Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2020; 42(5):496-503

Research Article /Araştırma Makalesi

Mediastinoscopy: A Depreciated or Still Viable Method For N-Staging of Non-Small Cell Lung Cancer?

Mediastinoskopi: Küçük Hücreli Dışı Akciğer Kanseri N-Evrelemesinde Hala Geçerli mi Yoksa Değersiz Bir Yöntem midir?

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Abstract: This study compares the two most frequently used methods, combined positron emission tomography-computed tomography (PET/CT) and mediastinoscopy, in detecting mediastinal lymph node metastases. It has been investigated whether PET/CT can be used as an alternative method to mediastinoscopy which is considered the gold standard in detecting mediastinal lymph node metastasis. Mediastinal lymph node metastasis is an important factor in treatment and prognosis of non-small cell lung cancer. A total of 102 patients diagnosed with non-small cell lung cancer by our clinic between 2012 and 2017, were enrolled in the study. In total 277 lymph nodes were compared with respect to their histopathologic results and their involvement in positron emission tomography. Specificity value of PET/CT was detected as 84.5% while its negative predictive value, positive predictive value and sensitivity were 82.7%, 69.5% and 66.6%, respectively. In patients who underwent only mediastinoscopy and whose frozen section samples did not demonstrate any metastatic involvement, when histopathological results of lymph node dissection performed by thoracotomy were analyzed, the negative predictive value of mediastinoscopy was calculated as 97%. In total 65 stations including 46 stations smaller than 1 centimeter and 19 stations larger than 1 centimeter, which did not demonstrate any uptake in PET/CT, were sampled. No metastasis was detected in histopathologic staging of these lymph nodes. For patients who do not demonstrate any uptake in mediastinal lymph nodes on PET/CT, invasive lymph node sampling is redundant. However, with the aim of avoiding unnecessary thoracotomies, invasive lymph node sampling is required, even though mediastinal lymph node uptake detected with PET/CT is below the threshold of malignancy.

Keywords: Lymph node, non-small cell lung cancer, mediastinoscopy, positron emission tomography

Özet: Mediastinal lenf nodu metastazı, küçük hücreli dışı akciğer kanserinin tedavisinde ve prognozunda önemli bir faktördür. Mediastinal lenf nodu metastazının tespiti için en sık kullanılan pozitron emisyon tomografi (PET) ile mediastinoskopinin karşılaştırılması yapıldı. PET'in mediastinal lenf nodu metastazının saptanmasında altın standart olarak kullanılan mediastinoskopiye alternatif bir yöntem olup olmadığı araştırıldı. Kliniğimizde 2012 ile 2017 yılları arasında küçük hücreli dışı akciğer kanseri tanısı alan 102 hasta çalışmaya dahil edildi. Bu hastalardan alınan toplam 277 lenf nodu biyopsileri histopatolojik sonuçları ve pozitron emisyon tomografisindeki tutulumları ile karşılaştırıldı. PET'in negatif öngörücülük değeri %82,7, pozitif öngörücülük değeri ise %69,5, duyarlılığı %66,6 iken özgüllüğü %84,5 olarak saptandı. Sadece mediastinoskopi yapılan ve frozen sonucunda tutulum saptanmayan hastalarda torakotomi ile yapılan lenf nodu diseksiyon sonuçları hastalar incelendiğinde mediastinoskopinin negatif öngörücülük değeri %97 olarak saptandı. PET'de tutulumu olmayan; 1 santimetreden küçük 46 adet istasyon ve 1 santimetreden büyük 19 adet olmak üzere toplam 65 istasyon örneklendi. Bu lenf nodlarının histopatolojik evrelemesinde metastaz saptanmadı. PET'inde mediastinal lenf nodlarında tutulum olmayan hastalarda invaziv mediastinal lenf nodu örneklemesinin gerekli değildir. Ancak gereksiz torakotomilerden korumak için, PET'de mediastinal lenf nodlarının tutulumunun, malignite eşiğinin altında olsa bile invaziv mediastinal lenf nodu örneklemesinin yapılması gerekmektedir.

Anahtar Kelimeler: Lenf nodu, küçük hücreli dışı akciğer kanseri, mediastinoskopi, pozitron emisyon tomografisi

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Received 06.11.2019 ***Accepted*** 17.01.2020 ***Online published*** 18.06.2020

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Cite this article as:
Keskin H, Akdeniz Baysal S, Gunduz E, Ergin M, Ozbilim G, Mediastinoscopy: A Depreciated or Still Viable Method For N-Staging of Non-Small Cell Lung Cancer?, Osmangazi Journal of Medicine, 2020; 42(5):496-503 ***Doi:*** *10.20515/otd.643685*

1. Introduction

Lung cancer is the leading cause of cancer-related death all over the world (%17,8-28) and 85% of lung cancer cases are non-small cell lung cancer (NSCLC) (1). Despite new advances in chemotherapy, radiotherapy and surgical techniques, five-year survival is about 10-15% (1). It is known that for NSCLC, the most important factor positively affecting disease-free interval and long-term survival is a lower staging of disease warranting surgical treatment (2). The presence or absence of mediastinal lymph node metastases or distant metastases are crucial determinants for successful surgical treatment of lung cancer, and likewise, mediastinal lymph node involvement is an important prognostic factor for patients (3).

The most frequently used interventional procedures in assessment of mediastinal lymph nodes are; transtracheal and/or transbronchial needle biopsies, ultrasonographic endobronchial or endoesophageal lymph node biopsies, mediastinoscopy and video-assisted thoracoscopic lymph node dissection. Computed tomography (CT) and combined positron emission tomography with 18-F fluorodeoxyglucose (FDG) and computed tomography (PET/CT) are frequently used imaging modalities for non-invasive clinical staging of mediastinal lymph nodes. Among these methods listed, mediastinoscopy is still considered as the gold standard method in mediastinal lymph node staging (4). However, the fact that mediastinoscopy, though accepted as the gold standard method, requires anesthesia and might be the cause of some complications, has initiated the argument whether PET/CT, as a conventional imaging method, can be an alternative in mediastinal lymph node staging.

PET/CT is a non-invasive method used in preoperative hilar and mediastinal lymph node staging of NSCLC at many clinics. PET/CT studies provide valuable information on primary tumors and mediastinal lymph node involvement thereof, based on metabolic tumor volume and standard maximum uptake values (SUVmax) (5).

In this study, we investigated whether PET/CT can be an alternative method to mediastinoscopy in N-staging of NSCLC by comparing clinical staging with PET/CT to postoperative histopathological staging for patients who underwent mediastinal lymph node staging by surgical methods due to NSCLC.

2. Materials and Methods

There were one hundred and thirty-nine patients who were diagnosed with NSCLC and underwent mediastinal lymph node staging referred to our clinic between January 2012 and April 2017 in our tertiary care university teaching hospital, and data from patient files were analyzed retrospectively. Of these, 37 patients who were considered either surgically inoperable due to technically unresectable primary tumors or the presence of distant metastases, or medically inoperable due to insufficient cardiac or pulmonary function were excluded from the study. The remaining 102 patients had a total of 277 mediastinal lymph node stations sampled with invasive procedures. Patients' gender, age, mediastinal lymph node involvement on preoperative PET/CT imaging and results of histopathological examination of sampled lymph nodes were compared.

The generally accepted malignant threshold for SUVmax is 2.5, however, there are studies recommending a threshold of 3.5 in tuberculosis-endemic countries (6-7). Since Turkey is considered a tuberculosis-endemic country, a cut-off value of 3 was used to normalize positive predictive value calculations in our study. The results of PET/CT scans were analyzed to categorize sampled mediastinal lymph node stations into three groups according to the presence or absence of lymphadenopathy and SUVmax values with a cut-off of 3. Those with a SUVmax value over 3 were accepted as positive while those with a lower value were accepted as negative and negative predictive value (NPV) and false positive rate were calculated on this basis. Absence of lymphadenopathy comprises the third group,

thus was evaluated separately, though it was included in the negative group.

Mediastinoscopy and thoracotomy were used for surgical sampling of mediastinal lymph nodes. If preoperative PET/CT showed either enlarged lymph nodes (short-axis wider than 1 cm) or lymph nodes with a SUVmax of 3 or higher, patients went through standard cervical mediastinoscopy with intraoperative frozen-section consultation before proceeding to anatomic tumor resection and systematic hilar and mediastinal lymph node dissection with thoracotomy. In mediastinoscopy, following a collar skin incision above the suprasternal notch and appropriate dissection until and through the pretracheal fascia, upper and lower paratracheal lymph nodes ipsilateral to the lung mass were sampled, as well as subcarinal and contralateral paratracheal lymph nodes if available. If intraoperative frozen-section analysis was positive for malignancy, patients were deemed inoperable and referred to the oncology department for neoadjuvant or definitive treatment. If intraoperative frozen-section analysis was negative for malignancy, we proceeded to thoracotomy with anatomic tumor resection and systematic hilar and mediastinal lymph node dissection. If, on the other hand, preoperative PET/CT showed either no lymph nodes at all, or lymph nodes with a SUVmax of less than 3, then the patients were scheduled for thoracotomy. All samples were sent to the pathology department for histopathological examination.

Ethical approval for this study was obtained from Akdeniz University Medical Faculty Clinical Research Ethics Committee.

Based on the results of histopathological examination of mediastinal lymph nodes, sensitivity, specificity, positive and negative predictive values of PET/CT and negative predictive value of mediastinoscopy were calculated.

Statistical analysis of acquired data was performed with IBM SPSS Statistics for Windows, version 20.00 (IBM Corp., Armonk, N.Y., USA). Continuous variables were expressed as means, standard deviations, minimum and maximum values; categorical variables were expressed as frequency and percentages. For comparisons between groups, chi-square test was used for categorical variables and Student's t test for continuous variables.

3. Results

Eighty three of our patients were men (81. 3%), 19 of them were women (18.7%). Average age was 62.1±9.8 (range 41-87). There were 71 patients who had 153 enlarged (short axis wider than 1 cm) or hypermetabolic (SUVmax higher than 3) mediastinal lymph nodes biopsied with mediastinoscopy, 81 of which were reported to be malignant and 72 of which were benign. There were 39 patients with an intraoperative frozen section consultation resulting in benign mediastinal lymph nodes, who were proceeded to thoracotomy for definitive surgery. An average of 2.2 lymph node stations were sampled per mediastinoscopy, ranging from minimum 2 stations, up to a maximum of 4 stations. There were in total 70 patients who went through thoracotomy and anatomical resection of lung cancer and mediastinal lymph node dissection, with or without prior mediastinoscopy, with either mediastinal lymph nodes that had SUVmax of less than 3 or mediastinoscopic frozen section analysis with a benign result. There were in total 124 lymph nodes stations dissected and sampled from these patients (excluding mediastinoscopic samples, if done), ranging from minimum 2 to a maximum of 5 for each patient (3,4±0,8). Histopathological examination of lymph nodes dissected during thoracotomy revealed that only 15 were metastatic for lung cancer. Among these, only 2 patients had mediastinoscopy before thoracotomy. In other words, only 2 patients had lymph nodes dissected during thoracotomy that were reported as metastatic for lung cancer, in spite of benign results of frozen-section analysis of lymph nodes biopsied with mediastinoscopy prior to thoracotomy.

Out of 71 mediastinoscopies, there was 1 case with a complication of minor vascular injury causing minimal hemorrhage, which did not

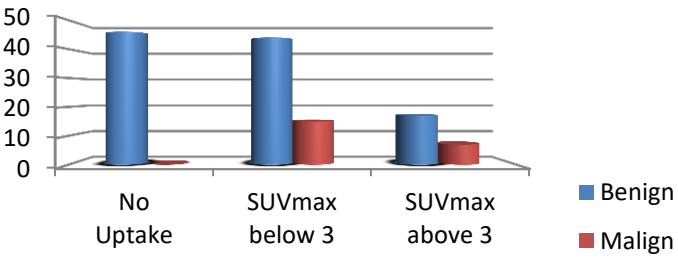
require emergency surgery and was controlled with compression only. As such, the complication rate for mediastinoscopy was calculated as 1.4%.

Based on these findings, sensitivity of PET was calculated as 66.6%, specificity as 84.5% while its positive predictive value (PPV) as 69.5% and negative predictive value (NPV) as 82.7%. For patients who underwent only mediastinoscopy and for whom frozen section examination results did not demonstrate any uptake, results of lymph node dissection on thoracotomy were studied and NPV of mediastinoscopy was detected as 97%. When NPV of mediastinoscopy and PET were compared, NPV of mediastinoscopy was found to be significantly higher based on the statistics. ($p<0.05$)

As a result of the general assessment made for PET, out of 277 stations in total, 28 stations showed false positive value (10,1%) while 32 stations showed false negative value (11,5%).

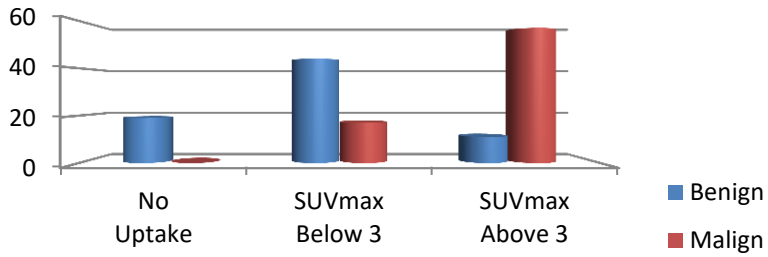
A total of 65 stations were sampled, which did not have PET involvement, consisting of 46 stations smaller than 1 centimeter and 19 stations greater than 1 centimeter. No metastasis was detected in histopathologic staging of these lymph nodes.

A comparison of sizes, SUVmax ratios and histopathological results of mediastinal lymph nodes is given on the Figures 1 and 2.



	No Uptake	SUVmax below 3	SUVmax above 3
Benign	46	44	17
Malign	0	15	7

Figure 1. A comparison of Standard maximum uptake value and histopathologic results of lymph nodes smaller than 1cm on Positron Emission Tomography.



	No Uptake	SUVmax Below 3	SUVmax Above 3
Benign	19	44	11
Malign	0	17	57

Figure 2. A comparison of Standard maximum uptake value and histopathologic results of lymph nodes greater than 1cm on Positron Emission Tomography.

Histopathological analysis of the primary tumor of the patients which was found to be malign as a result of the histopathological examination made after showing negative based on the uptake values from PET as well as its SUVmax on PET and location are given on Table 1. Demographic and tumor-related characteristics of the patients are summarized in Table 2.

Table 1. Characteristics of the primary tumors of the patients with a negative value on Positron Emission Tomography, which were found to be malignant as a result of the histopathologic examination..

Histopathology	Adenocarcinoma	9
	Squamous Carcinoma	6
Location	Central	9
	Peripheral	6
Suvmax Level	Higher Than Nine	10
	Lower Than Nine	5

Table 2. Demographic data of patients

		No:	%
Gender	Male	83	81,3
	Female	19	18,7
Age (years)	Mean±SD	62,1±9,8	
	Range	41-87	
Tumor size (mm)	Mean±SD	28,3±12,9	
	Range	12-63	
Tumor location	Right	64	62,4
	Left	38	37,6
Tumor histology	Squamous cell	32	31,4
	Adenocarcinoma	63	61,8
	Other type	7	6,8
Tumor SUVmax	Mean±SD	9,59±4,81	
	Range	5,2-24,7	

SD: Standard deviation SUVmax: maximum standardized uptake value

4. Discussion

In this study, while the lack of mediastinal lymph node involvement in PET-CT had a negative predictive value of 100%, the negative predictive value of mediastinal lymph node involvement in PET-CT below the cut-off value was found to be 74%. It was observed that the number of lymph node stations sampled in mediastinoscopy positively increased the efficacy of the procedure. We also observed that invasive mediastinal lymph node sampling gained more importance in cases in which the primary tumor had an SUVmax of higher than 9, central localization, invasion of vascular structures or a histopathological diagnosis of adenocarcinoma.

As in all oncological diseases, imaging methods play an important role in staging for lung cancer as well. The most frequently used imaging method for staging of lung cancer patients is CT. Studies have shown that lymph nodes larger than 1 centimeter can be considered to have a high probability of metastasis (8). However, as many as 40% of lymph nodes larger than 1 cm have no metastases in histopathological examination, yet, at least 20% of lymph nodes smaller than 1 centimeters are found to be metastatic (9). The inaccuracy of clinical staging of mediastinal lymph nodes for lung cancer only with CT have led researchers to focus on studies utilizing PET (and PET/CT).

Earliest studies on PET and NSCLC revealed a high ratio of specificity, NPV and PPV. In a study made by Bury and his friends in 1997, specificity was found to be 100%, PPV to be 100% while NPV to be 96%. (10) In another study made ten years after this, specificity

ratio was found to be 73%, PPV was 55% and NPV was 87%. In this study of us, we established the specificity ratio as 84,5%, PPV as 69.5% and NPV as 82.7%. Reason of the decline in specificity ratio of PET in years can be explained with the fact that while only a limited number of patients underwent PET at the beginning, now it is a routine method used for NSCLC.

Various researches have been made on PET with the highest specificity and negative predictive value among other conventional imaging methods. In a study made by Lee and his friends, it was established that if SUVmax was taken as 5,3 then its specificity ratio would go up to 98%. (11) Due to this high specificity and negative predictive value of PET, most authors suggest that patients who had negative results on PET should directly undergo thoracotomy. (12) However, again in the same study, thoracotomy demonstrated 18% positive mediastinal lymph nodes in patients who had negative results on PET.

Today the gold standard method used in mediastinal lymph node staging is mediastinoscopy. There is no sufficient information about the number of lymph nodes to be sampled by mediastinoscopy. In a study they made, Nelson and his friends suggest that besides suspicious lymph nodes to be sampled, other samples should be collected as well. In the same study, number of lymph nodes sampled per mediastinoscopy was reported as 2,1. (13) In this study, average number of lymph nodes sampled per mediastinoscopy was established as 2,2. Mediastinoscopy considered as the gold standard method in mediastinal lymph node staging brings some complications. Major complications are hemorrhage due to venous injury, vocal cord paralysis and hoarseness due to recurrent laryngeal nerve injury. And complication rates are about 0,5%. (14) In this study complication rate has been established as 1,4% which is higher than the complication rates recorded in literature. We believe this is due to insufficient number of the sample group. In the invasive mediastinal staging guide published in 2007 by ACCP, specificity and NPV of mediastinoscopy were given as 78% and 89% respectively. (15) Low NPV in mediastinoscopy can be sourcing from lack of enough surgical experience, patient-related factors (short neck, reasons avoiding extension of the head to achieve the desired position etc) and insufficient materials. We suggest that for an effective mediastinoscopy, biopsy samples should be collected from the accessible pretracheal lymph nodes no 2 and 4 on the left or right as well as from precarinal lymph node no 7. In this study NPV of mediastinoscopy was established as 97%. The reason of this high rate can be the excessive number of lymph nodes taken by mediatinoscopy. When NPV of mediastinoscopy and PET were compared, NPV of mediastinoscopy was found to be significantly higher based on the statistics. ($P<0.05$) Even though it is the gold standard, it is not possible for all patients to undergo mediastinoscopy due to unnecessary surgical risks and increasing cost. Therefore, today, the argument is which patients should undergo thoracotomy without having mediastinal lymph node sampling.

While Certain authors suggest that thoracotomy should be performed without lymph node sampling in cases where PET result is negative, certain authors suggest that in some cases invasive mediastinal lymph node sampling should be performed even though PET result is negative. (16-17) These cases they have suggested are; having SUVmax higher than 9, histopathological diagnosis of adenocarcinoma and invasion of centrally located and vascular structures. All these conditions are used to increase NPV of the procedure. In our study, NPV was established as 100% only in lymph nodes which did not show any uptake on PET: Apart from this NPV was established as 100% in none of other cases. In this study, PET was negative and when cases which were found to be malign as a result of histopathological examination during lymph node sampling, were studied, only 33% were observed to meet the criteria given above. (Table 1) It is possible to decrease unnecessary thoracotomies with mediastinoscopy that patients with negative PET results who meet the criteria given above, will undergo. However, it should be noted that even when these criteria are taken into consideration,

most patients may still undergo unnecessary thoracotomies.

Endobronchial ultrasound (EBUS) has gained widespread popularity for diagnosis and mediastinal staging of lung cancer (18). The addition of endoesophageal fine needle aspiration to the available techniques have increased efficacy of the procedure (17). Recent literature has ample evidence for efficacy of EBUS and cost-effectiveness, compared to mediastinoscopy (20). Navani et al. (21) have pointed out in their randomized and controlled study that EBUS as a first-line procedure for diagnosis and staging of lung cancer significantly increases survival. We did not include patients who went through EBUS for mediastinal staging of potentially operable lung cancer in this study, because EBUS has only been available in our hospital since 2016 (for less than a third of the study duration), and while EBUS is substantially practical in diagnosis and staging of lung cancer, intrinsic limitations of cytopathology samples with EBUS compared to histopathology of surgical samples of mediastinal lymph nodes, for the purposes of this study, precludes acceptable comparison of clinical implications of PET/CT to that of EBUS.

Today it is difficult to continue using PET effectively in mediastinal lymph node staging. It is more useful as a screen test. It is not meaningful to perform mediastinoscopy for every patient diagnosed with NSCLC since it will increase both the cost and surgical risks. In case PET results to be performed for patients diagnosed with NSCLC do not show any uptake in mediastinal lymph nodes, thoracotomy can be started without mediastinal staging. In contrary cases, histopathologic staging must definitely be performed. Until NPV of PET as a conventional method reaches 100% along with new studies to be made, it is not convenient to be used in mediastinal staging because it may cause unnecessary thoracotomies.

5. Conclusion

In conclusion, invasive lymph node sampling is redundant for patients whose PET results did not demonstrate any uptake in mediastinal lymph nodes however, it is still required for patients whose NPV on PET is not 100% although their SUVmax in mediastinal lymph nodes are below threshold of malignancy in order to avoid any unnecessary.

We suggest that during the mediastinoscopy to be performed, collecting biopsy specimens from pretracheal lymph nodes located by the mass and from precarinal lymph node if accessible, will increase effectiveness of the procedure.

REFERENCES

1. Yıldız O, Cangır AK, Kılıç D, et al. Importance of SUVmax threshold in positron emission tomography-computed tomography assessment of mediastinal and hilar lymph nodes in non-small cell lung cancer. *Turk Gogus Kalp Dama* 2016;24:333-9
2. Metin M, Çıtak N, Büyükkale S, et al. Akciğer kanserinin mediastinal evrelemesinde mediastinoskopinin etkinliği yıllar geçtikçe artmakta mıdır? *Turk Gogus Kalp Dama* 2015;23:499-506
3. Kandemir Z, Şentürk A, Özdemir E, et al. The Evaluation Of Hypermetabolic Mediastinal–Hilar Lymph Nodes Determined By Pet/Ct İn Pulmonary And Extrapulmonary Malignancies: Correlation With Ebus-*Tbna Turk J Med Sci* 2015;45:1234-42
4. Öneş T, Erdil TY. Toraks Malignitelerinin Evreleme Ve Yeniden Evrelemesinde Pet Uygulamaları. *Toraks Cerrahisi Bülteni* 2015; 6: 180-91
5. Erdoğan Y, Özyürek BA, Özmen Ö, et al. The Evaluation of FDG PET/CT Scan Findings in Patients with Organizing Pneumonia Mimicking Lung Cancer. *Molecular Imaging and Radionuclide Therapy* 2015;24: 60-5
6. Kim BT, Lee KS, Shim SS et al Stage T1 non-small cell lung cancer: preoperative mediastinal nodal staging with integrated FDG PET/CT—a prospective study. *Radiology* 2006;241:501-9
7. Lee SM, Park CM, Paeng JC, Im HJ, Goo JM, Lee HJ, Kang CH, Kim YW, Kim JI et al. Accuracy and predictive features of FDG-PET/CT and CT for diagnosis of lymph node metastasis of T1 non-small-cell lung cancer manifesting as a subsolid nodule. *Eur Radiol*. 2012;22:1556-63.
8. Shingyoji M, Nakajima T, Yoshino M, et al. Endobronchial Ultrasonography for Positron Emission Tomography and Computed

Tomography–Negative Lymph Node Staging in Non-Small Cell Lung Cancer. *Ann Thorac Surg* 2014;98:1762–8.
9. Perigaud C, Bridji B, Roussel JC, et al. Prospective preoperative mediastinal lymph node staging by integrated positron emission tomography–computerised tomography in patients with non-small-cell lung cancer. *European Journal of Cardio-Thoracic Surgery*,2009;36:731-6
10. Bury T, Dowlati A, Paulus P, et al. Whole-body 18FDG positron emission tomography in the staging of non-small cell lung cancer. *Eur Respir J* 1997;10:2529-34.
11. Lee BE, Redwine J, Foster C, et al. Mediastinoscopy might not be necessary in patients with non-small cell lung cancer with mediastinal lymph nodes having a maximum standardized uptake value of less than 5.3. *J Thorac Cardiovasc Surg* 2008;135:615-9.
12. Perigaud C, Bridji B, Roussel JC et al. Prospective preoperative mediastinal lymph node staging by integrated positron emission tomography-computerised tomography in patients with non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2009;36:731-6.
13. Nelson E, Pape C, Jørgensen OD, Olsen KE, Licht PB. Mediastinal staging for lung cancer: the influence of biopsy volume. *Eur J Cardiothorac Surg* 2010;37:26-9.
14. Lemaire A, Nikolic I, Petersen T, et al. Nine-year single center experience with cervical mediastinoscopy: complications and false negative rate. *Ann Thorac Surg* 2006;82:1185-9.
15. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:202-20.
16. Billé A, Pelosi E, Skanjeti A, et al. Preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer: accuracy of integrated positron emission tomography and computed tomography. *Eur J Cardiothorac Surg* 2009;36:440-5.
17. Al-Sarraf N, Aziz R, Gately K, et al. Pattern and predictors of occult mediastinal lymph node involvement in non-small cell lung cancer patients with negative mediastinal uptake on positron emission tomography. *Eur J Cardiothorac Surg* 2008;33:104-9.
18. Sampsonas F, Kakoullis L, Lykouras D, Karkoulias K, Spiropoulos K. EBUS: Faster, cheaper and most effective in lung cancer staging. *Int J Clin Pract*. 2018;72(2).
19. Hakrush O, Adir Y, Schneer S, Abramovic A, et al. Per-Esophageal Needle Aspiration of Parenchymal Lung Lesions and Mediastinal Lymph Nodes Using an Endobronchial Ultrasound Bronchoscope. *Isr Med Assoc J*. 2019;21:738-42.
20. Czarnecka-Kujawa K, Yasufuku K. The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer. *J Thorac Dis*. 2017;9:83-S97.
21. Navani N, Nankivell M, Lawrence DR, et al. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: An open-label, pragmatic, randomized controlled trial. *The Lancet Respiratory Medicine*. 2015; 3: 282- 9.