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Research Article

Evaluation of PET/CT Parameters and Postoperative Pathology Results in Patients with Laryngeal Carcinoma

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Abstract

Objectives: The aim of this study was to invastigate the relation between positron emission tomography/computed tomography(PET/CT) and postoperative pathology findings in larynx cancer.

Methods: Fifty patients with larynx cancer were included in the study.The SUVmax values and dimensions of larynx(Mass-SUVmax) and neck lymph nodes(Node-SUVmax) were measured by PET/CT.The specimens were examined pathologically, and the relationship between preoperative PET/CT values and pathology findings of the tumor was examined.

Results: The mean age of the patients with lymph node metastasis(65.71±9.20 years) was statistically significantly higher than the patients without lymph node metastasis(60.46±8.72 years)(p<0.05).PET/CT(Mass-SUVmax and Node-SUVmax) levels were found to be significantly higher in patients with lymph node metastasis compared to patients without metastasis(p<0.05). The DFS was found longer than 5 years in 64.0% (n=32) of the patients.A statistically significant relationship was found between the presence of lymph node metastasis and DFS.DFS was found to be shorter in patients with lymph node metastasis(p<0.05).The PET-CT(Node-SUVmax) levels were found to be statistically significantly higher in the poorly differentiated group compared to the well-differentiated group(p<0,05).

Conclusion: In our study, we showed that cervical lymph node metastasis was associated with short DFS in patients with larynx cancer, and high PET/CT levels and poor differentiation were associated with lymph node metastasis.

Keywords: Disease-Free Survival, Larynx, Lymphatic Metastasis, Neck Dissection, PET-CT

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Larynx cancer is the most common cancer of the head and neck region. The incidence of larynx cancers has significantly increased during the last decade and accounts for 2 to 5 % of all malignancies diagnosed annually worldwide.[1] According to the data received from the Ministry of Health, head-neck area cancers rank the 6th with a rate of 9.7% among the tumors observed most frequently in Turkey.[2]

In Larynx cancer patients, age, gender, tumor location, histologic grade and staging are among the prognostic factors. Staging the larynx cancers before the treatment is compulsory for comparing different treatment options and for an accurate treatment planning.[3] An ideal imaging modality should reflect the complex anatomy of the region in detail and assist the surgeon in pre-operative staging and deciding treatment option.[4] Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET/CT) are used as imaging options to investigate local and regional spread of the tumor, pre-treatment staging, and second primary tumors.[5]

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An ideal imaging modality should visualize complex regional anatomy in detail and assist the surgeon in preoperative staging and determining treatment options. Computed tomography (CT) has become an adjunct imaging modality to clinical examination in pre-treatment staging in the treatment of laryngeal cancer. CT has some advantages such as widespread availability, short acquisition times, good evaluation of bone structures, reliable demonstration of lymph node involvement and less artifacts. However low soft tissue resolution, radiation exposure, and incapability of distinguishing conditions such as tumor-associated tissue thickening and tissue destruction are among the disadvantages of CT imaging. Magnetic resonance imaging (MRI) is more effective at visualizing laryngeal and cervical soft tissue infiltration. Despite these features these anatomical imaging methods have less sensitivity and specificity in nodal staging because of their reliance on size.[6-8]

Positron emission tomography (PET) using the glucose analog fluorine-18-labeled fluorodeoxyglucose (FDG) is a functional imaging modality that provides information about tissue glucose metabolism. The combination of PET and CT into one fused modality, PET/CT, provided the functional information of PET with the anatomic detail of CT. PET/CT scanning has advantages over other imaging methods in case of extensive lesions, invasion to surrounding tissues, tumor staging, treatment planning and evaluation of outcome and recurrence. Maximum standardized uptake value (SUVmax), a semi-quantitative parameter in F18-FDG-PET/CT, represents the maximum metabolic activity of the tumor which is mostly proven as a predictor for the aggressiveness of most of cancer types.[9-12]

In this study, the pre-operative PET/CT and post-operative pathology reports of the patients, who were operated in our clinic due to larynx cancer, were evaluated, and compared statistically. The relationship between preoperative PET/CT findings, clinical staging and postoperative pathology results was investigated.

Methods

The present study was conducted by receiving the approval of the Ethical Committee of Dr. Lütfi Kırdar Education and Research Hospital. Forty-seven male and 3 female patients were included in the study. The patients received laryngectomy (partial/total) + neck dissection under general anesthesia due to larynx carcinoma in our clinic between the years 2013 and 2015. This study was conducted in a retrospective and single-centered. Patients with a histopathologically confirmed diagnosis of laryngeal carcinoma who had not received any previous treatment for this cancer and had no history of another cancer were included in the study. Treatment of all patients included in the study involved neck dissection for pathological diagnosis of cervical metastasis. Patients who had synchronous cancer or distant metastases detected with PET/CT or who had contraindications for surgical treatment and had allergic reactions to contrast material were excluded from the study.

Diagnosis

A full otorhinolaryngology and head-neck examination was performed to the patients, who had hoarseness in voice, cracked and rough voice, difficulty in swallowing and similar complaints when applying to our clinic. Biopsy was taken by microlaryngoscopy surgery from the patients with suspected malignancy with the examination performed by endoscopy and laryngostroboscopy.

Treatment Planning

Clinical staging of the patients, diagnosed with histopathologically as laryngeal carcinoma, was performed and PET/CT imaging was planned.

PET/CT Imaging Protocol

Baseline blood glucose levels of preoperative patients were determined after at least six hours of fasting. The glucose level was determined to be above 90 mg/dl and below 130 mg/dl for imaging the patients.18F-FDG was injected intravenously with a dose of 3.7–5.2 MBq/kg. All patients were allowed to rest for 50–70 min after injection. During this time, the patients were administered oral 1.5 l of water combined with 75 ml of 20% mannitol and 2 g carob bean powder to ensure neutral contrast in the gastrointestinal tract. All patients were imaged with an empty bladder.[13]

Siemens Biograph 16 LSO HI-REZ integrated PET/CT device (Siemens Molecular Imaging, Hoffman Estates, Illinois, USA) was used for PET-imaging protocol. The images were obtained in the supine position covering the area between vertex and upper thigh with a cross-sectional thickness of 5 mm. The CT part performed intravenous contrast. Whole body CT was performed in craniocaudal direction with parameters of 50 mAs, 140 kV and 5 mm slice thickness.

PET/CT images were evaluated by a nuclear medicine physician with 10 years of experience, who was blinded to the clinical findings and other imaging modalities. Evaluations were made both visually and semi-quantitatively on three-dimensional projections(maximum intensity projection) and on all three planes (transaxial, coronal, and sagittal). PET, CT and PET/CT fused images were evaluated together.

Foci showing an increase in 18F-FDG uptake in visual inspection evaluated as lesions (Fig. 1). CT images were also considered in the evaluation of foci with increased FDG-uptake. Maximum for semi-quantitative evaluation of visually

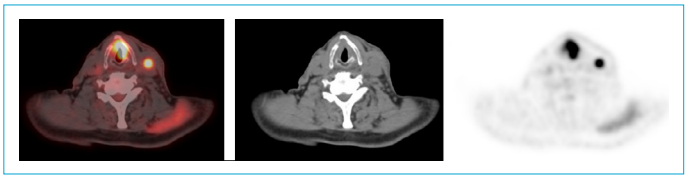

Figure 1. PET\CT image of laryngeal cancer with cervical lymph node metastasis.

suspicious lesions standardized uptake (SUVmax) values measured. SUVmax values of the suspected primary(Mass-SUVmax) and lymph nodes(Node-SUVmax) calculated on PET/CT images.

Clinical staging was done according to the "American Joint Committee on Cancer" clinical staging system. In TNM classification, T category describes the primary tumor characteristics,N category describes the regional lymph node involvement, M category describes the presence or otherwise of distant metastatic spread.[14]

Surgery

Treatment options were explained to all patients. Informed consent was obtained from patients who preferred surgical treatment. All surgeries were performed by the same surgical team. All patients received partial/total laryngectomy ± neck dissection. Modified radical neck dissection was preferred in all neck dissections. After removing the larynx and neck dissection specimen, the cervical areas were marked with a needle and sent directly for pathological examination.

Histopathologically, the intralaryngeal state of the tumor (Supraglottic, glottis, subglottic, transglottic) and cervical areas with metastasis were determined.

Patients were followed up for 5 years. 5 years was determined as the disease-free survival time (DFS). Patients who died of larynx cancer or had recurrence within 5 years and patients without tumor within 5 years were identified.

PET/CT values (Mass-SUVmax; Node-SUVmax), the presence of cervical metastasis, the degree of tumor differentiation and disease free survival (DFS) was analyzed and compared statistically.

Statistical Examinations

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analyses. In paired comparison of the quantitative data, the Student t Test was used in comparing the parameters that showed normal distribution, and the Mann Whitney U test was used in comparing the parameters which did not show normal distribution. In comparisons among three and over groups that do not show normal distribution, the Kruskal Wallis test was used. The Mann Whitney U test was used to determine which group caused the difference. In the comparison of the qualitative data, the Pearson Chi-Square test and Fisher-Freeman-Halton test were used.

Results

The study was conducted between 2013 and 2015 in Dr. Lütfi Kırdar Kartal Education and Research Hospital Otorhinolaryngology Clinic. A total of 50 patients with laryngeal carcinoma were included, 6.0% (n=3) female and 94.0% (n=47) male. Patient ages between 40 and 85 years and the mean is 62.98±9.25 years.

PET/CT (Node-SUVmax) measurements ranged from 1.8 to 11.9 with a mean of 3.60±1.79. PET/CT (Mass-SUVmax) measurements ranged from 4.7 to 16.4 with a mean of 10.04±2.69. PET/CT sizes ranged from 1.5 cm to 6.2 cm with a mean of 3.36 ± 1.17 cm and pathology sizes ranged from 1cm to 6 cm with a mean of 3.19±1.16 cm.

T stages of tumors were distributed as follows: 14.0% (n=7) T1, 8.0% (n=4) T2, 26.0% (n=13) T3 and 52.0% (n=26) T4. No lymph node metastases were found in 52.0% (n=26) of patients (lymph node(-) group) , while lymph node metastases were observed in 48.0% (n=24) of patients(lymph node(+) group). Nine (18 %) of the cases were well differentiated, 13 (26.0%) were moderately differentiated and 28 (56%) of them were poorly differentiated in histopathology.

FDS was less than 5 years in 36 % (n=18) of the patients, 16.0% (n=8) of the patients died, and more than 5 years in 64% (n=32) of the patients.

Assessments by the Presence of Pathological Lymph Node Metastasis

The mean age of the patients without lymph node metastasis was 60.46±8.72 years while the mean age in patients with lymph node metastasis was 65.71±9.20 years. The mean age of the patients with lymph node metastasis was statistically significantly higher than the patients without lymph node metastasis (p=0.044; p<0.05) (Table 1).

Statistically significant differences were detected between the histopathological examination results of the patients and PET/CT (Node-SUVmax) levels. PET/CT (Node-SUVmax)

Table 1. Relationship Between Pathological Results and Age

	Pathology		p
	Lymph node metastasis (-) (n=26) Mean±SD	Lymph node metastasis (+) (n=24) Mean ±SD	
Age (years)	60.46±8.72	65.71±9.20	0.044*

*Student T Test; p<0.05.

levels were found to be significantly higher in patients with lymph node metastasis compared to patients without metastasis (p=0.001; p<0.05). PET/CT (Mass-SUVmax) levels were significantly higher in in patients with lymph node metastasis compared to patients without metastasis. Although there was a difference between the sizes measured by PET/CT between the groups with and without lymph node metastasis, there was no statistically significant difference. A statistically significant relationship was found between lymph node involvement and T stage. Lymph node involvement was more common in T4 stage tumors (p=0.001; p<0.01). Although there was a higher rate of lymph node metastasis in patients with poorly differentiated tumors, no statistically significant relationship was found between the degree of differentiation and the presence of lymph node metastasis. A statistically significant relationship was found between the presence of lymph node metastasis and DFS. DFS was found to be shorter in patients with lymph node metastasis (p=0.048; p<0.05) (Table 2).

Table 2. Evaluations according to pathological examination results

	Pathology		p
	Lymph node metastasis (-) (n=26) Mean±SD	Lymph node metastasis (+) (n=24) Mean ±SD	
PET-CT (Mass-SUVmax)	9.26±2.35	10.89±2.82	[a]0.030*
PET-CT (Node-SUVmax)	2.47±0.48	4.82±1.90	[a]0.001*
PET-CT dimensions (cm)	3.05±1.15	3.69±1.11	[a]0.051
Pathological dimensions (cm)	3.00±1.17	3.39±1.14	[a]0.247
	n (%)	n (%)	
T (TNM)			
T 1-2	8 (72.7)	3 (27.3)	[b]0.007*
T 3	10 (76.9)	3 (23.1)	
T 4	8 (30.8)	18 (69.2)	
N (TNM)			
N 0	19 (61.3)	12 (38.7)	0.165
N 1-3	7 (36.8)	12 (63.2)	
Differentiation			
Well differentiated	6 (66.7)	3 (33.3)	0,131
Moderately differentiated	9 (69.2)	4 (30.8)	
Poorly differentiated	11 (39.3)	17 (60.7)	
DFS			
<5 year	6(33.3)	12 (66.6)	[b]0.048*
>5 year	20 (62.5)	12 (37.5)	

[a]Student t Test; *p<0.05; [b]Fisher-Freeman-Halton Test; *p<0.05; [c]Pearson's Chi-Square Test; *p<0.05.

Assessments By Differentiations

There was no statistically significant difference between the degree of differentiation and PET/CT (Mass-SUVmax) levels (p>0.05). However, a significant difference was found between PET/CT (Node-SUVmax) levels and the degree of differentiation (p=0.039; p<0.05). In paired comparisons of the groups, PET/CT (Node-SUVmax) levels were found to be statistically significantly higher in the poorly differentiated group compared to the well-differentiated group (p=0.009; p<0.05) (Table 3).

Discussion

Imaging methods have a very important role in laryngeal cancer management. CT and MRI are frequently used in clinics to detect the presence of lymph node metastasis affecting the prognosis of laryngeal cancer and to plan the optimal treatment. In a study conducted by Liao et al., the specificity and sensitivity of CT in determining the parameters used in staging laryngeal cancer were found to be 52% and 93%, respectively. However, the specificity and sensitivity of MRI were 65% and 81%, respectively. As a result, they reported that PET-CT was superior to both methods in terms of sensitivity and specificity (%66 and%91, respectively).[15] In a study conducted by Kim et al. the sensitivity and specificity of CT/MRI in detecting lymph node metastases in laryngeal carcinoma were 42% and 88%, respectively, however the sensitivity and specificity of PET/CT were found to be 58% and 90%, respectively.[16] In the light of all these data, PET/CT seems to be a superior method for preoperative staging, which is important in the treatment and prognosis of laryngeal cancer.

In a study conducted by Jégu et al., It was reported that advanced patient age is associated with recurrence or metastasis in laryngeal cancer.[17] In a study conducted by Castro et al with 2647 patients with laryngeal carcinoma, ad-

Table 3. Relationship between PET-CT values and differentiation

Pathology	PET-CT (Mass-SUVmax) Mean±SD (Median)	PET-CT (Node- SUVmax) Mean±SD (Median)
Differentiation		
Well (n=9)	8.71±3.11 (8.3)	2.63±0.96 (2.10)
Moderate (n=13)	9.99±2.06 (9.4)	3.41±1.35 (2.9)
Poor (n=28)	10.49±2.75(10.0)	3.99±2.06 (3.9)
p	0.331	0.039*

Kruskal Wallis Test; *p<0.05.

vanced patient age was found to be associated with high lymph node or distant metastasis rate.[18] Similar to these studies, we also found a statistically significant relationship between lymph node metastasis, which is a very important parameter in terms of prognosis, and advanced age.

High PET/CT (Node-SUVmax-Mass-SUVmax) values were found to be statistically significant in laryngeal cancer patients with lymph node metastasis.[19] In our study, similar to the literature, PET/CT (Node-SUVmax-Mass-SUVmax) levels were found to be significantly higher in patients with lymph node metastasis compared to patients without metastasis.

In the study of Haerle et al., no statistical significance was found between histopathological differentiation and tumoral SUVmax levels.[20] Similar results were found in the study conducted by Suzuki et al. In their study, a statistical relationship was not found between the PET/CT (Mass SUVmax-Node SUVmax) levels and histopathological differentiation.[21] In the study conducted by Laubenbacher et al., no relationship was found between histopathological differentiation and 18-FDG uptake, but SUVmax levels were found to be high in poorly differentiated cases.[22] In our study, PET/CT (Node-SUVmax) levels of patients with poor differentiation were significantly higher than those with well differentiation ($p<0.05$).

The presence of lymph node metastasis is one of the most important prognostic factor which reduces survival by 50% of particular importance for the development and of distant metastasis and for local control of the disease after treatment.[23] In the study conducted by Kim et al., the nodal SUVmax levels were high in laryngeal cancer patients with lymph node metastasis and the 5-year surveillance in this group was quite short.[24] In our study, similar to the literature, DFS was found to be shorter in patients with lymph node metastasis.

Conclusion

In conclusion, PET/CT is an important imaging modality that plays a role in cancer staging. In our study, we showed that cervical lymph node metastasis was associated with short DFS in patients with laryngeal carcinoma, and high PET/CT levels and poor differentiation were associated with lymph node metastasis.

Disclosures

Ethics Committee Approval: The present study was conducted by receiving the approval of the Ethical Committee of Dr. Lütfi Kırdar Education and Research Hospital (Date: 23.07.2015; Decision No: 54).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – D.C.; Design – M.G.Y.; Supervision – D.C.; Materials – M.G.Y.; Data collection &/or processing – M.G.Y.; Analysis and/or interpretation – D.C.; Literature search – D.C.; Writing – D.C.; Critical review – D.C.

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