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Original Article

Prognostic value of F-18 fluorodeoxyglucose uptake in primary tumor and reticuloendothelial system in patients with head and neck cancer

Fadime Demir

Department of Nuclear Medicine, Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Turkey

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Abstract

Aim: The aim of this study was to investigate the prognostic value of FDG uptake in primary tumor and reticuloendothelial system at 18 Fluorine-fluorodeoxyglucose positron emission tomography / computed tomography (^{18}F-FDG PET / CT) in patients with head and neck cancer.

Materials and Methods: A total of 56 head and neck cancer patients who underwent ^{18}F-FDG PET / CT imaging in our clinic for staging were included in study. A circular volume of interest (VOI) was drawn which include tumor tissue on axial images and thereafter SUVmax value of the primary tumor was measured. Bone marrow SUVmax was measured at Lumbal 3-5 th vertebraes. Bone marrow-to-liver uptake ratio (BLR) value was calculated by dividing the bone marrow SUVmax value to liver SUVmax. Bone marrow-to-spleen uptake ratio (BSR) ratio value was calculated by dividing bone marrow SUVmax value to the spleen SUVmax.

Results: Forty-five were male and 11 were female of the 56 patients included in the study. The average age was 62.71 ± 14.3. The SUVmax value of primary tumor and age had a significant predictive value in terms of overall survival (p = 0.027 and p = 0.037, respectively). There was a significant difference in overall survival when using 13.6 cut off for SUVmax and 65.5 cut off for age (p = 0.005, p = 0.019, respectively). Age (≥65.5), distant metastasis and SUVmax of primary tumor (≥13.6) values were independent prognostic factors in the multivariate analysis. The bone marrow SUVmax value and BLR and BSR ratios of the patients did not have a significant prognostic value in both univariate and multivariate analysis.

Conclusion: The SUVmax value of the primary tumor in 18F-FDG PET / CT in patients with head and neck cancer, had both predictive and independent prognostic value. Bone marrow SUVmax, BLR and BSR values which shows FDG uptake on RES system, were not predictive and prognostic.

Keywords: Head and neck cancer; ^{18}F-FDG PET / CT; FDG uptake of bone marrow; SUVmax

INTRODUCTION

The term of the head and neck malignancies include in skin, oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, paranasal sinuses as well as salivary glands malignancies. While squamous cell carcinoma is the most common type of head and neck cancers, neoplasms of mesenchymal, neural and other cellular origins can also be seen (1). Head and neck cancer are seventh in the most common cancers worldwide. The most common risk factors are smoking and alcohol consumption that being followed by human papillomavirus (HPV) infections. Other risk factors are male gender, advanced age, and poor oral hygiene (2). Fine needle aspiration biopsy accompanied by imaging is a highly sensitive test in diagnosis (3). Diverse methods are used for staging in head and neck cancers such as computed tomography (CT), diffusion-weighted magnetic resonance imaging (MR), positron emission tomography / computed tomography (PET / CT) and positron emission tomography / magnetic resonance imaging (PET / MR.) (4). PET / CT is a very valuable imaging method in head and neck cancers, in cases where primary focus cannot be found, staging and evaluating the response to treatment (5). In addition, PET / CT also helps to accurately detect recurrence and predict survival after treatment (6). As well, it was shown that the PET / CT parameters of the primary tumor before treatment had a prognostic value (7). 18F-FDG is a radioactive labeled glucose analog and is the most widely used radiator in PET studies applied for oncological purposes. FDG uptake of the reticuloendothelial system has been associated with prognosis in some cancer types (8-10). Studies have suggested that the reticuloendothelial system FDG uptake

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Corresponding Author: Fadime Demir, Department of Nuclear Medicine, Faculty of Medicine, Tokat Gaziosmanpasa University, Tokat, Turkey **E-mail:** drfadimedemir@hotmail.com

may be an indicator of systemic inflammatory response. Over the past 30 years, many markers of systemic inflammatory response such as C-reactive protein, albumin, neutrophil count, and lymphocyte count has been reported to have prognostic value in cancer patients (11). Recently, it has been reported that bone marrow FDG uptake has a prognostic value in head and neck tumors (12).

The aim of this study was to investigate the prognostic value of FDG uptake in the primary tumor and reticuloendothelial system in 18F-FDG PET / CT in head and neck tumors.

MATERIALS and METHODS

Patients

Fifty-six head and neck cancer patients who underwent ^{18}F-FDG PET / CT imaging in our clinic between January 2015 and January 2018 for staging included in this study. Inclusion criteria was to be a head and neck cancer patient and to have PET CT imaging before treatment. Patients whose clinicopathological information hadn't be reached were excluded from the study.

^{18}F-FDG PET / CT imaging and Analysis

After 6 hours of fasting, intravenous administration of 8-11 mCi ^{18}F-FDG was performed to patients whose blood sugar <200 mg / dL. ^{18}F-FDG PET / CT images were performed by using Siemens Biograph 2 Slice PET / CT device. The vertex-upper femur area was scanned one hour after injection. A circular volume of interest (VOI) which include tumor tissue was drawn with semi-automatically on axial images. SUVmax was measured from this VOI. Lumbal 3-5 th vertebraes were used for bone marrow SUVmax measurement. The average of the values calculated by drawing a 2.5 cm diameter VOI from the vertebrae was used. Liver SUVmax was calculated from the VOI drawn with a diameter of 5 cm to the right lobe of the liver. Spleen SUVmax value was calculated by drawing a 3 cm diameter VOI in the spleen. And the VOI area was drawn in the area without metastatic mass. Using the SUVmax values, BLR rate value was calculated by proportioning the bone marrow to the liver, and the BSR rate value was calculated by proportioning the bone marrow to the spleen.

Statistical analysis

All statistical analyzes were done with SPSS version 20.0 (SPSS Inc, Chicago, IL). The overall survival time was calculated as the time elapsed from the first FDG-PET / CT imaging to the time of death / follow-up. The area under the curve (AUC) and cut-of values were calculated using the Receiver Operator Characteristic ROC analysis to evaluate the overall lifetime prediction of PET / CT metabolic parameters. Univariate and mulrivariate Cox regression analysis was used to evaluate the effect of age, gender, histopathological parameters and PET parameters on survival. Survival analyzes were done with Kaplan-Meier with log rank test. P <0.05 was considered statistically significant.

RESULTS

A total of 56 patients were included in the study. 45 of the patients were male and 11 were female. The average age was 62.71 ± 14.3. When we look at the primary tumor location of patients with head and neck tumors included in this study; 20 of them were in the larynx, 19 in the nasopharynx, 6 in the hypopharynx and 11 in the oropharynx or oral cavity. Histological types of the tumors were 37 squamous cell carcinoma, 9 epidermoid carcinoma, and 10 other histological types. While 20 patients had no lymph node metastases, 36 had lymph node metastases. Distant metastases was present in 4 patients. The follow-up time was median 23.5 months. The clinical demographic data and ^{18}F-FDG PET / CT parameters of the patients are summarized in Table 1.

Table 1. Clinicodemographic characteristics and PET/CT parameters of patients (n=56)

	Characteristics	Number (%)	Mean ± SD or median (min-max)
Sex	Men	45 (80.4%)	
	Woman	11 (19.6%)	
Age			62.71 ±14.3
Tumor location	Larynx	20 (35.7%)	
	Nasopharynx	19 (33.9%)	
	Hypopharynx	6 (10.7%)	
	Oropharynx and oral cavity	11 (19.7%)	
Histology	Squamous cell	37 (66.1 %)	
	Epidermoid cell	9 (16%)	
	Other	10 (17.9%)	
Metastasis in the lymph node	Negative	20 (35.7%)	
	Positive	36 (64.3%)	
Distant metastasis	Negative	52 (92.9%)	
	Positive	4 (7.1%)	

Treatment	Chemotherapy alone	2 (3.6%)	
	Radiotherapy alone	4 (7.1%)	
	Surgery alone	5 (8.9%)	
	Surgery + chemotherapy, radiotherapy,	6 (10.7)	
	Chemoradiotherapy	39 (69.6%)	
Follow-up time			23.5 (1-77)
SUVmax of primary tumor			14.9 ± 8.2
SUVmax of BM			4.3± 1.6
BLR			0,9 ±0.2
BSR			1.2 ± 0.3

PET/CT: positron emission tomography/computed tomography; SUV: standardized uptake value; BM: bone marrow; BLR: bone marrow-to-liver uptake ratio;BSR: bone marrow-to-spleen uptake ratio

Considering the predictive value of clinical demographic data and ^{18}F-FDG PET / CT parameters in terms of overall survival prediction; the SUVmax value of the primary tumor and age had a significant predictive value, while the BM SUVmax, BLR and BSR values did not have (Figure1). Sensitivity was 74%, specificity was 68% and AUC was 68% when cut-off value was 13.6 for SUVmax (p = 0.027). When the cut-off value was 65.5 for age, the sensitivity was 63%, the specificity was 70% and the AUC was 67% (p = 0.037).

There was a significant difference in terms of overall survival when using 13.6 cut off for SUVmax and 65.5 cut off for age in the Kaplan-Meier analysis (Figure 2) (respectively; p = 0.005, p = 0.019). Median survival was

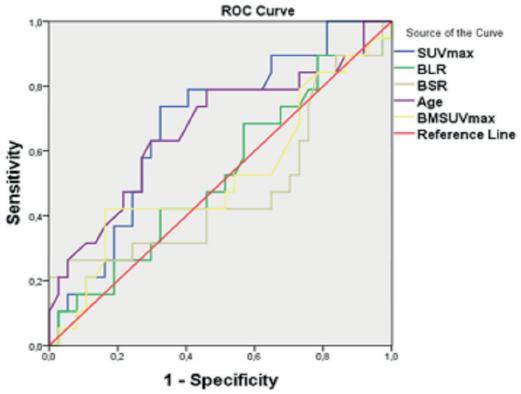

Figure 1. ROC curves for 18F-FDG PET/CT parameters

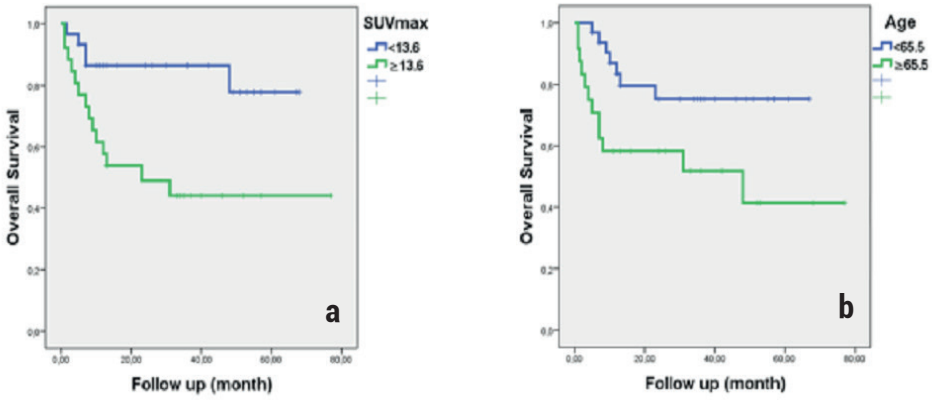

Figure 2. Kaplan–Meier curve depicts the overall survival according to SUVmax (p = 0.005) (a) and age (p = 0.019) (b)

28 months in patients with SUVmax <13.6 and 13 months in patients with SUVmax ≥ 13.6. Median survival was 27 months in patients <65.5 years of age and 14.5 months in patients ≥ 65.5 years of age.

When the prognostic value of clinico-demographic and PET / CT data was evaluated by Cox regression analysis; age (≥65.5), presence of distant metastases and primary tumor SUVmax value (≥13.6) had a prognostic value in univariate analysis(respectively p = 0.023, 0.001, 0.009). Age (≥65.5), distant metastasis and SUVmax value of the primary tumor (≥13.6) were independent prognostic factors in multivariate analysis (p = 0.019) (Table 2). The most valuable parameters among these was the presence of distant metastases (HR = 46.676) and ensuing parameter was the SUVmax value of the primary tumor (HR = 13.478). The bone marrow SUVmax value and BLR and BSR ratio of the patients did not have a significant prognostic value in both univariate and multivariate analysis. In addition, gender, tumor localization, histological subtype, presence of lymph node metastasis and treatment type had no prognostic value.

Table 2. Results of Cox regression analysis for overall survival

	Univariate Cox regression analysis				Multivariate Cox regression analysis (p=0.019)			
	Wald	HR	95 % CI	P	Wald	HR	95 % CI	P
Variables								
Sex (M)	0.250	1.326	0.438-4.012	0.617				
Age (≥65.5)	4.942	2.883	0.134-7.332	0.023*	7.555	10.446	1.961-55.659	0.006*
Tumor location	3.030	NA	NA	0.805				
Histology	2.309	NA	NA	0.511				
Metastasis in the lymph node (+)	0.691	1.541	0.555-4.287	0.406				
Distant metastasis (+)	10.558	7.139	2.181-23.336	0.001*	7.597	46.676	3.035-717.741	0.006*
Treatment	3.496	NA	NA	0.478				
SUVmax of primary tumor (≥13.6)	6.819	3.931	1.407-10.980	0.009*	4.669	13.478	1.274-142.641	0.031*
SUVmax of BM	0.138	1.053	0.802-1.383	0.711				
BLR	0.152	0.697	0.168-14.477	0.697				
BSR	0.006	1.060	0.244-4.616	0.938				

SUV: standardized uptake value; BM: bone marrow; BLR: bone marrow-to-liver uptake ratio; BSR: bone marrow-to-spleen uptake ratio

DISCUSSION

In our study, the predictive parameters in terms of overall survival in patients with head and neck cancer were SUVmax of primary tumor, and age. The cut-of value for SUVmax was 13.6 and 65.5 for age. BM SUVmax, BLR and BSR had no predictive value. When we look at the prognostic values, the primary tumor SUVmax (≥13.6), age (≥65.5) and distant metastasis were independent prognostic factors.

In general, 5-year overall survival is 90% for lip cancer, 60% for oral cavity and pharynx cancers, while it is 32% for hypopharyngeal cancer. Correct staging is provided primarily by clinical examination and imaging. Surgery, radiation therapy (RT) and chemotherapy constitute treatment options for head and neck cancers separately or in combination (5). 18F-FDG PET / CT plays an important role in staging of cases with head and neck cancer, especially in distant metastasis. It is also frequently used to search for an unknown origin of primary tumor as well as evaluate the response after chemotherapy, and to detect tumor recurrence (13). Staging with PET / CT has been shown to have a more prognostic value in head and neck cancers as than standard imaging methods (14). In addition, there are studies showing that positive findings observed in PET / CT after treatment may predict death or poor prognosis in patients (15). In a metaanalysis published by Huang et al., they found that SUVmax, MTV and TLG are prognostic factors in terms of overall survival in patients with nasopharyngeal carcinoma (16). Rasmussen et al. found that the SUVmax value of the tumor was a significant prognostic value in a study including 287 patients with squamous cell head and neck cancer (17). Pak et al. found that SUVmean is an independent prognostic factor in disease-free survival in the study which including patients with hypopharyngeal and oropharyngeal carcinoma and evaluating all PET / CT parameters. They stated that SUVmax is not an independent prognostic factor in this study (18). SUVmax was an independent prognostic factor in terms of overall survival in our study. It also has predictive value in terms of overall survival.

Cancer-related systemic inflammatory response has proven to be an independent prognostic factor, and various parameters (such as C-reactive protein, albumin, neutrophil – lymphocyte ratio) are used as a marker (19). Recent studies in various types of cancers have shown that bone marrow FDG uptake in PET / CT is associated with overall survival and progression-free survival. This bone marrow involvement was considered as an indicator of the systemic inflammatory response. In a metaanalysis conducted by Jeong et al., they found that there was a longer overall survival and disease-free survival in patients with solid tumor with low FDG involvement in the bone marrow (20). In the study by Lee et al. reported that bone marrow SUVmax was an independent prognostic factor in terms of disease-free survival after surgery in patients with colorectal cancer (21). In the study of Bang et al. reported that the FDG uptake of all RES organs such as spleen, liver and bone marrow are significant factors in predicting recurrence in breast cancer patients (9). There are limited studies evaluating the prognostic value of FDG uptake in the RES system at head and neck cancers. One of them was conducted by Ciccone et al., and reported that bone marrow FDG uptake was associated with general and disease-free survival in squamous cell head and neck cancer (22). High BLR values was associated with worse disease-free survival in a study including 157 patients with squamous cell head and neck cancer (12). In our study, bone marrow SUVmax, BLR and BSR values were not predictive and prognostic. Conflict between studies may be explained by limited number of participations in our study (n:56) or being included the all of subtype of the head and neck cancers. The studies involving more patients are needed in this area.

The prognostic factors known in head and neck cancers include age, T and N stage. The negative effects of cigarette and alcohol on recurrence have been shown. (23,24). Xi et al. found that age was associated with illness progression and survival was lower in patients whose age over 61 (25). Jeske et al. investigated the relationship between age and immune system in patients with head and neck cancer and reported that the immune system was blunt in elderly patients (26). In our study, age had both predictive and independent prognostic value in terms of overall survival. Patients aged 65.5 and above had significantly lower overall survival than patients below 65.5. Duprez et al. reported that distant metastasis led to poor prognosis in the study of including 1022 patients with head and neck cancer. The factors associated with distant metastasis were regional lymph node positivity, extranodal growth, residual disease, and human papillomavirus (HPV) in oropharyngeal squamous cell carcinoma (27). In our study, the presence of distant metastases was an independent prognostic factor and was the most valuable among the prognostic factors. The presence of lymph node metastasis was not a prognostic factor in our study.

CONCLUSION

The SUVmax value of the primary tumor had both a predictive and independent prognostic value in patients with head and neck cancer. Bone marrow SUVmax, BLR and BSR values showing the FDG uptake of the RES system in PET / CT had no predictive and prognostic value. Other independent prognostic factors were age and the presence of distant metastases.

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