ARTÍCULO ORIGINAL

Diagnóstico por imágenes, medicina interna

DIFFERENTIAL ROLE OF FLUORODEOXYGLUCOSE (FDG)-POSITRON EMISSION TOMOGRAPHY (PET)/ COMPUTED TOMOGRAPHY (CT) IN THE DIAGNOSIS OF BENIGN AND MALIGNANT PLEURAL EFFUSION

REVISTA ARGENTINA DE MEDICINA
ISSN 1515-3460
Buenos Aires
Unver M, Biber Ç, Avcı S, et al. Differential role of FDG-PET/CT in the diagnosis of benign and malignant pleural effusion. *Rev Arg Med* 2018;6(2):98-103

EL PAPEL DIFERENCIAL DE LA FLUORODESOXIGLUCOSA-TOMOGRAFÍA POR EMISIÓN DE POSITRONES/TOMOGRAFÍA COMPUTARIZADA (FDG-TEP/CT) EN EL DIAGNÓSTICO DE DERRAMES PLEURALES BENIGNOS Y MALIGNOS

Meriç Unver,[1] Çiğdem Biber,[2] Sema Avcı,[3] Ebru Tatçı,[4] Özlem Özmen,[5] Hacı Hasan Yeter[6]

Recibido: 2 de marzo de 2018.
Aceptado: 13 de abril de 2018.

[1] MD. Departamento de Neumonología del Hospital Estatal Kars Harakani, Kars, Turquía.
[2] MD. Departamento de Neumonología, Enfermedades y Cirugías de Tórax de Ataturk, Hospital Educativo y de Investigación de Ankara, Turquía.
[3] MD. Departamento de Emergencias del Hospital de Investigación y Capacitación Sabuncuoğlu Şerefeddin de la Universidad de Amasya, Amasya, Turquía.
[4] MD. Departamento de Medicina Nuclear, Enfermedades y Cirugías de Tórax de Ataturk, Hospital Educativo y de Investigación de Ankara, Turquía.
[5] MD. Departamento de Medicina Nuclear, Enfermedades y Cirugías de Tórax de Ataturk, Hospital Educativo y de Investigación de Ankara, Turquía.
[6] MD. Departamento de Medicina Interna del Hospital Estatal Adana Tufanbeyli, Adana, Turquía.

Abstract

Objective. Even though many nuclear medicine techniques exist in the diagnosis and investigation of pleural diffusion, nowadays the fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is the scanning method most frequently used in this field. In this study, we have aimed to establish the diagnostic power of FDG-PET/CT to define the pleural effusions malignant or benign pattern. **Material and methods.** With the permission granted from the ethical committee, this study was conducted based on retrospective patient records. The study included 106 patients, who underwent FDG-PET/CT scanning for having pleural effusion between 01.06.2014 and 01.06.2015. The pleural fluid maximum standard uptake value (SUVmax), the pleural fluid standard uptake value mean (SUVmean), pleural SUVmax and pleural SUVmean, pleural thickness have been statistically compared between benign and malignant groups. A receiver operating characteristic (ROC) analysis was performed for pleural fluid SUVmax, pleural fluid SUVmean, pleural SUVmax, pleural SUVmean and determined cut-off value. **Results.** 37 were female and 69, male. The average age of the patients was 65.1 ± 11.6 and the range of patients' age was from 14 to 86. Of the patients, 69 had malignant and 37, benign pleural effusion thickness of the pleural fluid. Pleural thickness was found statistically significant between the benign and malignant groups ($p < 0.05$). The cut-off value calculated was 4.26 for pleural thickening SUVmax and sensitivity: 75%, specificity: 73.9%, positive predictive value (PPV): 88.8% and negative predictive value (NPV): 51.5% were determined for this value. The cut-off value calculated was 3.08 for pleural thickening SUVmean with 71.9% sensitivity, 70.8% specificity, 86.8% PPV and 48.6% NPV determined for this value. The cut-off value calculated was 1.96 for pleural fluid SUVmax (sensitivity: 43.5%, specificity: 43.2%, PPV: 58.8%, NPV: 29.1%). The cut-off value calculated was 1.66 for pleural fluid SUVmean and had 44.9% sensitivity, 43.2% specificity, 59.6% PPV and 29.6% NPV determined for this value. **Conclusion.** The FDG-PET/CT scanning has respective sensitivity, specificity and PPV but not NPV for malign pleural thickness diagnosis. Negative findings under FDG-PET/CT should be confirmed through further tests. Besides, FDG-PET/CT alone has no diagnostic value to detect malign pleural effusions.

Key words. Pleural fluid, malignancy, FDG-PET/CT.

Resumen

Objetivo. *Aunque existen muchas técnicas de la medicina nuclear en el diagnóstico y la investigación del derrame pleural, hoy en día la fluorodesoxiglucosa-tomografía por emisión de positrones/tomografía computarizada (FDG-PET/CT, por sus siglas en inglés) es la exploración utilizada con más frecuencia en este campo. En este estudio, nuestro objetivo fue establecer el poder diagnóstico de la FDG-PET/CT para definir derrames pleurales malignos o benignos.* ***Material y métodos.*** *Después de obtener el permiso del comité de ética, este estudio se llevó a cabo sobre la base de registros retrospectivos de pacientes. El estudio incluyó 106 pacientes*

Los autores manifiestan no poseer conflictos de intereses.

AUTOR PARA CORRESPONDENCIA
Sema Avcı. Hospital de Investigación y Capacitación Sabuncuoğlu Şerefeddin de la Universidad de Amasya, Amasya, Turquía.
Correo electrónico: dnzlsema@gmail.com

*a los que se les realizó una FDG-PET/CT por derrame pleural entre el 01-06-2014 y el 01-06-2015. El valor máximo estandarizado de captación (*standard uptake value, *SUV) (SUVmax, su sigla en inglés) del líquido pleural, la media del SUV (SUVmedia) de líquido pleural, el SUVmax y la SUVmedia pleurales y el grosor pleural se compararon estadísticamente entre grupos benignos y malignos. Se realizó un análisis de curvas de eficacia diagnóstica (ROC) para el SUVmax del líquido pleural, la SUVmedia del líquido pleural, el SUVmax y la SUVmedia pleurales y el valor de corte determinado.* ***Resultados.*** *Treinta y siete pacientes eran mujeres y 69, varones. La edad promedio de los pacientes fue de 65,1 ± 11,6 y el rango de edad, de 14 a 86. Sesenta y nueve pacientes tenían malignidad y 37 presentaban un grosor del derrame pleural benigno del líquido pleural. El grosor pleural fue estadísticamente significativo entre los grupos benignos y malignos (*p *<0,05). El valor de corte se calculó en 4,26 para el SUVmax del grosor pleural, y se determinaron para este valor una sensibilidad del 75%, una especificidad del 73,9%, un valor predictivo positivo (VPP) del 88,8% y un valor predictivo negativo (VPN) del 51,5%. El valor de corte calculado fue de 3,08 para el SUV del grosor pleural, con una sensibilidad del 71,9%, una especificidad del 70,8%, un VPP del 86,8% y un VPN del 48,6%. El valor de corte calculado fue de 1,96 para el SUVmax del fluido pleural (sensibilidad: 43,5%, especificidad: 43,2%, VPP: 58,8% y VPN: 29,1%). El valor de corte calculado fue de 1,66 para la SUVmedia del fluido pleural, con una sensibilidad del 44,9%, una especificidad del 43,2%, un VPP del 59,6% y un VPN del 29,6%.* ***Conclusión.*** *La FDG-PET/CT brinda sensibilidad, especificidad, VPP pero no VPN respectivos para diagnosticar el grosor pleural maligno. Los hallazgos negativos en una FDG-PET/CT deben confirmarse mediante pruebas adicionales. Además, la FDG-PET/CT no tiene valor diagnóstico independiente para derrames pleurales malignos.*

Palabras clave. *Líquido pleural, malignidad, FDG-PET/CT.*

Introduction

Pleural effusion may occur not only due to local pleural diseases but also due to systemic diseases such as cardiac insufficiency and renal insufficiency, infections and drug use (1). Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) is a powerful method for the detection and diagnosis of pleural pathologies (2). FDG-PET/CT systems can monitor both metabolic functions and anatomic details in one session (3). As a result of using this technique, glucose metabolisms of lesions are evaluated and hypermetabolic lesions are reported in favor of malignancy (2). The aim of this study is to determine the efficiency and reliability of the fluorine-18 (F-18) FDG-PET/CT in differential diagnosis of benign and malignant pleural effusion.

Material and methods

This retrospective study was conducted with the approval of the ethical committee at Ankara Keçioren Training and Research Hospital. The study analysed 106 patients who underwent FDG-PET/CT for having pleural effusion between 01.06.2014 and 01.06.2015. Pleural fluid histopathology samples of all patients were available. Patients with transudate fluid quality were excluded from the study. Patients with pulmonary malignancy and pleural fluid were not included in the study unless their pleural fluid proved to be malignant. Pleural fluid maximum standard uptake value (SUVmax), pleural fluid mean standard uptake value (SUVmean), pleural SUVmax, pleural SUVmean of patients were compared between benign and malignant groups. A receiver operating characteristic (ROC) analysis was performed in terms of pleural fluid SUVmax, pleural fluid SUVmean, pleural SUVmax, pleural SUVmean and the cut-off value was determined. The Hounsfield Unit (HU) for density measurement in CT and SUV in PET images was used. While the SUVmean is the mathematical mean value of all pixels at the region of interest (ROI), minimum and maximum values show the lowest and the highest pixel values in ROI. The PET/CT images were being evaluated, and the highest SUV determined in pleural fluid or pleural thickening was included in the evaluation. A SUV over 2.5-3.0 can be accepted as sensitive and specific in terms of malignancy. However, recent studies show that the SUV does not have diagnostic value for differentiating malignant and benign patterns (4-7). The FDG-PET/CT images were taken at Ankara Ataturk Pulmonary Diseases and Thoracic Surgery Training and Research Hospital. A Siemens Biograph-6-HI-REZ (Siemens Medical Solutions, Knoxville, Tennessee, USA) integrated PET/CT was used for monitoring. The patients had fasted for six hours before the imaging. All patients who undertook monitoring had a fasting blood glucose value under 200 mg/dl. The images were taken in 6 to 8 bed positions, from the skull base to the upper femoral, after the patients were administered 370-555 MBq (10-15 mCi) FDG intravenously. For attenuation adjustments of the PET images, CT parameters were employed. The PET, CT and PET/CT fusion

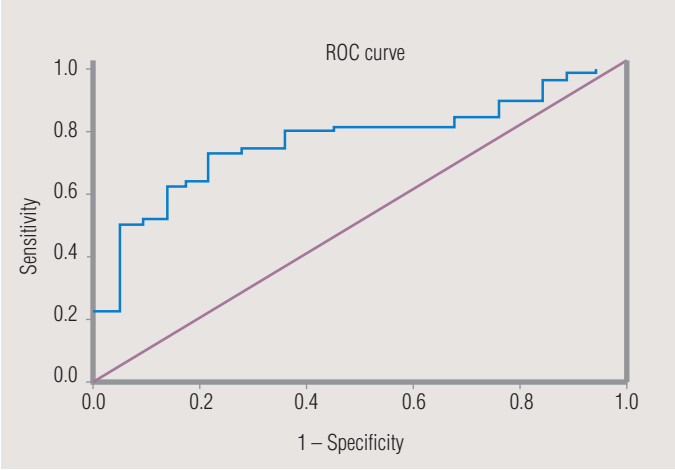

Figure 1. ROC analysis curve between pleural thickening SUVmax and diagnosis groups.

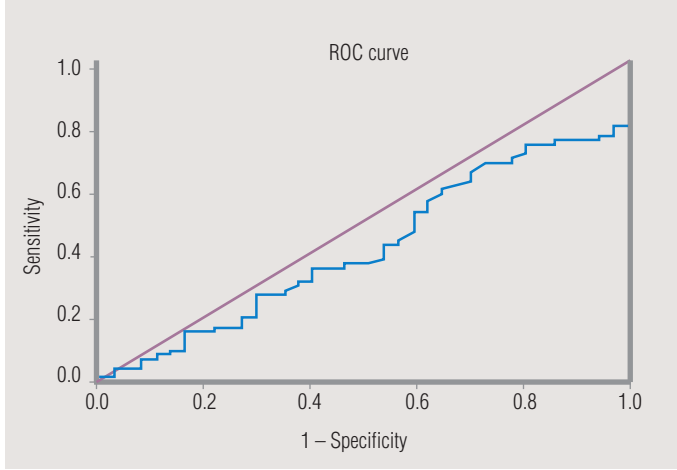

Figure 2. ROC analysis curve between pleural fluid SUVmax and diagnosis groups.

images were taken at trans-axial, coronal and sagital planes through whole body projection, and then patients were evaluated. Quantitative analyses of the images were performed. Patients were staged through PET/CT and other imaging techniques. The size of pleural effusion, thickness of pleural leaves, FDG uptakes (SUV) of pleural fluid and pleural thickening areas were identified in the qualitative evaluation. Parameters obtained in the study were analyzed through the SPSS 20 packet-program. The Shapiro-Wilk test was also used for the number of variable units. When examining the differences between the groups, the independent T-test was used for variables from normal distribution. When it was perceived that variables did not come from normal distribution, the Mann-Whitney U Test was applied. Since numbers of units were more than 20, a standardized z value was given for Mann-Whitney U test. A chi-square analysis was applied during the examination of the nominal variables' relations between the groups. At 2x2 tables, when expected values at cells do not have adequate volume, the Fisher's exact test was used. At rows and columns (RxC) tables, Pearson's chi-square analysis was applied with Monte Carlo simulation. The relationships between the variables which did not come from normal distribution were examined with Spearman's correlation coefficient. For the variables coming from normal distribution, Pearson correlation coefficient was used. The cut-off point was determined through a ROC analysis. Statistical significance for all analyses was set at a probability value of less than 0.05.

Results

Of the patients, 34.9% (n = 37) were female and 65.09% (n = 69) were male. Though they were not significant, 59.4% of the males and 75.7% of the females had a diagnosis of malignant pleural effusion (p = 0.144). The age of the patients ranged from 14 to 86, and the average age was 65.1 ± 11.6. Sixty-nine patients had malignant, and 37, benign pleural effusions.

The SUVmax pleural thickening of the benign group is significantly lower than that of the malignant group (p <0.05). The pleural thickening SUVmean of the benign group is significantly lower when compared to the malignant one (p <0.05) (Table 1). Pleural thickening SUVmax, pleural thickening SUVmean, pleural fluid SUVmax, and pleural fluid SUVmean ROC analysis results (Table 2): there is a statistically significant relation between the pleural thickening SUVmax which were determined with the PET/CT and diagnosis groups. With the ROC analysis, a cut-off value of 4.26 for SUVmax was calculated as 75%, 73.9, 88.9%, and 51.5% for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), respectively.

ROC analysis between pleural thickening SUVmax and diagnosis groups (Figure 1): a cut-off value of 3.08 for pleural thickening SUVmean was calculated as 71.9%, 70.8%, 86.8%, and 48.6% for sensitivity, specificity, PPV and NPV, respectively. A cut-off value of 1.96 for pleural fluid SUVmax was calculated as 43.5%, 43.2, 58.8%, 29.1% for sensitivity, specificity, PPV and NPV, respectively.

According to ROC analysis between pleural fluid SUVmax and diagnosis groups (Figure 2), there is no statistically significant relation between SUVmean diagnosis groups determined with the PET/CT. A cut-off value of 1.66 for pleural fluid SUVmean was calculated as 44.9%, 43.2%, 59.6%, 29.6% for sensitivity, specificity, PPV and NPV, respectively. Some PET/CT figures of the patients were given.

Discussion

Pleural effusions are common findings of pulmonary, heart and infectious diseases. Although the most common reason

of pleural effusions is congestive heart failure and parapneumonic effusion, studies showed that 29%-43.8% of exudate effusions were diagnosed as malignant effusions (8-10). Pleural involvement is not an uncommon finding in patients with lung carcinoma. However, differentiation between benign and malignant effusion has a key role for accurate determination of a lung tumor. However, the differentiation of a malignant pleural effusion is difficult with conventional imaging modalities. Despite all imaging and invasive diagnostic modalities, only 36% of pleural effusions can be diagnosed (11). Several studies showed that FDG-PET/CT has an important role in the diagnosis of malignant pleural diseases and distance metastasis (2). Besides, FDG-PET/CT can be a guide to biopsy areas which are decided with an increased FDG uptake of pleural or pulmonary masses or lymph nodes (12). FDG-PET/CT imaging may be more accurate and reliable (sensitivity 88.8-100%, specificity 94.1-94.4%, respectively) than repeated thoracentesis (13-15). Our study showed that the FDG uptake was significantly higher at malignant pleural thickness than benign thickness (SUVmean: 3.085, sensitivity 71.9%, specificity 70.8%, PPV 86.8% and NPV 48.6%, p <0.005, respectively). Nevertheless, the SUVmax cut-off value was determined as 4.26 by the ROC analysis. It showed sensitivity, specificity, PPV and NPV, respectively, as 75%, 73.9%, 83.9%, and 51.5%.

Liao et al. have reported similar results to ours in a 33-patient study (16). However, Kramer et al. and Orki et al. have reported a FDG-PET/CT NPV of 92% and 100% at malignant pleural diseases (17,18). They also showed a higher sensitivity, specificity and PPV (95% and 100%, 92% and 94.8%, 95% and 95.6%) than our study. Kramer et al. and Orki et al. analyzed 32 patients and 83 patients (17,18). Their studies had a higher

TABLE 1. THE SUVMAX PLEURAL THICKENING OF THE BENIGN GROUP IS SIGNIFICANTLY LOWER WHEN COMPARED TO THE MALIGNANT GROUP (p <0.05). THE PLEURAL THICKENING SUVMEAN OF THE BENIGN GROUP IS SIGNIFICANTLY LOWER WHEN COMPARED TO THE MALIGNANT ONE (p <0.05)

		Diagnosis						Mann Whitney U Test		
		n	Mean	Median	Min	Max	ss	Mean rank	z	P
Extent of pleural effusion (mm)	Benign	36	42.8	34.5	11	200	33.6	43.79		
	Malignant	68	70.3	52.5	8	215	56.4	57.11		
	Total	104	60.8	41	8	215	51.2		-2.143	0.032
Pleural thickness (mm)	Benign	35	5.1	5	2	10	2.4	33.39		
	Malignant	66	12.2	9	2	40	9.5	60.34		
	Total	101	9.7	7	2	40	8.5		-4.42	0.001
Pleural thickening SUVmax	Benign	23	3.9	3.4	1.34	11.69	2.1	25.39		
	Malignant	64	8.4	6.8	1.39	29.73	5.3	50.69		
	Total	87	7.2	5.6	1.34	29.73	5.1		-4.119	0.001
Pleural thickening SUVmean	Benign	24	2.8	2.8	0.86	5.54	0.9	25.52		
	Malignant	64	4.3	4	1.39	11.23	1.8	51.62		
	Total	88	3.9	3.4	0.86	11.23	1.7		-4.268	0.001

TABLE 2. PLEURAL THICKENING SUVMAX, PLEURAL THICKENING SUVMEAN, PLEURAL FLUID SUVMAX, AND PLEURAL FLUID SUVMEAN ROC ANALYSIS RESULTS

	Cut-off	Sensitivity %	Specificity %	PPV%	NPV%	AUC
Pleural thickening SUVmax	4.26	75.00	73.90	88.90	51.50	0.791
Pleural thickening SUVmean	3.085	71.90	70.80	86.80	48.60	0.797
Pleural fluid SUVmax	1.96	43.50	43.20	58.80	29.10	0.425
Pleural Fluid SUVmean	1.665	44.90	43.20	59.60	29.60	0.431

PPV: positive predictive value. NPV: negative predictive value. AUC: area under the curve.

TABLE 3. DIAGNOSTIC VALUE OF FDG-PET/CT AT PLEURAL THICKNESS: SUMMARY OF LITERATURE

Ref. No	Authors, publication year	Patient number (n)	Parameters	Sensitivity %	Specificity %	PPV %	NPV %
18	Orki et al, 2009	83	SUVmax >3	100	94.8	95.6	100
17	Kramer et al, 2004	32	SUVmax >2 Pleural uptake on PET	95	92	95	92
19	Kim et al, 2011	33	L/Prim*** >0.17 Pleural uptake on PET	79	56	83	50
21	Toaff et al, 2005	31	SUVmax >1.7 Pleural uptake on PET	43	70	75	37
1	Nakajima et al, 2015	36	TNR* (Th12**) >0.95 Pleural uptake on PET	57	91	80	77
16	Liao et al, 2012	33	SUVmax >2.5 Pleural uptake on PET	815	83.3	95.7	50
22	Alkhawaldeh et al, 2011	61	SUVmax >2.4	100	94	94	100
13	Letovanec et al, 2012	47	SUVmax >2.2	53	91	75	79
23	Duysinx et al, 2006	79	SUV normalized body weight >2.2	86	75	86	75
	Our study	106	SUVmax >4.26	75	73.9	83.9	51.5

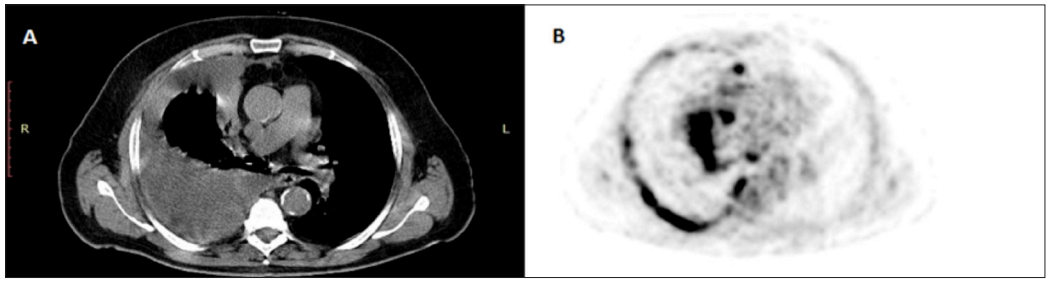

Figure 3. Adenocarcinoma infiltration in a 69-year-old man.

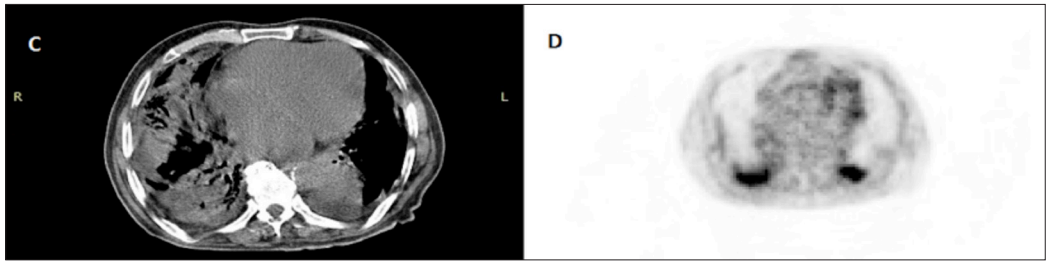

Figure 4. Pleural fluid inflammation in an 83-year-old man.

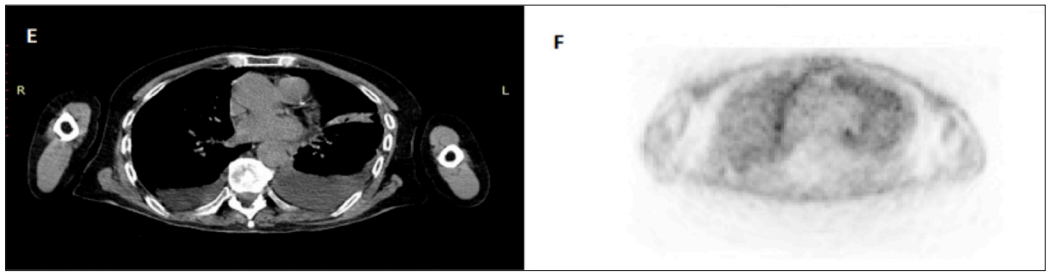

Figure 5. Chronic pleuritis in an 83-year-old man.

NPV and PPV because they had an inferior number of patients and they did not use a ROC curve to standardize the SUVmax cut-off value (Table 3). These results suggest that FDG-PET/CT can play a significant role in diagnosing lung cancer patients with pleural thickness with a low false-positive rate but negative findings under FDG-PET/CT should be confirmed by further tests. Our study also showed that a pleural effusion FDG uptake is not a good criterion for a malignant potential of the effusion. After the ROC curve analysis, we defined the SUVmax cut-off value as 1.96 and sensitivity, specificity, PPV and NPV as 43.5%, 43.2%, 58.8%, and 29.1%. Kim et al. found that the SUVmax values that were normalized for pleural effusion FDG uptake showed diagnostic values in the ROC analysis similar to those in our study (19). Porcel et al. have published a meta-analysis based on 14 studies with more than 600 patients and, as in our results, it suggests that FDG-PET/CT imaging does not seem to be sufficient in the routine workup for determining the cause of pleural effusion (20).

Conclusion

As in literature, FDG-PET/CT has respective sensitivity, specificity, PPV but not NPV to diagnose malign pleural thickness. Negative findings in FDG-PET/CT should be confirmed by further tests. Besides, FDG-PET/CT alone has no diagnostic value to detect malign pleural effusions. Among the known invasive imaging systems, PET/CT imaging is the most accurate technique with the highest sensitivity and specificity. On the other hand, the glucose metabolism in malignant cells of adenocarcinoma and mesothelioma is slow. This is the reason why differentiation of malignancy is not possible by PET/CT imaging only.

Acknowledgement

No sponsors supported this study. We thank Oznur Akhan Aşık for her contribution to the revision of this article. RAM

Referencias bibliográficas

1. Nakajima R, Abe K, Sakai S. Diagnostic ability of FDG-PET/CT in the detection of malignant pleural effusion. *Medicine* 2015;94(29)
2. Çelen YZ, Elboğa U, Kalender E. Plevra Hastalıklarının Görüntülenmesinde Nükleer Tıp Yöntemleri. *Plevra Bülteni* 2011;118-22
3. Warburg O. *The metabolism of tumors*. 1st Ed. New York: Richard R. Smith; 1931, p. 129-69
4. Sharma P, Singh H, Basul S, et al. Positron emission tomography/computed tomography in the management of lung cancer: An update. *South Asian J Cancer* 2013;3:171-8
5. Savaş R. PET/BT Nedir? Endikasyonları Nelerdir? *Klinik Gelişim* 2010;23:40-4
6. Cook GJR, Wegne EA, Fogelman I. Pitfalls and artifacts in 18FDG PET and PET/CT oncologic imaging. *Semin Nucl Med* 2004;34:122-33
7. Ambrosinia V, Nicolini S, Carolia P, et al. PET/CT imaging in different types of lung cancer: An overview. *Eur J. Radiol* 2012;81:988-1001
8. Arbak P, Karacan Ö, Erden F. 1990-1994 yılları arasında izlenen plevral sıvılı olguların özellikleri. *Tüberküloz ve Toraks* 1998;46:256-63
9. Ünlü M, Şahin Ü, Akkaya A, et al. Plevral efüzyonların etiyolojisinin araştırılması. *Solunum Hastalıkları* 2001;12:212-5
10. Romero-Canderia S, Hernandez L, Romero-Brufao S, et al. Is it meaningful to use biochemical parameters to discriminate between transudative and exudative pleural effusions? *Chest* 2002;122:1524-9
11. Erk M, Demir T, Gemicioğlu B, et al. Plörezide tanı zorlukları 1992;16:503-9
12. Yamamuro M, Gerbaudo VH, Gill RR, et al. Review Morphologic and functional imaging of malignant pleural mesothelioma. *Eur J Radiol* 2007;64:356-66
13. Letovanec I, Allenbach G, Mihaescu A, et al. 18F-fluorodeoxyglucose PET/CT findings in pleural effusions of patients with known cancer. *Nuklearmedizin* 2012;51(5):186-93
14. Erasmus JJ, McAdams HP, Rossi SE, et al. FDG PET of pleural effusions in patients with non-small cell lung cancer. *AJR Am J Roentgenol* 2000;175:245-9
15. Benard F, Sterman D, Smith RJ, et al. Metabolic imaging of malignant pleural mesothelioma with fluorodeoxyglucose positron emission tomography. *Chest* 1998;114:713-22
16. Liao R, Yang X, Wang S, et al. Clinical role of F-18 FDG-PET/CT in differentiating malignant and benign pleural effusion in patients with lung cancer. *Zhongguo Fei Ai Za Zhi* 2012;20(15):652-5
17. Kramer H, Pieterman RM, Slebos DJ, et al. PET for the Evaluation of Pleural Thickening Observed on CT. *J Nucl Med* 2004;45:995-8
18. Orki A, Akin O, Tasci AE, et al. The Role of Positron Emission Tomography/Computed Tomography in the Diagnosis of Pleural Diseases. *Thorac Cardiovasc Surg* 2009;57:217-21
19. Kim BS, Kim IJ, Kim SJ, et al. Predictive value of F-18 FDG PET/CT for malignant pleural effusion in non-small cell lung cancer patients. *Onkologie* 2011;34:298-303
20. Porcel JM, Hernández P, Martínez-Alonso M, et al. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. *Chest* 2015;147(2):502-12
21. Toaff JS, Metser U, Gottfried M, et al. Differentiation between malignant and benign pleural effusion in patients with extra-pleural primary malignancies. *Invest Radiol* 2005;40:204-9
22. Alkhawaldeh K, Biersack HJ, Henke A, et al. Impact daul-time-point F-18 FDG PET/CT in assessment of pleural effusions in patients non-small cell lung cancer. *Clin Nucl Med* 2011;36: 423-28
23. Duysinx BC, Larock MP, Nguyen D, et al. 18F-FDG PET imaging in assessing exudative pleural effusions. *Nucl Med Commun* 2006;27(12):971-76