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Comparison of PET-CT and Invasive Intervention Results of Mediastinal Lymph Nodes in Lung Cancer Cases: Descriptive Study

Akciğer Kanseri Olgularında Mediastinal Lenf Nodu Tutulumunun PET-BT ve İnvaziv Girişim Sonuçlarının Karşılaştırılması: Tanımlayıcı Çalışma

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ABSTRACT Objective: Appropriate treatment method in patients diagnosed with lung cancer tumor-lymph node-metastasis staging is used to identify and predict disease progression. Mediastinal staging is particularly valuable in this regard. This study was conducted to compare the positron emission tomography-computed tomography (PET-CT) involvement of mediastinal lymph nodes in patients with lung cancer with the results of invasive methods. **Material and Methods:** A research group of 100 cases diagnosed with lung cancer was made in our clinic between January 1, 2015-March 30, 2022. Based on the histopathological data of cases in which invasive diagnosis/treatment was performed in the evaluation of the mediastinum, the consistency of PET-CT in mediastinal staging will be determined by the percentage consistency method. **Results:** Of the patients, 87% were male and 13% were female. The mean age was 61.6 (34-78) years. In our study, sensitivity for mediastinal staging of PET-CT was determined 85%, specificity 75%, false positive value 25%, false negative value 15%, positive predictive value 70%, negative predictive value 88%, likelihood ratio 3.36 and accuracy rate 79%. **Conclusion:** We believe that the need for invasive staging is less in patients with low fluorodeoxyglucose uptake in mediastinal lymph nodes on PET-CT, but invasive staging is necessary according to the localization of the lymph node in high-risk cases, even if PET-CT is negative, in order to reduce false-negative results and protect patients from unnecessary surgery.

Keywords: Lung neoplasms; lymph nodes; mediastinum; positron emission tomography-computed tomography

ÖZET Amaç: Akciğer kanseri tanısı almış olgularda, uygun tedavi yöntemini belirlemek ve hastalık sürecini tahmin etmek için tümör, lenf nodu ve metastaz evrelemesinden yararlanılır. Mediastinal evreleme özellikle bu açıdan son derece kıymetlidir. Bu çalışma, akciğer kanserli hastalarda mediastinal lenf nodlarının pozitron emisyon tomografi-bilgisayarlı tomografi (PET-BT) tutulumunun, invaziv yöntemlerin sonuçlarıyla karşılaştırılması amacıyla yapıldı. **Gereç ve Yöntemler:** Kliniğimizde 1 Ocak 2015-30 Mart 2022 tarihleri arasında akciğer kanseri tanısı almış 100 olgulu araştırma grubu oluşturuldu. Mediastenin değerlendirilmesinde, invaziv tanı ya da tedavi yöntemi yapılmış olguların histopatolojik verilerine dayanarak PET-BT'nin mediastinal evrelemedeki tutarlılıkları yüzde tutarlılık yöntemiyle saptanacaktır. **Bulgular:** Hastaların %87'si erkek, %13'ü kadın idi. Ortalama yaş 61,6 (34-78) yıl idi. Çalışmamızda PET-BT'nin mediastinal evrelemesi için duyarlılık %85, özgüllük %75, yanlış pozitif değer %25, yanlış negatif değer %15, pozitif öngörü değer %70, negatif öngörü değer %88, olabilirlik oranı 3,36 ve doğruluk oranı %79 olarak tespit edildi. **Sonuç:** PET-BT'de mediastinal lenf nodlarında florodeoksiglukoz tutulumu düşük olan hastalarda invaziv evreleme ihtiyacının daha az olduğunu, ancak yanlış negatif sonuçları düşürmek ve olguları gereksiz cerrahiden korumak amacıyla yüksek riskli olgularda PET-BT negatif olsa bile lenf nodunun lokalizasyonuna göre invaziv evrelemenin gerektiği düşüncesindeyiz.

Anahtar Kelimeler: Akciğer neoplazileri; lenf nodları; mediasten; pozitron emisyon tomografi-bilgisayarlı tomografi

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Lung cancer is a common disease worldwide with a high mortality rate. Every year, 1.6 million people lose their lives due to lung cancer. Lung cancer causes for more than one-fifth of cancer-related deaths. Lung cancers are divided into 2 main groups; small cell lung cancer and non-small cell lung cancer. 85% of these are non-small cell lung cancer and the rest are small cell lung cancer.[1-4] Tumor-lymph node-metastasis staging is used to determine the treatment plan and disease process of patients diagnosed with lung cancer. In particular, mediastinal staging is extremely important in this process. Therefore, mediastinal staging should be meticulously examined before resection. Radiological methods such as computed tomography (CT) and positron emission tomography-CT (PET-CT) are generally preferred for this staging.[5] Different invasive techniques are used for histopathological diagnosis of lymph nodes located in the mediastinum. These include endoscopic/ultrasonographic transbronchial fine needle aspiration, transbronchial fine needle aspiration biopsy, percutaneous transthoracic needle aspiration biopsy, cervical mediastinoscopy, video-assisted thoracoscopic surgery, anterior mediastinotomy, extended mediastinoscopy and thoracotomy. Mediastinoscopy is generally considered the gold standard for pre-resection staging.[6] PET-CT is a frequently used and absolutely necessary noninvasive staging method in the evaluation of surgical operability.[7] The basic rule in the staging process is to determine the advanced stage of the disease. High fluorodeoxyglucose (FDG) uptake in the tumor or mediastinal lymph nodes may guide biopsy for histopathological diagnosis in cases such as distant metastasis.[8]

In non-small cell lung cancer cases with surgical operability, the best treatment option is surgical treatment. In addition to anatomic resection, complete removal of regional and mediastinal lymph nodes is required.[9] In lung cancer cases, curative treatment initiated before a metastatic tumor is detected does not show significant clinical benefit and unnecessary side effects and complications may develop. Therefore, curative treatments should not be initiated directly unless distant metastases are excluded by FDG PET-CT scanning. In patients other than those with known obvious and widespread metastases, if positive PET-CT findings that may cause uncertainty regarding curative treatment are detected, it is important to confirm these lesions with biopsy. The aim of this study is to compare the PET-CT involvement of mediastinal lymph nodes with the results of invasive methods by calculating the sensitivity, specificity, false positive and false negative results, negative and positive predictive values, likelihood ratio and accuracy rate of PET-CT in mediastinal staging based on histopathological data of lung cancer cases.

MATERIAL AND METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki. Dicle University Faculty of Medicine Clinical Research Ethics Committee approval was received for our research (date: April 14, 2022; no: 140).

The study group consisted of 100 cases of Dicle University Medical Faculty Hospital Chest Surgery Clinic diagnosed with lung cancer between January 1, 2015-March 30, 2022. The study criteria included patients between the ages of 20-80 diagnosed with lung cancer and those who underwent biopsy of their mediastinal lymph nodes (N2) using various invasive methods after PET-CT scans. In this study, patients with diabetes mellitus, those in any inflammatory or infectious process, those who received neoadjuvant radiotherapy/chemotherapy, and those who had PET-CT imaging less than a month ago were not included in the study. Hospital files and PET-CT results that met the above characteristics in the last 7 years were retrospectively included in the study. The second stage of the study was planned within this framework based on histopathological evidence in terms of mediastinal staging after PET-CT in the case group.

In the evaluation of mediastinum, the sensitivity, specificity, negative predictive value and positive predictive value of PET-CT in mediastinal staging were measured by comparing the histopathological data of the cases in which invasive diagnosis/treatment method (endobronchial ultrasound, mediastinoscopy, thoracotomy) was applied. The consistency of PET-CT with the histopathological results of invasive surgical interventions applied in me-

diastinal staging was obtained by percentage consistency method. IBM SPSS 21.0 for Windows statistical measurement program was used in the statistical evaluation of our study data. Measurable variables were categorized with mean±standard deviation and measured with number and percentage (%). Chi-square (χ^2) test was applied in the comparison of qualitative variables. Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and accuracy rate were obtained for mediastinal staging of PET-CT. Hypotheses were taken as 2-sided, and statistical result was accepted as significant if $p \leq 0.05$.

RESULTS

At Dicle University Faculty of Medicine, Department of Chest Surgery January 1, 2015-March 30, 2022. The study was conducted on a total of 100 patients, 50 of whom had a SUV_{max} value of 2.5 and above on FDG PET-CT and 50 of whom had a SUV_{max} value of less than 2.5 and were diagnosed with lung cancer between 2000-2010. The majority of these patients were male (87%) and the mean age was 61.6. The most common type of cancer in the study was adenocarcinoma. Thoracotomy was determined to be the most commonly used method in the evaluation of samples taken from mediastinal lymph nodes. Samples taken by thoracotomy generally had low SUV_{max} values, indicating that the sampling method may affect SUV_{max} values (Table 1). Histopathologically, 59% of the cases were adenocarcinoma, 36% were squamous cell carcinoma, and 5% were small cell carcinoma. In our study, lung cancer was found to be associated with gender, and the chi-square test found that lung cancer was more common in men than in women, which was statistically significant ($p \leq 0.05$), (Table 2).

TABLE 1: Sampling table of mediastinal (N2) lymph nodes

Sampling methods	SUV_{max}<2,5	SUV_{max}≥2,5	Count (n)
EBUS	0	13 (1N, 12P)	13
Mediastinoscopy	0	6 (0N, 6P)	6
Thoracotomy	43 (38N, 5P)	5 (3N, 2P)	48
EBUS+mediastinoscopy	2 (1N, 1P)	5 (0N, 5P)	7
EBUS+thoracotomy	4 (4N, 0P)	6 (1N, 5P)	10
Mediastinoscopy+thoracotomy	0	13 (9N, 4P)	13
EBUS+mediastinoscopy+thoracotomy	1 (1N, 0P)	2 (1N, 1P)	3
Total	50 (44N, 6P)	50 (15N, 35P)	100

EBUS: Endobronchial ultrasound; P: Positive; N: Negative

TABLE 2: Evaluation of the relationship between lung cancer and gender using the chi-square (χ^2) test

		Gender			
Histopathological diagnosis		Female	Male	Total	p value
Adenocarcinoma	Count (n)	13	46	59	
	Histopathological diagnosis related %	22.0%	78.0%	100.0%	
	Gender related %	100.0%	52.9%	59.0%	
Squamous cell carcinoma	Count (n)	0	36	36	
	Histopathological diagnosis related %	0.0%	100.0%	100.0%	**0.006**
	Gender related %	0.0%	41.4%	36.0%	
Small cell carcinoma	Count (n)	0	5	5	
	Histopathological diagnosis related %	0.0%	100.0%	100.0%	
	Gender related %	0.0%	5.7%	5.0%	

TABLE 3: Analysis of PET-CT and histopathological results in mediastinal lymph nodes

Pathological diagnosis	PET-CT (+) Pathology (+)	PET-CT (+) Pathology (-)	PET-CT (-) Pathology (+)	PET-CT (-) Pathology (-)	Total
Adenocarcinoma	21 (21%)	6 (6%)	5 (5%)	27 (27%)	59 (59%)
Squamous cell carcinoma	10 (10%)	9 (9%)	1 (1%)	16 (16%)	36 (36%)
Small cell carcinoma	4 (4%)	0 (0%)	0 (0%)	1 (1%)	5 (5%)
Total	35 (35%)	15 (15%)	6 (6%)	44 (44%)	100 (100%)

PET-CT: Positron emission tomography-computed tomography

TABLE 4: Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio and accuracy rate for mediastinal staging of PET-CT

Sensitivity	85%
Specificity	75%
False positive value	25%
False negative value	15%
Positive predictive value	70%
Negative predictive value	88%
Likelihood ratio	3,36
Accuracy rate	79%

PET-CT: Positron emission tomography-computed tomography

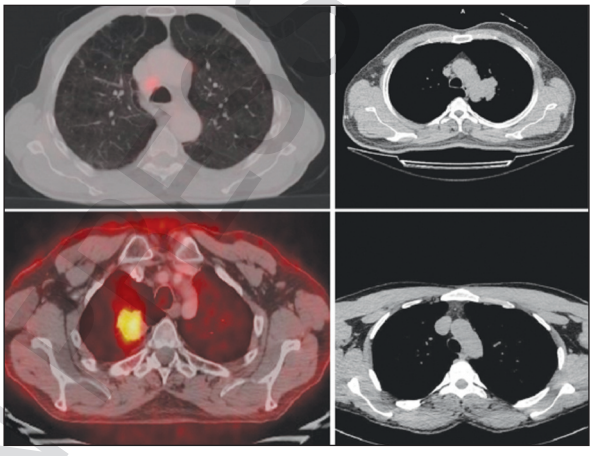

FIGURE 1: CT and PET-CT images of the mediastinum in lung cancer
PET-CT: Positron emission tomography-computed tomography

In the comparison of PET-CT and histopathological results, no tumor was observed in lymph node histopathology in 6 of 27 adenocarcinoma patients with positive PET-CT, and similarly, no tumor was observed in 9 of 19 squamous cell carcinoma patients. Tumor was detected in the mediastinal lymph nodes in 4 of 4 patients with small cell carcinoma and PET-CT involvement. Histopathological malignancy was observed in the mediastinal lymph node in 5 of 32 adenocarcinoma patients without malignant involvement in PET-CT and in 1 of 17 squamous cell carcinoma patients (Table 3). PET-CT was found to have high sensitivity (85%) and specificity (75%) overall, and low false positive and negative rates. Positive and negative predictive values (70% and 88%) support PET-CT as a reliable diagnostic tool (Table 4).

DISCUSSION

Lung malignancy is still a common type of cancer today and despite advances in medical treatment options, it is the leading cause of cancer-related deaths.[1] In lung cancer, tumor-lymph node-metastasis staging and especially mediastinal staging are important to determine the stage of the disease and the treatment method. Today, FDG PET/CT has a critical role in treatment planning. This examination determines conditions with a high risk of metastasis, and these conditions require histopathological examination. Curative treatment should not be initiated unless metastases are excluded with FDG PET-CT. It is important to confirm positive PET-CT findings with biopsy. The limited accuracy of FDG PET-CT in evaluating lymph nodes has been demonstrated in many studies.[10] There are still uncertainties regarding whether surgery will be performed and whether additional invasive examinations are necessary in lung cancer patients whose mediastinal lymph nodes are negative with PET-CT. Although there are studies supporting that PET-CT can reduce some invasive procedures, it is still recommended to use additional invasive methods for detailed diagnosis and staging.[11] FDG PET-CT can be misleading in detecting lymph node metastases. While it provides 85% sensitivity

in lymph nodes larger than 1 cm, this rate may decrease to 32% in smaller nodes. Lesions with a SUV_{max} value of more than 2.5 usually indicate malignancy, but many benign conditions can also cause similar FDG uptake. These include tuberculosis, sarcoidosis, aspergillosis, coccidioidomycosis, vasculitis and organizing pneumonia.[12-14] It has been reported that FDG uptake on PET-CT may differ in the evaluation of the possibility of mediastinal malignancy in patients living in regions where granulomatous diseases are endemic. In these patients, the sensitivity of PET-CT was calculated as 87% and the specificity as 82%.[15,16] In another study, a meta-analysis of 16 studies, the average sensitivity and specificity of FDG PET-CT for lymph node staging on a case-by-case basis were found to be 53% and 83%, respectively, in countries where tuberculosis is endemic, and 74% and 89%, respectively, in countries where tuberculosis is not endemic.[13] Our region is also endemic in terms of granulomatous diseases, and the sensitivity and specificity of our study were found to be 85% and 75%, respectively, and were consistent with the literature. Therefore, metastasis cannot be excluded in mediastinal lymph nodes without FDG uptake on PET-CT, and not all lymph nodes with FDG uptake should be considered metastatic.[7]

Mediastinal lymph node staging is extremely important in diagnostic and therapeutic studies as it affects the prognosis and management of lung cancer. The European Society of Thoracic Surgery (ESTS) published an algorithm for mediastinal staging, which combines imaging, endoscopic and surgical techniques and has a high negative predictive value of 94%.[15] In our study, the negative predictive value was found to be 88%. N2 disease is still controversial due to its high heterogeneity. Rusch et al. studied 4,277 N2 lung cancer patients who underwent R0 surgical resection without inductive therapy. The results of the study in 2,876 patients showed the following: (I) The prognosis of patients with a single lymph node station (N2a) was similar to that of N1 patients (34% vs. 35% 5-year survival); (II) Patients with more than one pathological N2 pattern (N2b) had a worse outcome than N2a (34% vs. 20% 5-year survival).[17] In addition, according to the American College of Chest Physicians (ACCP) Guidelines, N2b pattern should be distinguished from N2 bulky disease, which is characterized by radiological findings of mediastinal lymph node infiltration that does not differentiate morphologically or dimensionally.[18] Schmidt-Hansen et al. reviewed 45 reports on mediastinal staging with FDG PET-CT. The data were analyzed according to different threshold values. For the threshold of "Nodal SUV_{max}>mediastinal blood pool", sensitivity was 77.4% and specificity was 90.1%; for the threshold of "Nodal SUV_{max}>2.5", sensitivity was 81.3% and specificity was 79.4%. The researchers stated that the SUV_{max} threshold value was sufficient for PET-CT scanning. The results showed that lung adenocarcinoma affected the diagnostic accuracy of the cases diagnosed. It was stated that lung adenocarcinoma had different FDG uptake than other types.[19] In the 3rd edition of ACCP, it was recommended not to perform invasive staging in cases where mediastinal lymph nodes were evaluated negative on PET-CT scans. In addition, in cases where mediastinal lymph nodes were radiologically negative, invasive staging was recommended only for patients with centrally located primary tumors or N1 lymph nodes.[18] ESTS Guidelines suggested an additional criterion that the primary tumor size should be greater than 3 cm before proceeding to invasive staging. However, there are no clear guidelines yet on how to evaluate FDG avidity of lymph nodes on PET-CT scans or the importance of primary tumor SUV_{max} in mediastinal lymph node staging. Therefore, the relevant recommendations are generally of low level of evidence.[13] PET-CT is frequently used in hilar and mediastinal lymph node studies. However, its results and benefits may be inconsistent due to false-negative and false-positive results.[20] In a review of the first relevant studies, the false-positive value was reported as 7% to 16%.[21] In our study, the false positive value was found to be 25% and the false negative value was found to be 15%. It has been reported that high glycemic metabolism, inflammatory and infectious processes can increase SUV_{max} and therefore cause false negative results.[22] Therefore, we did not include patients with diabetes mellitus diagnosis and inflammatory and infectious processes in our study. We believe that the reason why our false positive value is higher than the literature is because we con-

ducted our study in an endemic region for granulomatous diseases. Kaseda et al. in their study on non-small cell lung cancer, the team found that mediastinal lymph node involvement was detected in 19.6% of patients with PET-CT scans. The positive predictive value for these patients was calculated as 87.7% and the negative predictive value as 56.3%. In addition, false-negative results were reported in 12.3% of the cases. It was stated that these false-negative results were related to the histological type of adenocarcinoma, central tumor and tumor diameter of 3 cm or more.[23] In a study by Gómez-Caro and his team, the prevalence of occult nodal disease was determined as 32%.[24] In a study by Park and his colleagues, the rate of pathologically positive lymph nodes in studies including 144 lung cancer cases and preoperative PET-CT scans was determined as 14.3%; the true frequencies of N1 and N2 involvement were found to be 9.3% and 4.8%, respectively.[25] In the study by Casiraghi et al. occult nodal metastases were reported at a rate of 13% (29 of 190 non-small cell lung cancer cN0 patients were pN+).[26] However, a history of lung disease ($p<0.001$) and centrally located tumor ($p=0.021$) were accepted as risk factors for false-positive results.[26] In our study, sensitivity for mediastinal staging of PET-CT was calculated 85%, specificity 75%, false-positive value 25%, false-negative value 15%, positive predictive value 70%, negative predictive value 88%, likelihood ratio 3.36 and accuracy rate 79%, and our results were consistent with the literature.

CONCLUSION

In conclusion, the role of FDG PET-CT in lung cancer staging is important, but false positive and negative results, especially in granulomatous diseases, can make accurate diagnosis and treatment planning difficult. Therefore, PET-CT results should be confirmed with histopathological examination. In addition to FDG PET-CT, the use of other invasive and noninvasive tests can provide more accurate results in lung cancer staging. In particular, the use of methods such as CT in addition to PET-CT can provide a more comprehensive approach in lung cancer diagnosis and staging. Although FDG PET-CT is an important tool in lung cancer staging, it can give misleading results. Therefore, when planning treatment for the patient, it is important to evaluate PET-CT results in detail and confirm them with histopathological examination.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Metin Çelik, Menduh Oruç;* ***Design:*** *Metin Çelik, Menduh Oruç;* ***Control/Supervision:*** *Menduh Oruç;* ***Data Collection and/or Processing:*** *Metin Çelik;* ***Analysis and/or Interpretation:*** *Metin Çelik, Menduh Oruç;* ***Literature Review:*** *Metin Çelik;* ***Writing the Article:*** *Metin Çelik;* ***Critical Review:*** *Menduh Oruç;* ***References and Fundings:*** *Metin Çelik;* ***Materials:*** *Metin Çelik.*

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