

Comparison of PET/CT with Invasive Staging and Pathological Staging of Lung Cancer; Analysis of 240 Cases

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ABSTRACT

Objective: After a lung cancer diagnosis, determination of tumor invasion and involvement of mediastinal lymph nodes will indicate tumor stage and operability. The aim of this study was to compare and analyze the lymph node metastasis findings of positron emission tomography-computed tomography (PET/CT) using invasive staging methods and pathological staging in 240 lung cancer cases.

Methods: The PET/CT examination of 240 patients included in the study revealed true positivity in 60 patients, false positivity in 45, true negativity in 103, and false negativity in 4 patients. Univariate analysis indicated that the incidence of occult N2 disease was found to be statistically significantly higher in right upper lobe tumors ($p=0.01$).

Results: Of the 240 patients evaluated, mediastinal sampling was performed using endobronchial ultrasound (EBUS) in 160 patients, and mediastinoscopy in 80 patients. The high specificity rate of mediastinoscopy was found to be close to the accuracy of EBUS.

Conclusion: As a result of the high specificity and accuracy rates, EBUS and mediastinoscopy are among the predominant staging methods. However, we think that mediastinoscopy is still the gold standard method. Total mediastinal lymph node dissection can determine the accurate stage of the disease and aid in determining the prognosis and treatment protocol.

INTRODUCTION

Cancer ranks at the top of the most important health problems in the world. Lung cancer is responsible for 17.8% of cancer-related deaths and 12.8% of all cancer cases.^[1,2] Since lung cancer is usually diagnosed after extensive intrathoracic spread or the development of metastatic disease, the chance of cure after surgical treatment can be as low as 30%.^[3] The reported incidence rate for advanced disease in Turkey is higher (86.7%) than the figures reported for the US and Europe.^[4] Surgical treatment of

non-small cell lung cancer (NSCLC) is the most effective treatment for operable cases. Correct staging is extremely important both in the prognosis and the choice of treatment. The TNM Classification of Malignant Tumours staging system is used for long-term treatment of NSCLC and distant organ metastasis, and the involvement of mediastinal lymph nodes is very important in the selection of treatment.^[5] Tumor spread, mediastinal spread, and involvement of mediastinal lymph nodes after a diagnosis of primary tumor are important in the evaluation of tumor stage and operability.^[6] At diagnosis, lymph node invasion

is present in 28% to 38% of NSCLC cases.^[7] Among noninvasive staging tools, thoracic computed tomography (CT) has been largely replaced by positron emission tomography integrated computed tomography (PET/CT) to determine mediastinal lymph node status, and there are many studies reporting the superiority of PET/CT.^[8,9] PET imaging using radioactively labeled F-18-2-fluorodeoxy-D-glucose (FDG) has been employed as a screening method in noninvasive staging of many cancers, including lung cancer.^[10]

It is suggested that this imaging method based on the principle of visualizing the involvement of tumor cells can replace the invasive staging of the mediastinum, especially when evaluating mediastinal lymph node metastasis.^[11] The aim of this study was to investigate the efficacy of PET/CT findings and demonstration of lymph node metastasis by comparing invasive staging methods with pathological staging in 240 lung cancer cases.

MATERIAL AND METHODS

Between June 2013 and June 2016, the records of 240 patients who were diagnosed with NSCLC were examined retrospectively after obtaining archive screening permission. A detailed history of 240 patients had been obtained and subjected to extensive pre-operative evaluation after a physical examination was performed. Patients without respiratory function tests, cardiac examinations, or with an obstructive pathology after anesthesia assessment were included in the study. Pathological diagnoses were identified with transthoracic needle aspiration or transbronchial needle aspiration after the lesions were detected using thoracic CT and posteroanterior chest X-rays of the cases. PET/CT and cranial magnetic resonance imaging were performed for noninvasive staging.

Patients who were medically inoperable or operable but did not accept surgical treatment were excluded from the study. The results of PET/CT imaging with an SUVmax value of 2.5 or more were evaluated as malignancy and included in the study. Endobronchial ultrasound (EBUS), standard cervical mediastinoscopy, videomediastinoscopy, and mediastinotomy were used for invasive mediastinal staging. For mediastinal staging, patients underwent EBUS (n=240), standard mediastinoscopy (n=60), videomediastinoscopy (n=20), EBUS + mediastinoscopy (n=36), and EBUS + mediastinotomy (n=4). The pathology results of lymph node stations numbered 2, 4, 7, 10, and 11 detected by EBUS and stations 2, 4, 7, and 10 detected by mediastinoscopy and mediastinal lymph node dissection of the patients who underwent video-assisted thoracoscopic surgery (VATS) or surgical resection were compared.

In the pathology results of cases, lymph node stations 10, 11, and 12 were evaluated as N1, while other sta-

tions were reported as N2. The pathological results of 240 lymph node stations were determined and the true negative (TN), true positive (TP), false negative (FN) and false positive (FP) values of PET/CT were detected. All results were uploaded to IBM SPSS Statistics Base 22.0 (IBM Corp., Armonk, NY, USA). The negative predictive value (NPV), positive predictive value (PPV), accuracy, specificity, and sensitivity values for the pathological results of N1 and N2 lymph nodes in all cases, the lymph node stations and numbers, and lymph node counts and results of the PET/CT scans were calculated. The following formulas were used for these calculations

Accuracy: $TP + TN / \text{total number of cases}$

NPV: $TP / TP + FP$

PPV: $TN / TN + FN$

Specificity: $TN / TN + FP$

Sensitivity: $TP / TP + FN$

The correlation between the positive lymph node stations reported with PET/CT and the invasive staging and the positively detected lymph node stations was calculated using the McNemar test. The accepted limit value according to the lymph node station was determined with receiver operating characteristic analysis. $P < 0.05$ was considered significant within the 95% confidence interval.^[7] The staging of all the cases according to the TNM staging system was evaluated. Clinical and pathological TNM staging was compared with the general stages of patients identified. The PET/CT results of 240 cases who underwent invasive mediastinal staging were evaluated with regard to the rate of NPV, PPV, accuracy, specificity, and sensitivity.

RESULTS

Between June 2013 and June 2016, 240 patients with a diagnosis of NSCLC evaluated as operable were included in the study. Of the cases, 195 (81.25%) were male and 45 (18.75%) were female. The median age was 63.90 years for

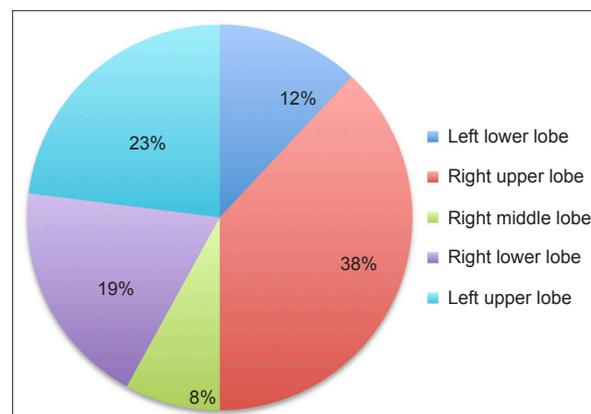


Figure 1. Lobar localization of the tumor.

males and 62.16 years for females, and 63.15 years for the total study population (range: 39–82 years). Tumors were detected in central (n=164; 68.3%) and peripheral locations (n=76; 36.6%). The tumors were located in the right lobe (n=155; 64.58%) left lobe (n=85; 35.41%), and within the boundaries of the upper lobe (n= 91; 38%) (Fig. 1).

Adenocarcinoma was detected in 128 (53.3%), squamous cell carcinoma in 107 (44.58%) and other cell types in 5 (2.08%) patients. The distribution of the operations performed was: lobectomy (n=180; 75%), sleeve lobectomy (n=3; 1.25%), and pneumonectomy (n=57; 23.75%).

1. PET/CT results

In our study, PET/CT examination of 240 cases revealed the presence of 103 TN and 4 FN cases (Table 1).

Detection of mediastinal lymph node metastases using PET/CT had

- Negative predictive value (NPV): 93.1%
- Positive predictive value (PPV): 60.1%
- Specificity: 57.04%
- Sensitivity: 93.8%
- Accuracy rate: 72.08%

A total of 1540 mediastinal lymph node stations (median 6.4 stations/patient) were pathologically examined after PET/CT and invasive sampling (Table 2). In all, 1076 lymph node stations were invasively sampled with EBUS and/or mediastinoscopy (median 4.9 stations/patient). The other 364 stations were examined using lymph node dissection performed with VATS/thoracotomy. Of these 364 stations, EBUS could not detect 215, and 5, 6, 8, and 9 stations could not be detected with mediastinoscopy.

Detection of mediastinal lymph node stations using PET/CT had

- NPV: 96.1%
- PPV: 45.1%
- Specificity: 85.7%
- Sensitivity: 76.8%
- Accuracy rate: 86.8 %

FP was detected in 100 mediastinal lymph nodes in 45 cases. Reactive hyperplasia (n=25), anthracosis (n=66), fibrosis (n=6), and granulomatous inflammation (n=3) were observed in the pathological examinations of the FP lymph nodes.

The incidence of occult pathological N2 was 3.7% (4/107) in these NSCLC cases without involvement in mediastinal lymph node stations on PET/CT (Table 3).

The incidence of occult pathological N2 stage in right upper lobe tumors was statistically significantly higher ac-

ording to the results of univariate analysis (p=0.01). No statistically significant difference was found in the analyses performed comparing genders in terms of centrally located tumors and cell types (p>0.05).

Table 1. Comparison between PET/CT and pathology results

	PET positive	PET negative	Total
Mediastinal LN positive	92	6	98
Mediastinal LN negative	61	81	142
Total	153	87	240

PET: Positron emission tomography; CT: Computed tomography; LN: Lymph node.

Table 2. Comparison of PET/CT results according to lymph node stations

	PET positive	PET negative	Total
Metastatic lymph node	156	47	203
Normal lymph node	190	1147	1337
Total	346	1194	1540

PET: Positron emission tomography; CT: Computed tomography.

Table 3. Analysis of the factors related to occult pathological N2

Variable	Pathologic N2 (n=8)	Pathologic N1 (n=232)	p
Gender			>0.05
Male	8 (100%)	187	
Female	0	45	
Cell type			>0.05
Squamous	6	89	
Adenocarcinoma	2	126	
Other		17	
Hemithorax			>0.05
Right	8 (100%)	147	
Left	0	85	
Localization			>0.05
Central	5	159	
Peripheral	3	73	
Lobar distribution			
Right upper lobe	8 (100%)	91	0.01*

* p<0.05 significantly.

2. EBUS Results

Mediastinal sampling was performed using EBUS with 160 each of 240 patients evaluated. Pathological examination revealed results of TN in 120, TP in 22, and FN in 18 cases. No FP results were found (Table 4).

Evaluation of mediastinal lymph node metastases using EBUS had

- Specificity: 86.6%
- NPV: 82.7%
- Sensitivity: 55.1%
- Accuracy: 88.75%

3. Mediastinoscopy Results

Of the 240 patients evaluated, 80 cases underwent staging mediastinoscopy. Pathological examination revealed a TN result in 64, TP in 8, and FN in 8 cases. No FP results were found (Table 5).

Determination of mediastinal lymph node metastases using mediastinoscopy had

- Specificity: 100%
- NPV: 90.2%
- Sensitivity: 57.1%
- Accuracy rate: 90.9%

Table 4. Comparison of the results of EBUS and histopathological findings

	EBUS positive	EBUS negative	Total
Mediastinal LN positive	22	18	49
Mediastinal LN negative	–	120	120
Total	22	138	160

EBUS: Endobronchial ultrasound; LN: Lymph node.

Table 5. Comparison between mediastinoscopy and histopathology results

	Mediastinoscopy positive	Mediastinoscopy negative	Total
Mediastinal LN positive	8	8	16
Mediastinal LN negative		64	64
Total	8	72	80

LN: Lymph node.

DISCUSSION

The involvement of distant organ metastases and mediastinal lymph nodes should be evaluated early in the treatment of small cell lung cancer. After evaluation, palliative treatment, surgery, adjuvant, or neoadjuvant therapy may be applied.^[12] Accurate staging is very important, since the most important treatment selection criterion and prognostic indicator is the condition of the mediastinum in cases without distant metastases. PET/CT, using the principle of imaging the activity of tumor cells, is used as the most effective non-invasive imaging method for preoperative staging. PET/CT has a guiding role for invasive methods in demonstrating invasion of the mediastinal lymph node and detecting distant organ metastasis when evaluating T-stage.^[13]

Higher FP rates of PET/CT reduce the accuracy of the examination. In the detection of mediastinal lymph node metastasis, the sensitivity and specificity of PET/CT were found to be 87.5 to 90% and 85%, respectively. Since these studies were performed with fewer than 50 participants, they did not reach the level of statistical significance. According to the results of a meta-analysis consisting of 1959 cases and 32 studies, the specificity and median sensitivity of PET/CT was reported as 79% and 61%, respectively.^[14] There are studies comparing the rates of specificity, sensitivity, accuracy, NPV, and PPV of PET/CT with those of mediastinoscopy. In a study performed in our country in 2018 for PET/CT, the following rates were reported: PPV 58%, NPV 87%, specificity 76%, sensitivity 74%, and accuracy 76%.^[15] Again in our country, in a 2007 study consisting of 59 cases, PPV and specificity were indicated as 79% and 67%, respectively. In another study of 170 cases published in 2008, the PPV and specificity rates were reported as 55% and 73%, respectively.^[16] As a result of these studies, there are publications that suggest increasing the SUVmax limit value in order to prevent a high FP in PET/CT. In a study involving 110 cases and 765 mediastinal lymph nodes published by Lee et al.^[17] in 2008, for an SUVmax value of 5.3, 2.5, the authors reported accuracy, PPV, and specificity rates of 97%, 64%, and 98%, respectively. Compared with the SUVmax value of 2.5, these values were statistically significantly different.^[17]

In another study conducted in our country in 2009, the most appropriate SUVmax limit value was reported as 2.8 in an analysis of 254 cases and 1010 of mediastinal lymph nodes.^[18] Studies are also underway to increase the accuracy of PET/CT, rather than increasing the SUVmax value. In our study, we evaluated preoperative mediastinal examinations and found rates of specificity (57.04%), sensitivity (93.8%), PPV (60.11%), NPV (93.1%), and accuracy (72.08%) for PET-CT in 240 patients. When compared with the literature, we detected a higher sensitivity rate, but a lower specificity rate, which we attributed to the higher FP rates in both groups. In our opinion, PET/

CT positivity should be demonstrated histopathologically, because specific and non-specific active conditions that increase FDG uptake by producing an inflammatory response in lymph nodes induce FP results.

It has been demonstrated that inflammatory processes, such as pneumonia, active tuberculosis, bronchiectasis, sarcoidosis, fungal infections, and the close proximity of the primary tumor to the mediastinal structures can cause FP results.^[19] In addition, it should not be forgotten that, similar to active inflammation, healed or inactive pulmonary complications, such as previous tuberculosis, silicosis, anthracosis, may cause increased FDG uptake in the hilar or mediastinal lymph nodes.^[20] The rates of mediastinal lymph node positivity in PET/CT imaging may be high in countries like ours, where granulomatous infections are common.

In a study published in our country, the incidence of mediastinal lymph node positivity was found to be 59.4% (101/170) in PET/CT results, while it was 40.7% (24/59) in another study conducted in this country (16). Reports from countries with a lower incidence of granulomatous diseases, such as Western Europe and North America, indicated lower rates of mediastinal lymph node positivity using a PET/CT scan. In another study, Gonzalez-Stavrinski et al.,^[21] reported lymph node positivity on PET/CT scan as 32.2% (65/202) while Lee and his colleagues^[21] found a rate of LNP on PET/CT of 34.1% (43/126). In countries where granulomatous infections are common, the rate of mediastinal lymph node positivity is reported to be higher in PET/CT images. This rate is 16% to 55% in the literature.^[21]

In our study, the rate of mediastinal lymph node was 25.41%. The causes of FP results in our cases included anthracosis in 58.4%, reactive hyperplasia in 29.8%, fibrosis in 8.01%, and granulomatous inflammation in 3.2%. Although the sensitivity, specificity, PPV, NPV, and accuracy rates of PET/CT were evaluated in terms of the number of patients, these rates were found to be 94.1%, 79%, 49.3%, 98.4%, and 81.6%, respectively in a multicenter literature study performed with 469 cases.^[22]

A meta-analysis involving 1045 cases reported a specificity of 89%, PPV of 79%, NPV of 93%, and sensitivity of 84% with PET/CT.^[23] In another meta-analysis involving 1292 cases, these rates were determined as follows: specificity of 92%), PPV of 85%, NPV of 94%, sensitivity of 88%, and accuracy of 91%.^[22] In our study, the specificity, NPV, and accuracy rates were found to be higher, while the sensitivity rate was lower, and the PPV was comparable in consideration of the number of patients in the PET/CT group. In a study performed with 826 dissected mediastinal lymph nodes that compared histopathological and PET/CT results, PET/CT demonstrated a 93.42% specificity, 63.07% sensitivity, 96.73% NPV, 45.55% PPV, and 92.13% accuracy rate.^[24]

In our study, it was observed that the rates of all parameters detected for 1540 lymph node stations were consistent with the literature. Therefore, we recommend that the mediastinal lymph node dissection should be performed in at least 3 stations (one of which should be subcarinal) and that the disease stage of the patient should be determined in order to be able to perform real staging after resection. The necessity of invasive mediastinal staging in patients whose mediastinal lymph node involvement is not observed on PET/CT is debatable. In our study, the incidence of occult pathological N2 was 3.3% (8/240) in NSCLC cases with no mediastinal lymph node involvement on PET/CT examination.

According to the results of univariate analysis, the incidence of occult pathological N2 was statistically significant in right upper lobe tumors ($p=0.01$). Pathologically occult N2 was mostly detected in the right paratracheal lymph node ($n=5$). In 2 cases, occult pathological N2 involvement was detected in the subcarinal lymph node station, and in 1 case in the right upper paratracheal lymph node station. It has been reported that right upper lobe tumors frequently metastasize to the right paratracheal lymph node.^[25] Invasive staging is recommended to exclude occult pathological N2 in N1-positive PET/CT cases, especially in tumors with central localization, large tumors, and lymph nodes in the pathological dimension detected with CT.^[21]

In the preoperative guideline for mediastinal staging published by the European Society of Thoracic Surgery, it has been reported that mediastinoscopy may not be necessary in cases with peripherally located tumors without the involvement of mediastinal lymph nodes on PET/CT.^[26] The choice of an invasive staging method for NSCLC is also important. Transbronchial needle aspiration, endobronchial needle aspiration, and esophageal ultrasonography-guided needle aspiration are less invasive methods to evaluate the mediastinal lymph nodes. These methods, which have high specificity rates, have a low NPV.

In this case, a negative lymph node should be confirmed using mediastinoscopy. In addition, positive results obtained from fine needle aspiration biopsies are sufficient to detect N2 or N3 disease.^[27] Endoscopic (EBUS-EUS) and surgical techniques can be used in the restaging of patients receiving neoadjuvant therapy for the treatment of NSCLC. Detection of N2 disease using endoscopic techniques at first staging will facilitate restaging for surgical treatment after neoadjuvant therapy. This approach will prevent difficulties of re-mediastinoscopy and the success of mediastinoscopy will increase. The most common indication for mediastinoscopy in lung cancer is mediastinal staging performed before resection.^[28] It has been reported that the survival rate increases after neoadjuvant therapy that “understages” single-station N2-positive patients who may be suitable for surgical resection.

Therefore, pre-resection evaluation of the mediastinal lymph nodes is of great importance in terms of prognosis. In areas where granulomatous infections are common, the positivity of mediastinal lymph nodes in PET/CT images is more common when compared with North America and Western Europe. For this reason, we should not forget the importance of invasive staging, considering the FP rates of PET/CT. In the selection of staging methods, a protocol that considers noninvasive methods first should be followed. We think that priority should be given to these methods (EBUS-EUS) with the widespread use of endoscopic methods in consideration of patient's compliance and its ease of application. However, because of the high accuracy and specificity rates, it is suggested that mediastinoscopy still be used as the gold standard method in the evaluation of mediastinal lymph nodes. We think that total mediastinal lymph node dissection should be performed during resection in order to determine the prognosis, the actual stage of the patient's disease, and the treatment protocol.

Ethics Committee Approval

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: K.B.Ö.; Design: K.B.Ö.; Data collection &/or processing: A.Ö., S.Ş.C.; Analysis and/or interpretation: K.B.Ö.; Literature search: T.F.Ö.; Writing: E.E.C.; Critical review: R.D.

Conflict of Interest

None declared.

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Akciğer Kanserinin Evrelemesinde PET/BT ve İnvaziv Evrelemenin Patolojik Evreleme İle Karşılaştırılması: 240 Olgunun Analizi

Amaç: Akciğer kanseri tanısı sonrası tümörün yayılımının ve mediastinal lenf nodlarının tutulumunun belirlenmesi; tümör evresinin ve operabilitenin ortaya konması açısından önem taşımaktadır. Çalışmamızda kliniğimizde ameliyat edilen 240 akciğer kanserli olgunun, pozitron emisyon tomografi/bilgisayarlı tomografi (PET/BT) bulguları ile invaziv evreleme yöntemlerini, patolojik evreleme ile karşılaştırarak, bu yöntemlerin lenf nodu metastazını göstermedeki etkinliğini belirlemeyi amaçladık.

Gereç ve Yöntem: Haziran 2013–Haziran 2016 tarihleri çalışmaya alınan 240 hastanın PET/BT incelemesinde 60 hastada gerçek pozitif, 45 hastada yalancı pozitif, 103 hastada gerçek negatif, dört hastada ise yalancı negatif sonuç saptandı. Yapılan univariant analiz sonucu sağ üst lob yerleşimli tümörlerde ($p=0.01$) gizli N2 hastalık insidansı istatistiksel olarak anlamlı derecede yüksek bulundu.

Bulgular: Değerlendirmeye alınan 240 hastanın 160'ına EBUS, 80'ine mediastinoskopi yapıldı. EBUS'un patoloji incelemelerinde 22 hastada gerçek pozitif, 120 hastada gerçek negatif, 18 hastada ise yalancı negatif sonuç saptandı. Mediastinoskopisi yapılan 80 hastanın patoloji sonuçlarının karşılaştırılmasında; sekiz hastada gerçek pozitif, 64 hastada gerçek negatif, sekiz hastada ise yalancı negatif sonuç saptandı. Spesifite oranları yüksek olan mediastinoskopinin doğruluk oranları EBUS ile yakın olarak bulundu.

Sonuç: Çalışmamızın sonucunda evreleme yöntemleri arasında EBUS ve mediastinoskopi, yüksek spesifite ve doğruluk oranlarıyla ön plana çıkmaktadır. Ancak mediastinoskopinin halen daha altın standart yöntem olduğunu düşünmekteyiz. Hem prognozu tayin etme hem de tedavi protokolünü uygulama açısından hastaların gerçek evresinin belirlenmesi için, rezeksiyon yapılan hastalara total mediastinal lenf nodu diseksiyonu yapılması gerektiği kanaatindeyiz.

Anahtar Sözcükler: Akciğer kanseri; akciğer kanseri evrelemesi; EBUS; lenf nodu diseksiyonu; mediastinoskopi; PET/BT.