Acta Scientific Otolaryngology

Volume 3 Issue 1 January 2021

Research Article

Determining the Relation between PET/CT and Staging in Larynx Carcinoma

Doğan Çakan[1]* and Muhammet Gazi Yildiz[2]

[1]*Taksim Training and Research Hospital, Turkey*

[2]*Kahramanmaraş Sütçü Imam University Medicine School, Turkey*

***Corresponding Author:** Doğan Çakan, Taksim Training and Research Hospital, Turkey.

Received: October 16, 2020

Published: December 28, 2020

Abstract

Purpose: The purpose of this study is to determine the relation between the positron emission tomography/computed tomography (PET/CT) findings and post-operative pathology findings, which is a guiding characteristic for staging in patients with larynx cancer.

Materials and Methods: In order to evaluate the PET/CT in terms of diagnostics, preoperative PET/CT was applied to the patients who received laryngectomy ± neck dissection in 2013 - 2015 period. The specimens were examined in pathological terms, and the relation between the preoperative PET/CT and pathology findings of the tumor was investigated. The statistical analysis of the data was made with the NCSS 2007 computer program.

Results: The mean age of the patients who were included in the study was determined as 62, and the gender discrimination was as follows; 47 males and 3 females. A statistically significant difference was determined in the PET/CT (Mass - SUVmax) levels of the different groups of T (TNM) staging ($p < 0.05$); in which, the PET/CT (Mass-SUVmax) levels of the T_4 subgroup were higher than those of T_{1-2} subgroups at a significant level ($p = 0.015$). Considering the tumor differentiation in histopathology, no statistically significant differences were detected between the PET-CT (Mass -SUVmax) levels of the tumors with various differentiations ($p > 0.05$).

Conclusion: The imaging methods used in larynx staging and in determining the treatment plan are inadequate. The use of PET/CT may change the proper surgical planning in terms of the staging of the disease.

Keywords: Laryngectomy; Laryngeal Neoplasms; Lymphatic Metastasis; Neck Dissection; Neoplasm Staging; PET-CT

Introduction

Larynx cancer is the most frequently observed cancer type in the head-neck area. Larynx cancers constitute nearly 30% of all head-neck area cancers [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]. 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 [4].

PET/CT is a diagnostic nuclear medicine method that performs three dimensional (3D) imaging (tomography) of the diffusion of the radionuclides that diffuse positrons after intravenous administering of the fluorodeoxyglucose (FDG) marked with Fluorine (F)-18 to human body. PET images are firstly evaluated in a visual (qualitative) manner, and then in a semi-quantitative manner. In visual evaluation, the foci that show increased involvement when compared with the background and surrounding tissue are evaluated. In semi-quantitative evaluation, a parameter called as Maximum Standard Uptake value (SUVmax) is used [SUV=Amount of activity in relevant areas (mCi/ml)/injected dose (mCi)/body weigh] [5].

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 prospectively, and the data of these processes were compared statistically the relationship between preoperative PET/CT findings and postoperative pathology results was investigated.

Materials and Methods

The present study was conducted by receiving the approval of the Ethical Committee of Dr. Lütfi Kirdar Education and Research Hospital. 47 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 prospective 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 minutes after injection. During this time, the patients were administered oral 1.5l 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 [6].

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 (Figure 1). CT images were also considered in the evaluation of foci with increased FDG-uptake. Maximum for semi-quantitative evaluation of visually 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.

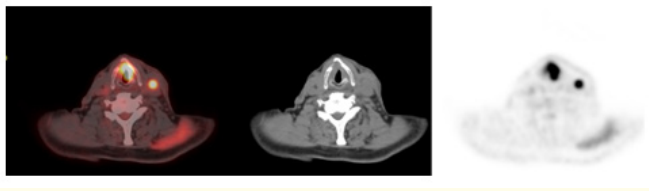

Figure 1

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 [7].

Surgery

Treatment options were explained to all patients. Informed consent was obtained from patients who preferred surgical treat-

ment. 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 and patients with recurrence within 5 years and patients without tumor within 5 years were identified.

PET/CT values (Mass-SUVmax; Node-SUVmax) and the status of tumor according to TNM classification, the stage of the tumor, the presence of cervical metastasis, the degree of tumor differentiation and disease free survival (DFS) were analyzed and compared statistically.

Statistical examinations

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analyses. When the study data were being evaluated, descriptive statistical methods (Mean value, Standard Deviation, Median, Frequency, Rate, Minimum, Maximum) were used in the study. 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, Fisher-Freeman-Halton test, Fisher's Exact test and Yates' Continuity Correction test (Yates corrected Chi-Square) were used.

Results

The study was conducted between 2013 and 2014 in Dr. Lütfi Kirdar 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 (Mass-SUVmax) measurements of the cases varied between 4.7 and 16.4, and the mean value was 10.04 ± 2.69. Pet CT Mass sizes varied between 1.5 and 6.2 cm, and the mean value was 3.36 ± 1.17 cm. Pathological diagnostic sizes varied between 1 and 6 cm, and the mean value was 3.19 ± 1.16 cm (Table 1).

	Min-Max	Mean ± SD
PET/CT (Mass - SUVmax)	4,7 - 16,4	10,04 ± 2,69
PET/CT tumor size	1,5 - 6,2 cm	3,36 ± 1,17 cm
Pathologic tumor size	1,0 - 6,0 cm	3,19 ± 1,16 cm

Table 1: Evaluation of tumor sizes and PET/CT.

In histopathalogical examination, there were 36% (n = 18) supraglottic,16% (n = 8) glottic, 4% (n = 2) subglottic and 44% (n = 22) transglottic patients by tumor location. Cervical lymph node metastasis was detected in 24 (48%) patients. When patients were evaluated with TNM classification according to T, there were 7 (14%) in the stage 1 (T_1), 4 (8%) in stage 2 (T_2), 13 (26%) in stage 3 (T_3) and 26 (52%) in stage 4 (T_4) patients. According to N, there were 31 (%62) in stage 0 (N_0), 17 (%34) in stage 1 (N_1) ve 2 (%4) in stage 3 (N_3) according to N. No patients had distance metastasis (M_0). According to the staging made with this classification, 6% (n = 3) of the patients were stage 1, 6% (n = 3) were stage 2, 32% (n = 16) were stage 3, 52% (n = 26) were stage 4a and 4% (n = 2) were stage 4b. Stage 1 and 2 tumors considered as early stage laryngeal cancer were statistically considered in the same group. 9 (18%) of the cases were well differentiated, 13 (26.0%) were moderately differentiated and 28 (56%) of them were poorly differentiated in histopathalogy (Table 2).

		n	%
Tumor Localization	Supraglottic	18	36
	Glottic	8	16
	Subglottic	2	4
	Transglottic	22	44
T	T_1	7	14
	T_2	4	8
	T_3	13	26
	T_4	26	52
Differentiation	Well	9	18
	Moderate	13	26
	Poor	28	56

Table 2: Tumor localization, T and differentiation distribution. T: Tumor in TNM classification.

13 (26%) of the patients underwent supraglottic laryngectomy, 3 (6%) of them supracricoid laryngectomy, 1 (2%) of them near total laryngectomy, 33 (66%) patients underwent total laryngectomy.

A statistically significant difference was found between PET/CT (Mass - SUVmax) levels of the cases according to the extent of the main tumor (T) ($p = 0.022$; $p < 0.05$). PET/CT (Mass - SUVmax) levels of T_4 cases were significantly higher than T_1+T_2 cases ($p = 0.015$; $p < 0.05$) (Table 3).

T(TNM)	PET-CT (Mass - SUVmax) Mean+SD (Median)	P	
T_1+T_2 (n = 11)	8,34 ± 3,27 (8,2)	0,022*	0.015**
T_4 (n = 26)	9,54 ± 1,54 (9,3)		
T_3 (n = 13)	11,02 ± 2,52 (10,9)		

Table 3: PET-CT evaluations according to T staging.

T describes tumor in TNM classification.

*Kruskal Wallis Test: $p < 0.05$.

**The Mann Whitney U test: $p < 0.05$.

A statistically significant difference was found between the PET/CT (Mass - SUVmax) levels of the cases according to their stages ($p = 0.013$; $p < 0.05$). PET/CT (Mass - SUVmax) levels of stage 4 cases were found to be statistically significantly higher than stage 1 + 2 cases ($p = 0.011$; p0.05). PET/CT (Mass - SUVmax) levels of stage 3 cases were found to be lower than stage 4 cases, although it was not statistically significant ($p = 0.073$; $p > 0.05$) (Table 4).

A statistically significant difference was found between the PET/CT (Node-SUVmax) levels of the cases according to their stages ($p = 0.001$; $p < 0.01$). According to the paired comparisons; PET/CT (Node-SUVmax) levels of stage 4 cases were significantly higher than stage 3 and stage 1 + 2 cases ($p = 0.005$; $p = 0.011$, $p < 0.05$). There was no statistically significant difference in PET/CT (Node-SUVmax) levels of stage 3 and stage 1 + 2 cases ($p = 0.395$; $p > 0.05$) (Table 4).

According to the differentiation, PET/CT (Mass - SUVmax) levels of the cases do not show a statistically significant difference ($p > 0.05$), but there was a significant difference between PET/CT (Node-SUVmax) levels ($p = 0.039$; $p < 0.05$). According to the paired comparisons made; PET/CT (Node-SUVmax) levels of patients with poor differentiation were significantly higher than those with good differentiation ($p = 0.009$; $p < 0.01$) (Table 5).

Stage	PET-CT (Mass-SUVmax) Mean+SD (Median)	p		PET-CT (Node-SUVmax)	p		
1+2	7,50 ± 2,3 (7,3)	0,013*	0.011**	2,43 ± 0,49 (2,4)	0,003*	0.011**	0.005**
4	10,91 ± 2,75 (10,9)			4,29 ± 2,05 (4,2)			
3	9,47 ± 1,99 (9,2)			2,83 ± 0,90 (2,5)			

Table 4: PET-CT evaluation according to stage (TNM).

*Kruskal Wallis Test: $p < 0,05$.

**The Mann Whitney U test: $p < 0.05$.

	Differentiation			p
	Well (n = 9)	Moderate (n = 13)	Poor (n = 28)	
	Mean ± SD (Median)	Mean ± SD (Median)	Mean ± SD (Median)	
PET-CT (Mass - SUVmax)	8,71 ± 3,11 (8,3)	9,99 ± 2,06 (9,4)	10,49 ± 2,75(10,0)	0,331
PET-CT (Node- SUVmax)	2,63 ± 0,96 (2,10)	3,41 ± 1,35 (2,9)	3,99 ± 2,06 (3,9)	0,039*

Table 5: PET-CT evaluation according to differentiation.

Kruskal Wallis Test: *$p < 0.05$.

According to the DFS results, statistically significant differences were determined between the pathology results of the cases (p = 0.040; p < 0.05). In cases with lymph node metastasis, the rate of ex occurrence is significantly higher than cases with DFS duration more than 5 years (Table 6).

Patient Survival	N + (n = 26)	N - (n = 24)	P
Ex	1 (12,5)	7 (87,5)	0,040*
DFS < 5 years	5 (50,0)	5 (50,0)	
DFS > 5 years	20 (62,5)	12 (37,5)	

Table 6: Relationship between DFS and lymph node metastasis.

N; Cervical lymph node metastasis.

*Fisher-Freeman-Halton Test; p < 0,05.

Discussion

In Larynx cancer patients, age, gender, tumor localization, histologic grade, staging (TNM), primer tumor and nodal SUVmax levels are among the prognostic factors [3]. Accurate staging is important for the planning treatment in Larynx cancers. In routine microlaryngoscopy, tumor mass, location, extension, invasion of the anterior commissure and subglottic region can be evaluated. However, its accuracy and consistency should be questioned due to subjective examination that may vary according to the surgeon. In addition, preepiglottic region, paraglottic region and cartilage invasion cannot be evaluated by microlaryngoscopy. Imaging methods are applied to evaluate these important areas.

CT is an effective radiological imaging method to show the primary localization, tumor size, local extension and presence of metastatic lymph nodes. However, CT may not be able to distinguish inflammatory changes, edema, and fibrosis from the tumor and may not detect small lesions [8]. MRI is superior to CT in soft tissue pathologies, in the detection of central necrosis in metastatic tissues and irregularity in soft tissues. In the study conducted by Liao., *et al*. It was determined that the sensitivity of CT in laryngeal carcinomas was 52% and the specificity was 93%. In this study, it was shown that MRI sensitivity was 65%, specificity was 81% and the sensitivity and specificity of PET/CT was 66%, 91% in laryngeal carcinomas [9].

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. Lymph node metastasis changes the stage and therefore treatment [10,11]. In many studies, PET/CT has been shown to be superior to CT and MRI in detecting cervical lymph node metastasis in patients with laryngeal cancer. In the study conducted by Kim., *et al*. the specificities of PET/CT and CT/MRI for the detection of lymph node metastasis in patients with laryngeal carcinoma were 88% and 90%, respectively and the sensitivities were 42%, specificity 88% and 58% respectively [12]. Ferlito., *et al*. conducted another study and reported the sensitivity of PET- CT as 56% and specificity as 84%, and the sensitivity of CT/MRI as 42% and specificity as 71% [13]. As these studies show, PET-CT is the superior imaging method for staging this disease with high morbidity and mortality. Many previous studies have examined the relationship between PET/CT parameters and different prognostic factors of laryngeal cancer.

One of the most important prognostic factors in laryngeal cancer patients is TNM staging. In the staging determined by AJCC, the correct treatment method is planned considering the changes caused by the tumor in the laryngeal structures and the size and number of nodal involvement. High FDG uptake due to increased tumor burden in advanced stage tumors has been shown in some studies. In the study of Demirci., *et al*. SUVmax levels were found to be higher in advanced stage tumors [14]. In a study by Haerle., *et al*. FDG uptake was found to be associated with T staging [15]. In the study conducted by Suzuki., *et al.* a statistical significance was determined between SUVmax uptake of the primary tumor and T and stage of the tumor [16]. In our study, TNM staging was compared with both primary tumor and nodal SUVmax values. A statistically significant difference was found between PET/CT (Mass - SUVmax) levels of the cases according to the extent of the main tumor (T) (p = 0.022; p < 0.05). PET/CT (Mass - SUVmax) levels of T_4 cases were significantly higher than T_1+T_2 cases (p = 0.015; p < 0.05). And also a statistically significant difference was found between the PET/CT (MASS - SUVmax) and PET/CT (Node-SUVmax) levels of the cases according to their stages (p = 0.013, p = 0.001; p < 0.05). The SUVmax values increase in proportion to the stage.

Histological differentiation level is one of the important factors affecting prognosis in laryngeal carcinoma. In the study of Haerle., *et al*. no statistical significance was found between histopathological differentiation and tumoral SUVmax level [15]. Similar results were found in the study conducted by Suzuki., *et al* [16]. In their study, a statistical relationship was not found between the SUVmax of the primary tumor and lymph nodes and histopathological differentiation. In the study conducted by Laubenbacher., *et al*. No rela-

tionship was found between histopathological differentiation and 18-FDG uptake, but SUVmax levels were found to be high in poorly differentiated cases [17]. In our study, PET/CT (Node-SUVmax) levels of patients with poor differentiation were significantly higher than those with good differentiation ($p = 0.009$; $p < 0.01$).

The prognosis is poor in patients with supraglottic and subglottic localized, local invasive, local or distant metastasized tumors [18]. In the study conducted by Kim., *et al*. It was stated that PET/CT was better than other imaging modalities in staging, which is a prognostic factor, and it was stated that the primary tumor and nodal SUVmax levels were high in laryngeal cancer patients with lymph node metastasis and the 5-year surveillance in this group was quite short [19]. In the study of Nakajo., *et al*. An inverse proportional relationship between high tumor SUVmax value and disease-free survival was reported [20]. In our study, statistically significant difference was determined between the pathology results of the cases according to the DFS results ($p = 0.040$; $p < 0.05$). In the presence of lymph node metastasis, the mortality rate due to tumor was found to be higher than disease-free survival.

As a result of our study, we found that high PET/CT SUVmax values were associated with the presence of cervical lymph node metastasis and advanced tumor stage, and consequently, short DFS and poor prognosis.

Conclusion

High PET/CT SUVmax values are associated with advanced stage cancer. Advanced stage shows poor prognosis. Therefore, more care should be taken in staging and treatment planning of patients with high PET/CT values. The purpose of the present study is to lead the way for future studies and help to determine accurate surgical planning in preoperative period. We believe that this viewpoint will improve even more with wider studies.

Bibliography

1. Castelijns JA. "Diagnostic radiology of head and neck oncology". *Current Opinion on Oncology* 3.3 (1991): 512-518.

2. Kaya S. "Larynx Hastalıkları". Ankara: Bilimsel Tıp Yay Ocak (2002): 539-716.

3. Özlügedik S and Ünal A. "Baş boyun kanserlerinde epidemiyoloji ve risk faktörleri". KBB Baş Boyun Cerrahisi'nde Güncel Yaklaşım. 1.3 (2005): 51-56.

4. Yousenm DM., *et al*. "Resectability issues with head and neck cancer". *AJNR American Journal of Neuroradiology* 27.10 (2006).2024-2036.

5. Yüksel M and Kalaycı G. "Göğüs Cerrahisi". Bilmedya Grup (2001): 291-302.

6. Tatar G., *et al*. "The value of whole-body contrast-enhanced 18F-FDG PET/CT imaging in the diagnosis and staging of patients with laryngeal carcinoma". *Nuclear Medicine Communications* 39.4 (2018): 334-342.

7. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer International Publishing (2017).

8. Archer CR and Yeager VL. "Computed tomography of laryngeal cancer with histopathological correlation". *Laryngoscope* 92 (1982): 1173-1180.

9. Liao LJ., *et al*. "Detection of cervical lymph node metastasis in head and neck cancer patients with clinically N0 neck-a meta-analysis comparing different imaging modalities". *BMC Cancer* 12 (2012): 236.

10. Jemal A., *et al*. "Global cancer statistics". *CA: A Cancer Journal for Clinicians* 61 (2011): 69.

11. Kumar V., *et al*. "Pathologic basis of disease, 7th edition". China: Elsevier (2005): 786-787.

12. Kim JK., *et al*. "Evaluation of 18F-FDG PET/CT and CT/MRI with histopathologic correlation in patients undergoing central compartment neck dissection for squamous cell carcinoma of the larynx, hypopharynx, and esophagus". *Oral Oncology* 49 (2013) 449-453.

13. Ferlito A., *et al*. "Prognostic value of Delphian lymph node metastasis from laryngeal and hypopharyngeal cancer". *Acta Otolaryngology* 122 (2002): 456-457.

14. Demirci U., *et al*. "The Nodal Standard Uptake Value (SUV) as a Prognostic Factor in Head and Neck Squamous Cell Cancer". *Asian Pacific Journal of Cancer Prevention* 12 1817-1820.

15. Haerle SK., *et al*. "Is there a correlation between 18F-FDG-PET standardized uptake value, T-classification, histological grading and the anatomic subsites in newly diagnosed squamous cell carcinoma of the head and neck?" *European Archives of Otorhinolaryngology* 267.10 (2010): 1635-1640.

16. Suzuki K., *et al*. "Value of fluorodeoxyglucose positron emission tomography before radiotherapy for head and neck cancer: does the standardized uptake value predict treatment outcome?" *Japanese Journal of Radiology* 27.6 (2009): 237-242.

17. Laubenbacher C., *et al*. "Comparison of fluorine-18-fluorodeoxyglucose PET, MRI and endoscopy for staging head and neck squamous-cell carcinomas". *The Journal of Nuclear Medicine* 36.10 (1995): 1747-1757.

18. Abgral R., *et al*. "Prognostic value of volumetric parameters measured by 18F-FDG PET/CT in patients with head and neck squamous cell carcinoma". *European Journal of Nuclear Medicine and Molecular Imaging* 41.4 (2014): 659-667.

19. Kim SY., *et al*. "Evaluation of 18F-FDG PET/CT and CT/MRI with histopathologic correlation in patients undergoing salvage surgery for head and neck squamous cell carcinoma". *Annals of Surgery Oncology* 18.9 (2011): 2579-2584.

20. Nakajo M., *et al*. "FDG PET/CT and diffusion-weighted imaging of head and neck squamous cell carcinoma: comparison of prognostic significance between primary tumor standardized uptake value and apparent diffusion coefficient". *Clinical Nuclear Medicine* 37.5 (2012): 475-480.