS was seen in 84% of responder group with 16% recurrence (7/45). Baseline SUV_{max} >14.2 and primary tumor size (PTS) > 41 mm were found significant predictors of recurrence in responder group. In the non-responder group, the PFS was found in 54% patients while 46% patients (n=13/28; 2 expired) had disease progression. No significant predictor was found for PFS in the non-responder group. In DFS the mean survival was significantly higher in patients with SUV_{max} ≤14.2 versus >14.2 (Mean Survival 67.390 vs. 38.283 months; Logrank 9.899; p=0.0017*). However, near significant difference was observed in non-responder group in their PFS at SUV_{max} ≤11.9 vs. >11.9 (Mean Survival 10.00 vs. 7.05 months; Logrank=3.096; p=0.0798). Conclusion: ^{18}FDG PET/CT scan precisely stratifies the treated NPC patients into responders having longer DFS and non-responders having shorter PFS. Higher BMI, SUV_{max} of primary tumor and metastatic disease were found to have significant association in non-responders. In responders, PTS >41 mm and its SUV_{max} >14.2 were found significant predictors of recurrence. In non-responders, SUV_{max} >11.9 was found to have near significant association with disease progression.

Keywords: Nasopharynx cancer- PET/CT- recurrence- disease free survival-predictor- progression free survival

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Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer with a distinct geographical distribution that is particularly prevalent in South China, Southeastern Asia, and North Africa [1]. Intensity modulated radiotherapy with or without chemotherapy (depending upon stage stage) has resulted in excellent disease control. According to American cancer society, 5 years survival rate for patients with localized disease is 80% and for those with advance disease is 49% [2]. ^{18}-Flouro-DeoxyGlucose (18FDG) positron emission tomography with computerized tomography (PET/CT) has significantly higher diagnostic accuracy especially in N and M staging than conventional imaging [3]. Since precise staging guides about treatment strategy and prognosis, ^{18}FDG PET/CT has grown to have an indispensable role in NPC management. Prognostic factors for treatment outcomes in NPC are age, physical status, stage, gross tumor volume (GTV) and Ebstein-Barr Virus (EBV) DNA level [4]. Some studies have also explored ^{18}FDG PET/CT based parameters like maximal standardized uptake value (SUV_{max}), metabolic

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tumor volume (MTV), and total lesion glycolysis (TLG) with variable results [3].

In this study we used non-imaging and baseline ^{18}FDG PET/CT based metabolic parameters to determine disease free survival (DFS) and progression free survival (PFS) and their predictors in patients having achieved complete (CMR) and partial metabolic response (PMR) on post-chemoradiation (CRT) ^{18}FDG PET/CT.

Materials and Methods

This was a retro-prospective study conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital (AKUH), Karachi, Pakistan. The study was duly approved by the ethical review committee of AKUH (ERC#: 2021-6294-17851). We included patients with biopsy proven nasopharyngeal cancer who had had baseline ^{18}FDG PET/CT for staging and/or radiation planning and post-chemoradiation study for metabolic response assessment. On post-CRT ^{18}FDG PET/CT, patients who had a complete metabolic response (CMR) were labelled as responders while those with partial metabolic response (PMR) were labelled as non-responders. These patients were prospectively followed from April 2016 till January 2024 till the occurrence of predefined study end points like recurrence, disease progression or death. By using logistic regression and receiver operating characteristic (ROC) curve analyses, the predictors of recurrence and disease progression were analyzed in both responder and non-responder groups. Kaplan Meier's survival plots were analyzed to measure disease free survival (DFS) in metabolic responders and progression free survival (PFS) in metabolic non-responders respectively.

^{18}FDG PET/CT Imaging: ^{18}FDG PET/CT was performed as per institutional protocol adopted from European Association of Nuclear Medicine (EANM) guidelines [5]. All patients had at least 6 hour fasting (only plain water was allowed) and a fasting blood sugar less than 200 mg% before receiving an intravenous 18FDG dose of 3 MBq/Kg in the uptake room. During the uptake period (mean: 55 -75 minute) patients were requested to lie comfortably and allowed to take about 500-1000 ml of plain water. Bladder was emptied prior to call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low dose CT examination (mid brain to mid-thigh) followed by acquisition of PET imaging using 3 minute/bed position from mid-thigh to head in all patients. Follow-up scans were performed with same protocols, keeping 18FDG dose, uptake time and hepatic SUVmean of baseline and follow-up studies within ± 10%, ± 15% and 20% minutes respectively as per published recommendations [6]. On follow-up scan, CMR was defined as no or minimal ^{18}FDG uptake ≤ background over all tumor sites. While PMR was defined as 18FDG uptake > background over primary and or site of nodal and distant metastasis.

Statistical Analysis: Comparisons between metabolic responder and non-responder groups were performed using Student's t test for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean ± standard deviation (SD). The logistic regression analysis was performed to calculate the odd ratio and coefficient in estimation of significant predictors of recurrence in responder and disease progression in non-responder group respectively. The area under the curve (AUC) and specific criterion (cut off values) for various predictors for recurrence and disease progression in both groups were also calculated by ROC curve analysis. Kaplan Meier's survival plots were analyzed to measure disease free survival (DFS) in responders and progression free survival (PFS) in non-responders respectively. Statistical significance was defined as $P<0.05$. Commercially available packages Microsoft excel 2010, Medcalc® 2024 version 22.019 and statistical package for social sciences (SPSS 19®) were used.

Results

Total 73 patients with biopsy proven NPC were included and based on post-treatment ^{18}FDG PET/CT, 45 patients were labelled as responders due to achievement of CMR. While 28 patients were labelled as non-responders due to PMR found on post-treatment ^{18}FDG PET/CT. No significant difference was found between responder and no-responder groups for age, gender, primary tumor size, regional nodal involvement (Table 1). However, body mass index (BMI), SUV_{max} of primary tumor, Stage-IV disease with extra nodal, hepatic, adrenal and bony metastases were found significantly higher in non-responder group (Table 1). EBV test was available in limited patients (n=16) and found significantly high positivity in responder group. DFS in responders was significantly higher than PFS in non-responder (60.157 month ± 8.047 Vs 8.145 months ± 1.851). On follow-up, DFS was seen in 84% of responder group with 16% recurrence (7/45). Baseline SUV_{max} >14.2 and primary tumor size > 41 mm were found significant predictors of recurrence in responder group using ROC ($p<0.05$; Table 2). In the non-responder group, the PFS was found in 54% patients while 46% patients (n=13/28; 2 expired) had disease progression. No significant predictor was found for PFS in the non-responder group (Table 3). Based on ROC derived cut-off values of SUV_{max} for DFS and PFS in both groups, the Kaplan Meier survival curves were compared. In DFS the mean survival was significantly higher in patients with SUV_{max} ≤14.2 versus >14.2 (Mean Survival 67.390 vs. 38.283 months; Logrank 9.899; p=0.0017*; Figure 1). However, near significant difference was observed in non-responder group in their PFS at SUV_{max} cut-off value ≤11.9 vs. >11.9 (Mean Survival 10.00 vs. 7.05 months; Logrank=3.096; p=0.0798; Figure 2).

Discussion

In this study 62% (45/73) of patients achieved CMR while 38% (28/73) had PMR on post-CRT ^{18}FDG PET/CT. This treatment outcome is lower than a recently published study from United Kingdom which revealed a CMR in 87% and PMR in 13% participants [7]. The plausible explanation is likely an aggressive treatment protocol (65 Gy in 30 fractions ± weekly cisplatin). In

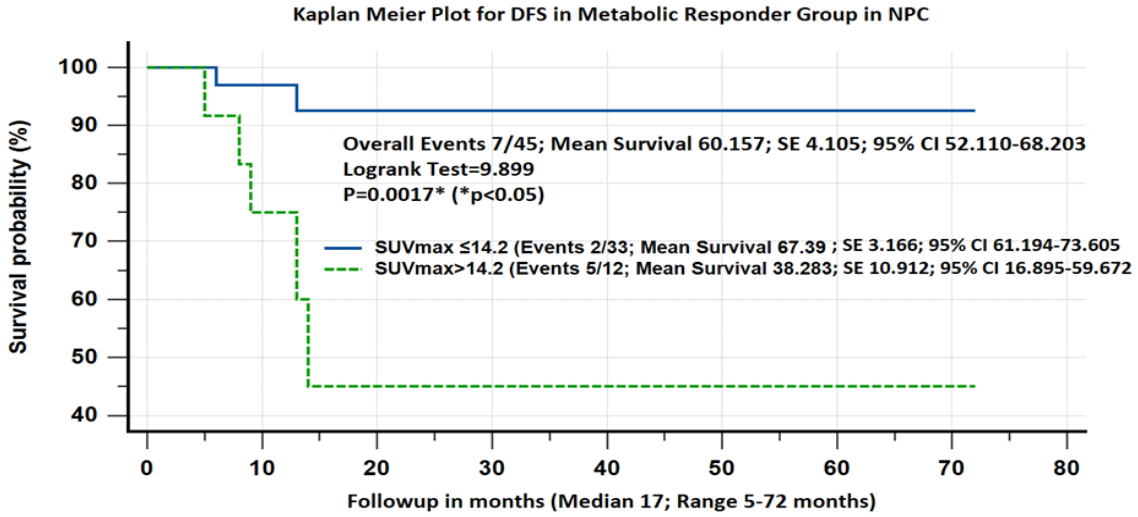

Figure 1. Kaplan Meier Plot for Disease Free Survival in Responder Group of Nasopharyngeal Cancer Patients Using ROC Derived Cut off Value of SUV_{max} >14.2. SE, Standard Error; CI, Confidence Interval; *p<0.05

this study, non-responders found to have significantly higher SUV_{max} of primary tumor, BMI, stage IV disease with nodal, hepatic, adrenal and bony metastasis. It is a well-known fact that SUV_{max} on ^{18}FDG PET/CT is an indicator of density of tumor cells and rate of glucose metabolism in tumor [8]. Studies have also shown that NPC patients with higher SUV_{max} have poor prognosis [9]. Reported incidence of stage-IV disease with distance metastasis in NPC at initial diagnosis is about 5-8% and is associated with significantly lower overall survival (for liver metastasis: 3-5 months) [10]. Longer DFS in responders and short PFS in our cohort are in accordance

Table 1. Patients' Demographic Comparison of Metabolic Responders and Non-Responders based on FDG PET/CT Following Chemoradiation Therapy in Nasopharyngeal Cancer Patients

Variables N=73	Responders (n=45)	Non-Responders (n=28)	X^2 or t-test values	p value
Age in years	48 (13-76)	49 (23-84)	1.088	0.2802
Median (range)				
Gender (Male: Female)	29: 16 (64% v: 36%)	23: 05 (82% v: 18%)	2.674	0.102
BMI (Kg/m^2) Mean ± SD	24.684 ± 6.183	27.688 ± 6.355	1.997	0.0496*
EBV (positive /test done)	7/10 (70%)	2/6 (33%)	0.945	0.0021*
Primary tumor SUVmax	12.2 ± 5.8	14.8 ± 4.5	2.022	0.0047*
Mean ± SD; Median (range)	10.6 (4.4-26.8)	14.2 (6.9-26.2)		
Primary Tumor size in mm	42 ± 17 (10-87 mm)	36 ± 17 (12-70 mm)	-1.466	0.147
Mean ± SD (range)				
Regional nodal involvement	38 (84%)	27 (96%)	2.482	0.1192
Stage IV	08 (18%)	15 (54%)	10.172	0.0014*
Distant involvement				
Extra cervical nodal	03 (07%)	07 (25%)	4.608	0.0318*
Pulmonary	01 (02%)	02 (07%)	1.131	0.2876
Hepatic	01 (02%)	05 (18%)	5.83	0.0158*
Bone	05 (11%)	13 (46%)	11.298	0.0008*
Intracranial extension	01 (02%)	01 (04%)	0.253	0.6149
Adrenal	00 (00%)	03 (11%)	5.097	0.0240*
% Survival function	DFS 84%	PFS 54%	-33.571	<0.0001*
(Events)	(Events 07/45)	(Events 13/28)		
Mean; SE	Mean 60.157;	Mean 8.145;		
(95% CI)	SE 4.105	SE 0.944		
	(52.110-68.203)	(6.294-9.996)		

*p <0.05; SD, Standard deviation ; BMI, Body mass index; DFS, Disease Free Survival; PFS, Progression Free Survival; SE, Standard Error ; CI, Confidence Interval

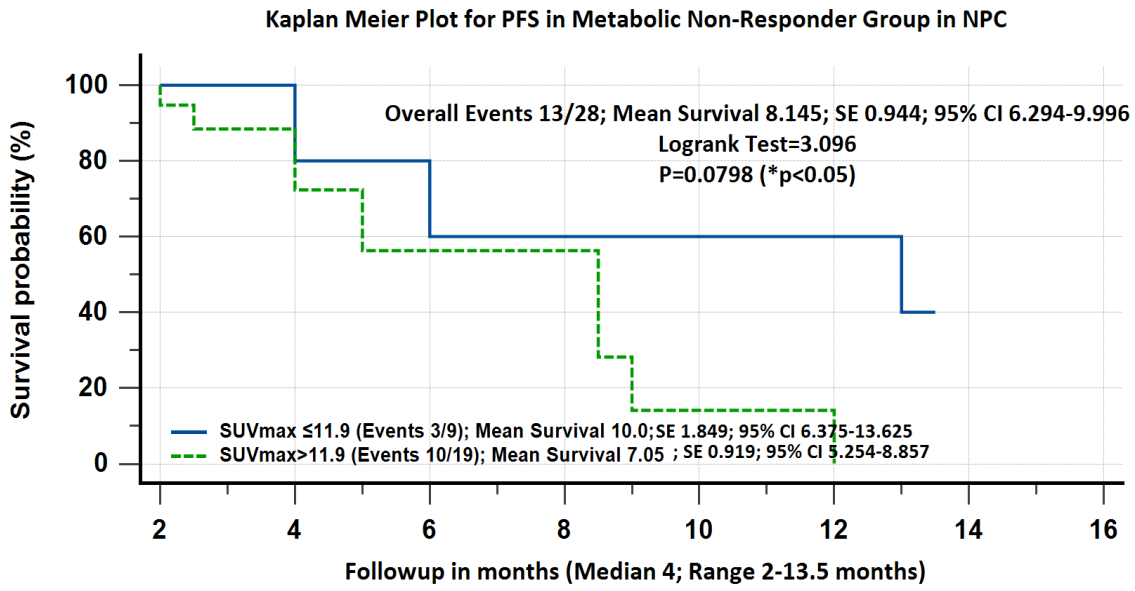

Figure 2. Kaplan Meier Plot for Progression Free Survival in Non-Responder Group of Nasopharyngeal Cancer Patients Using ROC Derived Cut off Value of SUV_{max} >11.9. SE, Standard Error; CI, Confidence Interval; *p<0.05

Table 2. Logistic Regression and Receiver Operating Characteristics Analyses of Variables on Baseline ^{18}FDG PET/CT in Responder Group of Nasopharyngeal Cancer Patients in Prediction of Recurrence.

Test Variables	Coefficient	SE		95% Confidence Interval		Wald	AUC	P value
			Odd Ratio	lower limits	upper Limits	(*p<0.05)	Specific Criterion	
Age (years)	0.046	0.029	1.048	0.989	1.109	2.5277	0.635 (>60)	0.301
BMI (kg/m^2)	-0.123	0.104	0.884	0.722	1.083	1.41	0.568 (≤23.510)	0.63
SUV_{max}	0.18	0.102	1.198	0.981	1.463	3.126	0.737 (>14.2)	0.054*
PTS (mm)	0.037	0.037≤	1.038	0.965	1.116	1.007	0.72 (>41)	0.016*

SE=Standard Error; BMI, Body Mass Index; SUV_{max}, Maximum Standardized Uptake Value; PTS, Primary Tumor Size; AUC, Area Under Curve; *p<0.05

with published studies. Study by Xie et al. [11] has shown that 5-year OS and DFS were 74% and 65%, respectively, in patients with CMR and 46% and 38% in patients with PMR (p = 0.027 and p = 0.018) [11].

In this study, SUV_{max} of primary tumor > 14.2 in responders found to be a significant predictor of disease recurrence. In non-responders, SUV_{max} >11.9 was found to have near significant association with disease progression.

Table 3. Logistic Regression and Receiver Operating Characteristic Analyses of Variables on Baseline ^{18}FDG PET/CT in Nasopharyngeal Cancer Patients in Prediction of Non-Responders.

Test Variables (n=28)	Coefficient	SE	Odd Ratio	95% Confidence Interval		Wald (*p<0.05)	AUC Specific Criterion	P value
				lower limits	upper Limits			
Age (years)	-0.008	0.033	0.979	0.93	1.058	0.057	0.508 (>57)	0.946
BMI (kg/m^2)	0.083	0.076	1.087	0.937	1.262	0.272	0.631 (>23.424)	0.233
SUV_{max}	0.02	0.094	1.201	0.848	1.228	0.047	0.531 (>11.9)	0.789
PTS (mm)	-0.039	0.028	0.961	0.911	1.015	0.155	0.677 (≤43)	0.098

SE, Standard Error; SUV_{max}, Maximum Standardized Uptake Value; BMI, Body Mass Index; PTS, Primary Tumor Size; AUC, Area Under Curve; *p<0.05

This finding is in accordance with a large cohort study which found that $SUV_{max} \geq 9.3$ of the primary tumor was associated with lower 5-year distant metastases–free survival (DMFS) and OS than those with tumor below the cut-off [12]. Higher BMI was found to have a significant association with disease progression in non-responder than responders. Studies have shown that adiposity in overweight and obese patients has been linked to increased circulating levels of insulin and insulin-like growth factor-1, which promote cell proliferation and inhibit apoptosis in NPC [13]. In our study, male gender was predominant and non-significantly higher in proportion in non-responder group. It is traditionally considered that female gender is a protective factor in patients with NPC. According to study published in 2012, favorable prognosis of female patients with NPC is not only attributed to the early diagnosis and treatment but might also be attributed to some intrinsic factors of female patients [14]. Stage-IV disease has also been found a predictor of non-responder group. Reported incidence of distant metastasis in NPC is about 5-8% [9] with negative impact on survival depending upon site involved but shortest median survival of 18 months for liver metastasis [15]. EBV tests were available in limited patients and found to have significant positivity in responder than non-responder group.

Our study has few limitations. First, patients were recruited retrospectively from a single center hence prone to selection bias. Second, our sample size was small which could be due to relatively lower incidence of NPC in our non-endemic region. Third, we could not show a meaningful correlation between EBV and disease outcome as it was available in only few patients. However, we would like to mention that strict adherence to standardized imaging protocol for follow-up studies is an undeniable strength of this study.

^{18}FDG PET/CT has an important role in the diagnosis and management of NPC. It can precisely stratify the treated patients into responders having longer DFS and non-responders having shorter PFS. Higher BMI, SUV_{max} of primary tumor and metastatic disease were found to have significant association in non-responders. In responders, PTS >41 mm and its SUV_{max} >14.2 were found significant predictors of recurrence. In non-responders, SUV_{max} >11.9 was found to have near significant association with disease progression.

Author Contribution Statement

Nosheen Fatima: Interpretation, Statistics, drafting, final approval. Areeba Zaman: Conception, Design, Critical revision. Sara M Azam: Literature search, data collection. Sidra Zaman: Literature search, drafting, critical revision. Wajiha Shahid: Literature search, drafting, critical revision. Maseeh uz Zaman: Conception, interpretation, critical revision, final approval

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Ethical Approval

This study was approved by ethical review committee of Aga Khan University Hospital via ERC#: 2021-6294-17851.

Conflict of Interest

There is no financial or institutional conflict of interest.

References

1. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet. 2019;394(10192):64-80. https://doi.org/10.1016/s0140-6736(19)30956-0.
2. American cancer society. Survival Rates for Nasopharyngeal Cancer. Available from: Https://www.Cancer.Org/cancer/types/nasopharyngeal-cancer/detection-diagnosis-staging/survival-rates.Html (visited on 30.1.2024).
3. Mohandas A, Marcus C, Kang H, Truong MT, Subramaniam RM. Fdg pet/ct in the management of nasopharyngeal carcinoma. AJR Am J Roentgenol. 2014;203(2):W146-57. https://doi.org/10.2214/ajr.13.12420.
4. Sun XS, Liang YJ, Jia GD, Liu SL, Liu LT, Guo SS, et al. Establishment of a prognostic nomogram to identify optimal candidates for local treatment among patients with local recurrent nasopharyngeal carcinoma. Oral Oncol. 2020;106:104711. https://doi.org/10.1016/j.oraloncology.2020.104711.
5. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. Fdg pet/ct: Eanm procedure guidelines for tumour imaging: Version 2.0. Eur J Nucl Med Mol Imaging. 2015;42(2):328-54. https://doi.org/10.1007/s00259-014-2961-x.
6. Boellaard R. Need for standardization of 18f-fdg pet/ct for treatment response assessments. J Nucl Med. 2011;52 Suppl 2:93s-100s. https://doi.org/10.2967/jnumed.110.085662.
7. Iqbal MS, Tin A, Mian A, Ali A, O'Hara J, Kovarik J, et al. Survival outcomes for patients with nasopharyngeal carcinoma in non-endemic region in the uk treated with intensity modulated based radiotherapy 65 gy in 30 fractions ± weekly cisplatin chemotherapy. Rep Pract Oncol Radiother. 2022;27(3):401-9. https://doi.org/10.5603/RPOR.a2022.0062.
8. Huang SC. Anatomy of suv. Standardized uptake value. Nucl Med Biol. 2000;27(7):643-6. https://doi.org/10.1016/s0969-8051(00)00155-4.
9. Lee SJ, Kay CS, Kim YS, Son SH, Kim M, Lee SW, et al. Prognostic value of nodal suvmax of 18f-fdg pet/ct in nasopharyngeal carcinoma treated with intensity-modulated radiotherapy. Radiat Oncol J. 2017;35(4):306-16. https://doi.org/10.3857/roj.2017.00115.
10. Tseng RH, Wu HC, Chung CH, Lai GM, Lin JT. Elimination liver metastasis of npc (nasopharyngeal carcinoma) might improve overall survival: A case report and review of the literature. Journal of Cancer Research and Practice. 2016;4. https://doi.org/10.1016/j.jcrpr.2016.10.001.
11. Xie P, Yue JB, Fu Z, Feng R, Yu JM. Prognostic value of 18f-fdg pet/ct before and after radiotherapy for locally advanced nasopharyngeal carcinoma. Ann Oncol. 2010;21(5):1078-82. https://doi.org/10.1093/annonc/mdp430.
12. Hung TM, Wang HM, Kang CJ, Huang SF, Liao CT, Chan SC, et al. Pretreatment (18)f-fdg pet standardized uptake value of primary tumor and neck lymph nodes as a predictor of distant metastasis for patients with nasopharyngeal carcinoma. Oral Oncol. 2013;49(2):169-74. https://doi.

org/10.1016/j.oraloncology.2012.08.011.
13. Iwakiri D, Sheen TS, Chen JY, Huang DP, Takada K. Epstein-barr virus-encoded small rna induces insulin-like growth factor 1 and supports growth of nasopharyngeal carcinoma-derived cell lines. Oncogene. 2005;24(10):1767-73. https://doi.org/10.1038/sj.onc.1208357.
14. Lu X, Wang FL, Guo X, Wang L, Zhang HB, Xia WX, et al. Favorable prognosis of female patients with nasopharyngeal carcinoma. Chin J Cancer. 2013;32(5):283-8. https://doi.org/10.5732/cjc.012.10058.
15. Xu Y, Huang T, Mao M, Zhai J, Chen J. Metastatic patterns and prognosis of de novo metastatic nasopharyngeal carcinoma in the united states. Laryngoscope. 2021;131(4):E1130-e8. https://doi.org/10.1002/lary.28983.