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ORIGINAL ARTICLE

Relation between Histopathology of Head and Neck Cancers and FDG-PET/CT Parameters

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OBJECTIVE

To analyse the relationship between histology of head and neck cancers and maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV).

METHODS

Positron-emission tomography (PET)/computed tomography (CT) examinations of patients with head and neck squamous cell carcinoma (SCC) and non-squamous cell carcinoma (non-SCC) tumors with 52 patients reviewed from 2007 to 2019 retrospectively. MTV and SUVmax values of primary tumor were measured in PET/CT and both groups were statistically compared.

RESULTS

The median SUVmax value was 17.88 (3–52) and MTV was 5.40 (0-329). No significant difference was established between the groups in terms of age, gender and MTV (p=0.948, p=0.166 and p=0.189) respectively. SUVmax value in SCC group was significantly higher (p=0.003) than the non-SCC group.

CONCLUSION

Head and neck squamous cell carcinomas (HNSCC) have higher SUVmax values than non SCC tumors. No significant difference was established between the groups in terms of MTV.

Keywords: Head and neck cancer; metabolic tumor volume; positron emission tomography; squamous cell carcinoma; standardized uptake value.

Introduction

Head and neck cancer (HNC) constitutes 5.1% (>633.000) of all new cancers and relates to 4.8% of all cancer deaths annually worldwide with Head and Neck Squamous Cell Carcinomas (HNSCC) contributing by far the largest number.[1] Major risk factors are smoking, alcohol abuse and HPV infection.[2] The main sites for HNSCC are the larynx, pharynx and oral cavity.[1]

The malignancies occurring in this region are generally diagnosed by clinical, endoscopic examinations and histologic methods, after imaging methods are used to evaluate the spread and staging of the tumors.

Positron Emission Tomography (PET) and Computed Tomography (CT) are used together (PET/CT) as a molecular imaging method. PET scan provides important information about the metabolic activity and physiology of the body, while CT images allow the determination of anatomical changes in the body. Although the radiopharmaceuticals generally vary according to the type of cancer, the most frequently used radiopharmaceutical for cancer imaging is Fluoride-18 Fluorodeoxy-

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glucose (FDG). As glucose metabolism is increased in cancer, FDG uptake also increases compared to ground activity. Maximum standardized uptake value (SUVmax) and metabolic tumor volume (MTV) are the most used PET parameters in clinical practice.

PET/CT offers limited local evaluation due to physiological FDG involvement in the evaluation of tumors located in areas close to the lymphoid tissues. Distant metastasis at the time of diagnosis in head and neck cancers is found in approximately 15% of patients. Whole-body imaging is of great importance in this patient group due to the frequent occurrence of second and third primary malignancies accompanying head and neck cancers due to similar carcinogenic factors.[3] PET can be quantified with SUV. It has been shown that SUVmax is strongly related to advanced stage, lymph node involvement, local extension and tumor differentiation.[4-7] MTV has been reported as additional diagnostic and prognostic imaging biomarkers in various human solid tumors.

FDG-PET was associated with several histopathological parameters as reported previously. One of these is Ki 67, a widely used proliferation index, which is of prognostic relevance in various tumor entities.[8] However, Meyer et al. reported that there was a weak correlation between SUV values derived from FDG-PET and proliferation index Ki 67 in HNSCC in a large patient sample.[9] p16 positive carcinomas showed significantly lower SUV values than p16 negative tumors.[10,11]

There is no study investigating the relationship between histopathology and PET/CT SUV max and MTV values of head and neck cancers in the literature. The goal of this paper is to investigate whether there is a correlation between FDG-PET/CT SUVmax value and MTV and histopathological features of head and neck cancers.

Materials and Methods

A total of 52 patients who were diagnosed with primary head and neck cancer between 2007 and 2019 at the Department of Otorhinolaryngology & Head and Neck Surgery of the the Istanbul Training and Research Hospital Turkey, were retrospectively assessed. Patients with a prior history of head and neck cancer, neck surgery and chemoradiotherapy were excluded. All patients underwent a conventional preoperative work up, including endoscopy, ultrasound, contrast enhanced CT, and magnetic resonance imaging (MRI), in addition to FDG-PET/CT imaging.

A case file review was performed and information collected regarding age, sex and primary tumor site. Fifty two patients were divided into two groups as squamous cell carcinoma (SCC) and other malignant tumors according to histopathological diagnosis MTV and SUVmax values of primary tumor were measured in PET/CT and both groups were statistically compared. All patients were staged according to the AJCC classification (7th edition).

18F-FDG PET/CT Imaging Protocol

Patients with blood glucose levels lower than 140 mg/dl after at least 6 hours of fasting were admitted for the procedure. Whole-body PET/CT imaging was obtained including the area from the vertex to the upper thigh with the patients in the supine position, 60 min after a standard 3.7–5.2 MBq/kg 18F-FDG intravenous injection. İmaging performed by Siemens mCT 20 ultra HD LSO PET/CT (Siemens, Siemens molecular imaging, Hoffmann Estates, Illinois, USA).

CT imaging for PET/CT was performed using a multi-detector scanner with 20 slices, at 80-140 kV, 20-266 mAs, 0.8 pitch and 512x512 matrix [personalized settings determined by automatic exposure control system; automatically defined by the software used by manufacturer (CareDose 4D) depending on the patient and region assessed]. CT imaging was performed in craniocaudal direction with 5 mm of slice thickness and 0.5 seconds of rotation time. Then, PET imaging was performed in the same range through craniocaudal direction at 8 to 9 bed positions, 1.5 minutes for each PET bed. Ultra HD images were acquired using Time of flight+True X algorithm at iteration 2 and subset 16 values for reconstruction.

Interpretation of PET/CT Images

Images acquired from all patients were evaluated by a nuclear medicine physician, at the workstation visually and semi-quantitatively in axial, coronal and sagittal planes. PET/CT image evaluation was done unaware of previous imaging results of subjects. For visual evaluation, foci of increased 18F-FDG uptake compared to background and CT findings were evaluated in conjunction. For semi-quantitative analysis, SUVmax was measured by placing the "volume-of-interest" (VOI) around the 18F-FDG positive primary tumors and nodal metastatic lesions in visual evaluation. Focal FDG uptakes with an abnormal soft tissue mass or a lymph node on CT counterpart was considered significant for malignancy. SUVmax was

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calculated according to the following formula: Maximum activity inside the VOI (MBq/gr) /injected 18F-FDG dosage (MBq/kg body mass). A 3-dimensional globular VOIs including each primary tumor were drawn manually. MTV(expressed in cm^3) was calculated automatically from PET data by grouping all spatially connected voxels within a threshold of 40% of the SUVmax.

Statistical Analysis

Individual and aggregate data were summarized using descriptive statistics including mean, SD, medians (minimum–maximum), frequency distributions, and percentages. Normality of data distribution was verified using the Kolmogorov–Smirnov test. To compare distribution among samples, the non-parametric Mann Whitney U test was used for two samples. Chi-square test was used in the analysis of qualitative independent data. A p-value lower than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS® 22.0. software program.

Results

Fifty two consecutive patient's notes were reviewed, who presented to the HNC clinic as stated above. The mean age was 62 (31–94). As expected, there was a clear male predominance with 44(84.6%) male and 8 (15.4%) female patients. The median SUVmax value was 17.88 (3–52) and MTV was 5.40 (0-329) for the whole patients. 31 of the patients were in squamous cell carcinoma and 21 were in the other malignant tumor group (Table 1).

Distribution of the SCC patient group are shown in Table 2 and other malignant tumor group sites and histopathologic distribution are shown Table 3. While the majority of the SCC group was in the larynx, thyroid and parotid were the most common primary tumor localization in the other group.

No significant difference was established between the groups in terms of age, gender and MTV (p=0.948, p=0.166 and p=0.189 respectively). SUVmax value in SCC group was significantly higher (p=0.003) than the other group (Table 4). T staging of all patients can be seen in Table 5. PET and CT images examples of patients are seen increased FDG uptake in the left sided vocal cord SCC and thyroid medullary carcinoma in the right lobe (Figs. 1, 2).

Table 1 Patient demographics and clinical characteristics

	Min	Max	Median	Mean	SD/n-%
Age	31	91	62	61.63	11.34
Sex					
Male				44	84.60
Female				8	15.40
MTV	0	329	5.4	22.02	55.55
SUV max	3	52	17.88	18.91	11.06
SCC				31	59.60
Non SCC				21	40.04

SD: Standart deviation; MTV: Metabolic tumor volume; SUV max: Maximum standardized uptake value; SCC: Squamous cell carcinoma

Discussion

To the best of our knowledge, this study is the first study to investigate the relationship between histopa-

Table 2 Anatomical regions of SCC

Region	n (%)
Larynx	25 (80.64)
Unknown primary	3 (9.67)
Oropharynx	1 (3.22)
Hypopharynx	1 (3.22)
Temporal bone	1 (3.22)

Table 3 Cancer subtypes of non-SCC group

Cancer subtypes	%
Thyroid (n=8)	
Papillary carcinom (n=5)	62.5
Medullary carcinom (n=2)	25
Anaplastic carcinom (n=1)	12.5
Parotid gland (n=5)	
Mucoepidermoid carcinoma (n=3)	60
Carcinosarcoma (n=2)	40
Skin (n=2)	
Indifferentiated pleomorphic sarcoma (n=1)	50
Clear cell carcinoma metastasis (n=1)	50
Larynx (n=2)	
Adenocarcinoma (n=1)	50
Indifferentiated carcinoma (n=1)	50
External auditory canal (n=1)	
Adenocarcinoma (n=1)	100
Paranasal sinus (n=2)	
Mucoepidermoid carcinoma (n=1)	50
Malign melanoma (n=1)	50
Tonsilla palatina (n=1)	
Indifferentiated carcinoma (n=1)	100

Table 4 Comparison of SCC and non-SCC groups

	SCC			Non SCC			p
	Mean	S.D±n-%	Median	Mean	S.D±n-%	Median	
Age	62	10.7±	62	61±	12.5	62	0.948[m]
Sex							
Male	28	90.3		16	76.2		0.166[x2]
Female	3	9.7		5	23.8		
MTV	15.4	22.0±	6.3	31.8±	83.5	3.5	0.189[m]
SUVmax	22.2	10.2±	19.5	14.0±	9.9	13.0	0.003[m]

[m]Mann-whitney u test/X^2 Chi-square test; MTV: Metabolic tumor volume; SUV max: Maximum standardized uptake value; SCC: Squamous cell carcinoma

Table 5 Tumor classification of patients

	T	n	%
SCC	T1	2	6.45
	T2	7	22.58
	T3	15	48.38
	T4	7	22.58
Non SCC	T1	8	38.09
	T2	7	33.33
	T3	3	14.28
	T4	3	14.28

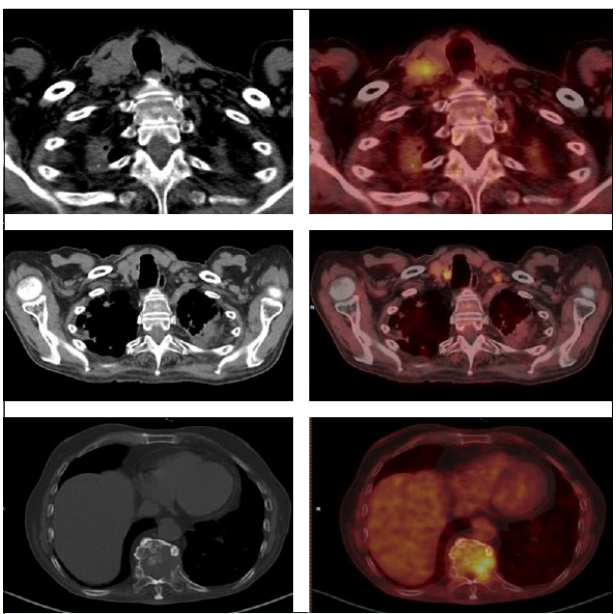

Fig. 2. Lightly hypodense nodule with SUVmax 2.4 in the right lobe in FDG-PET/CT. L10 in the T10 vertebra and multiple hypermetabolic LAP in the neck. Thyroid right lobectomy+right neck dissection: 1.6 cm Medullary thyroid carcinoma in the right lobe.

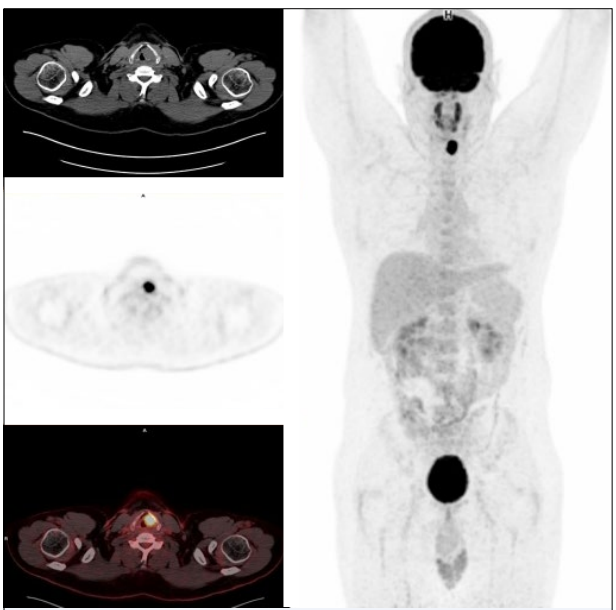

Fig. 1. Thirty seven years old male patient diagnosed with larynx ca, intense FDG involvement is observed in the left vocal cord level, in the widest area narrowing the airway, measuring 2.4x1.8 cm in size (SUVmax: 27.4) in PET/CT performed for staging.

thology of head and neck cancers and SUVmax values and MTV. The primary goal of this study was to investigate whether there was a correlation between FDG-PET/CT SUVmax value and histopathological features of head and neck cancers.

Smoking is one of the main risk factors for HN-SCC and the main source of carbon monoxide (CO). [12, 13] Increased HbCO in HNC patients who smoke, results in a decreased oxygen unloading capacity and a rise of HbCO results in a 25 % reduction in oxygen available to the tumor.[14] Also, cigarette smoke contains nicotine which decreases wound

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healing by vasoconstriction thus reducing blood flow to the wound. Nicotine plays a role in tumor progression and metastasis by increasing oxidative stress and activating agents such as proteins and NF-kappa B.[15,16] In the light of this information we can clearly see the effect of smoking-induced hypoxia results tumor aggression in HNSCC.[17] The present study was revealed that SUV max values in the SCC group were higher than the non SCC group to support the above information. Previous studies reported that more than 50% of solid tumors display heterogenous hypoxic areas irrespective of their size and histological characteristics.[18-20] Morever, larger tumor volume and increasing hypoxia emerged as putative prognostic imaging biomarkers in HNSCC.[21] However, we found no significant difference between the two groups for MTV. Tumors with high FDG uptake have more active tumor metabolism. Some studies have reported that deterioration of tumor oxygenation (tumor hypoxia) is associated with chemoradiotherapy (CRT) resistance.[22,23]

In a study investigating the role of FDG uptake in molecular subgroups of 493 primary breast cancer patients, it was reported that SUVmax value was highest in apocrine tumors and lowest in lobular carcinomas and high SUVmax value was associated with aggressive histopathological subgroups.[24]

Zheng et al.[25] reported that 18F-FDG PET/CT SUVmax values were higher in patients with large tumor size and advanced stage in addition, primary tumor SUVmax value was an important marker in determining the invasion of the surrounding tissue in 104 patients with oral squamous cell cancer.

In the study conducted with 97 advanced stage larynx and hypopharyngeal SCC patients for organ protection and survi analysis; it has been reported that the primary tumor SUVmax value may have a predictive value for preservation of larynx before CRT in hypopharyngeal cancers, but it is not predictive for organ preservation in laryngeal cancers and high SUV max values decrease the possibility of laryngeal preservation.[26]

Pencharz et al.[27] reported that SUVmax ratio between tonsils of 1.6 is highly suspicious for SCC and could be used to direct the site of biopsy. Some malignant tonsils had normal FDG uptake. In terms of tonsilla palatina carcinomas, human papilloma virus (HPV)-positive primary tumors have been found to demonstrate lower FDG avidity than HPV-negative tumors.[28]

Limitations of the Study

There are several limitations of the present study to address. First, it is retrospective in nature, therefore the potential for selection bias exists. Second, the study analyzed only a small number of patients overall.

Conclusion

In our study, HNSCC have higher SUVmax values than other malignant tumors. It can be explained by the fact that The first group has significantly higher rates of smoking related issues than the non-SCC group, and the effects of smoking on the hypoxia pathway furthers the explanation even more.

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