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Comparative Evaluation of Mediastinal Lymph Nodes in Non-small Cell Lung Cancer with Computed Tomography, 99mTc-MIBI SPECT, and Video-Mediastinoscopy

ORIGINAL INVESTIGATION

Ömer Önal, Ömer Faruk Demir

ABSTRACT

Objective: The aim of this study is to evaluate the mediastinal lymph node (MLN) metastasis comparatively with Tc99m-MIBI SPECT scintigraphy, thoracic computed tomography (CT), and video-mediastinoscopy (VM) in the staging of non-small cell lung cancer (NSCLC).

Materials and Methods: Forty consecutive patients (36 men, 4 women, average age 59.3 years) who were to undergo surgical treatment for NSCLC between June 2008 and June 2009 were included in this prospective study. All patients underwent chest 99mTc-MIBI SPECT before VM. SPECT results were evaluated visually and semi-quantitatively. Thoracotomy and MLN dissection were applied in patients who did not have MLN metastasis.

Results: The MLN involvement was demonstrated in 6 patients via VM. 99mTc-MIBI SPECT correctly staged 5 out of 6 patients, and CT 2 out of 6 patients. The 99mTc-MIBI SPECT showed better results than CT with regard to positive and negative predictive values and accuracy.

Conclusion: This study indicates that Tc99m-MIBI SPECT has a better diagnostic value than CT in detecting MLN metastases in NSCLC.

Keywords: Lymph nodes, non-small cell lung cancer, technetium-99-m methoxy isobutyl isonitrile

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Department of Thoracic Surgery, Erciyes University Faculty of Medicine, Kayseri, Turkey

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Correspondence Ömer Önal, Department of Thoracic Surgery, Erciyes University Faculty of Medicine, Kayseri, Turkey
Phone: +90 352 207 66 66
e.mail: omeronal@erciyes.edu.tr

INTRODUCTION

The most important factor affecting the treatment type and prognosis in non-small cell lung cancer (NSCLC) is whether or not mediastinal lymph node (MLN) metastasis is present (1, 2). Clinically, the examination of MLN metastasis mostly depends on the imaging methods, but they have no reliable rates alone (3). Today, direct radiography, computed tomography (CT), and magnetic resonance imaging are non-invasive methods that are selected for the evaluation of the tumor in the lung. However, these methods have limited value in determining the nature of suspicious lung nodules, evaluating mediastinal involvement and also the tumor viability (4). Various radionuclide substances such as 67 Ga, 201Tl, and 99mTc-tetrofosmin, 99mTc-MIBI (technetium 99m hexakis 2- methoxy isobutyl isonitrile), and 18F-fluorodeoxyglucose are used in NSCLC staging, treatment response, and follow-up (4-6). The aim of this study is to evaluate the mediastinal lymph nodes (MLN) comparatively by using video-mediastinoscopy (VM), 99mTc-MIBI SPECT scintigraphy, and thoracic CT in the staging of NSCLC.

MATERIALS and METHODS

Forty consecutive patients, 36 men and 4 women between the ages of 43 and 75 years (average age 59.3 SD±8.75 years), for whom resection was planned due to NSCLC, were included in this prospective study (2008-2009). An assessment of MLN with 99mTc-MIBI SPECT scintigraphy before VM was conducted in all the patients who were proven as operable via physical examination, blood count, biochemistry, blood gas, respiratory function tests, bronchoscopy, bone scanning, and contrast whole-body CT scanning. To obtain a definitive diagnosis, techniques such as transthoracic biopsy, cytology, bronchoscopy, VM, and thoracotomy were used. The MLN biopsies were done in all patients by VM. Thoracotomy and MLN dissection were conducted in those patients who did not have MLN metastasis. None of the patients received chemotherapy or radiotherapy before the operation. Thoracic CT, 99mTc-MIBI SPECT scintigraphy, and MLN pathology results were comparatively evaluated by means of statistical analysis. Prior to the inclusion of patients in the study, the ethics committee approval and patient informed consent form were obtained (Decision no: 249).

99mTc-MIBI SPECT Protocol: 20 mCi 99mTc-MIBI was intravenously administered to the patients. SPECT data were collected 20 minutes after the injection by using a double-head right-angled gamma camera (ECAM; Siemens, Erlangen, Germany) with a wide-area image. For SPECT images, Butterworth filtering (0.43/7) was used. The 99mTc-MIBI images were qualitatively and quantitatively evaluated as follows:

1) In the qualitative analysis, when an increased activity involvement was determined in one or more areas of the lung, the SPECT was accepted as positive. MLN involvement was evaluated when there were one or more foci of well-defined increased 99mTc-MIBI uptake in the mediastinum, compared with the background activity.
2) In the quantitative analysis, the highest area of the involvement on the tumor was marked, and the opposite side was marked by using the mirror image technique at the same size in normal lung. The 99mTc-MIBI uptake values of the mediastinal lymph nodes were compared separately, both with the background mediastinal tissue and the contralateral MLN detected via the mirror image technique.

The mean activity counts of the tumor mass were divided by the mean activity counts of the normal lung on the opposite side so that the tumor involvement rate (Tumor/Normal lung involvement rate, T/N) could be calculated. The mean activity counts of the lymph node were divided by the mean activity counts of the background mediastinum so that the mediastinal lymph node/normal mediastinum involvement rate (MLN/Nm ratio) could be calculated. Then, the high MLN/Nm ratio was divided by the low MLN/Nm ratio to compare 99mTc-MIBI uptake values of the both sides' lymph nodes and to create the term of MLN ratio. Via the MLN ratio, we aimed to detect the difference between the MIBI involvement in metastatic MLN and MIBI involvement in reactive or anthracotic lymph nodes. An MLN ratio greater than 1 was considered as metastasis. Thus, the Region of Interest terms were developed to evaluate the increased activity involvement areas semi-quantitatively.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) Windows version 15.0 (SPSS Inc.;Chicago, IL, USA) software package were used to evaluate the study data. Chi-square test was used to determine the difference between the variables. Mann-Whitney U test was used to examine the correlation between the SPECT results and other variables (age, gender, histological type). Kappa analysis was applied to specify the consistency power between the examinations. Pathological evaluation was accepted as the gold standard for the calculation of specificity and sensitivity. For all the statistical analyses, values of $p<0.05$ were accepted as statistically significant.

RESULTS

In the tomographic assessment, there was a mass in the right upper lobe in 42% (n=17), the right lower lobe in 25% (n=10), the left upper lobe in 18% (n=7), and the left lower lobe in 15% (n=6) of the patients. Malignancy was diagnosed by bronchoscopy in 55% (n=22) and by transthoracic fine-needle aspiration biopsy in 30% (n=12) of the patients. In 15% (n=6) of the patients with negative cytology, the diagnosis was made through thoracotomy. Epidermoid carcinoma in 64% of the patients (n=26), adeno carcinoma in 28% (n=11), and large cell carcinoma in 8% (n=3) were detected. The average size of lesions was 4.75±SS 1.75 cm (range 3–10 cm). 99mTc-MIBI SPECT defined focal lesions in all the primary mass lesions by showing an increased marking accumulation. The average T/N ratio was 2.14±0.64 SD (range 1.26–3.81). VM was applied to all 40 patients, and biopsies were taken from 144 MLN stations. Sampling was performed from 37 units of right no. 4, 32 units of right no. 2, 26 units of left no. 4, 25 units of no. 7, and 24 units of left no. 2 MLN stations. MLN metastases were detected in 7 MLN stations of 6 patients by VM (Table 1). Five of these patients were staged correctly with 99mTc-MIBI SPECT. The mean MLN/Nm ratio was 2.1±0.66 SD (range 1.06–3.5). CT was able to stage only 2 of those patients correctly. Although 99mTc-MIBI SPECT identified all epidermoid carcinoma metastases, it could not detect the metastatic MLN with adeno carcinoma. CT could only specify 2 patients having epidermoid carcinoma metastasis. The results of a comparative evaluation of CT, 99mTc-MIBI SPECT, and VM in detecting MLN metastases are given in Table 2. No statistical difference was observed between mediastinoscopy, 99mTc-MIBI SPECT, and CT by using the McNemar test ($p>0.05$). Mann-Whitney U test is used to compare the numerical values of independent groups. Age, gender, mass size, and histological type did not affect the SPECT results ($p>0.05$). Kappa analysis was used in order to observe the strength of the concordance between the methods. Accordingly, good concordance was observed between 99mTc-MIBI SPECT and mediastinoscopy (kappa value=0.725). Weak concordance was observed between CT and mediastinoscopy (kappa value=0.138). Moderate concordance was observed between 99mTc-MIBI SPECT and CT (kappa value=0.426). It was seen that 99mTc-MIBI SPECT was superior to CT due to a good concordance between the high sensitivity, specificity, accuracy, NPV and PPV results, and mediastinoscopy. Thoracotomy and MLN dissection were conducted in 34 patients who did not have MLN metastasis. No metastases were detected in MLN specimens.

DISCUSSION

The method of MLN staging should have a high specificity and sensitivity in determining whether or not MLNs are metastatic. Genereux et al. (7) reported that 89% to 95% of normal lymph nodes were under 11 mm in size. As the size increases, the risk of lymph node metastasis also increases. However, in the literature, it was shown that 8% to 17% of normal-size lymph nodes were metastatic, and 30% of pathological-size lymph nodes were reactive (8, 9). Thus, it may be faulty to evaluate the MLN enlargement as metastatic or reactive depending on the CT results and to define it as an inoperability criterion. Because CT evaluates only the size of the lymph node, it cannot differentiate the inflammatory disease-related lymph node enlargements from metastasis. In the literature, the sensitivity of thoracic CT was 20%–86%, specificity 50%–93%, PPV 26%–86%, and NPV 40%–93% (10, 11). In this study, the sensitivity of thoracic CT was 33%, specificity 82.3%, PPV 25%, and NPV 87.5%. As seen from the study results and the literature review, despite the technological developments in thoracic CT, no significant change was observed in the sensitivity and specificity rates, and it is not a reliable method in MLN staging. Thus, the interest toward functional imaging methods has increased (12, 13). 99mTc-MIBI SPECT scintigraphy has a

Table 1. Characteristics of the patients and evaluation of MLNs with thoracic CT, 99mTc-MIBI SPECT, and VM

Case No:	Age/ Gender	Mass size (cm)	Histopathologic diagnosis	MIBI Mass (T/N)	CT MLN	MIBI MLN (MLN/Nm)	MIBI MLN ratio	VM MLN	Thoracotomy MLN
1	63/M	4x3	Adeno	2.16	N2 (+)	1.52	N2(+)(1.45)	R,A	R
2	50/M	4x3	Epidermoid	3.44	0	2.77	1	A	A
3	58/M	6x4	Adeno	1.99	0	1.89	1	R	R
4	67/M	5x4	Epidermoid	2.31	0	2.08	1	R	R
5	74/M	7x4	Epidermoid	1.45	N2 (+)	1.54	1	R	R
6	67/M	3x2	Epidermoid	2.43	0	3.4	1	A	A
7	54/F	6x5	Adeno	1.99	0	2.57	1	A	A
8	70/M	4x3	Epidermoid	1.52	N2 (+)	1.72	1	R	R
9	65/M	3x3	Epidermoid	1.43	0	1.56	1	R	R
10	68/M	3x2	Epidermoid	1.4	0	1.27	1	R	R
11	50/F	5x4	Epidermoid	1.72	0	1.12	1	R	R
12	61/M	4x4	Epidermoid	1.51	0	1.64	N3(+)(1.69)	N3(+)	-
13	57/M	4x4	Basal cell	1.88	0	1.94	1	R	R
14	58/M	6x5	Basal cell	1.99	0	2.33	1	R	R
15	73/M	3x2	Epidermoid	1.59	0	1.55	1	R,A	R,A
16	43/M	5x3	Epidermoid	2.08	0	1.84	1	R	R
17	55/M	7x5	Adeno	3.81	0	2.63	1	R	R
18	66/M	4x3	Epidermoid	1.86	0	1.12	1	R	R
19	51/M	5x4	Epidermoid	1.26	0	1.06	1	R	R
20	58/M	7x6	Epidermoid	2.44	0	2.58	N3(+)(1.72)	N3(+)	-
21	54/M	3x3	Epidermoid	1.84	0	1.84	1	R	R
22	51/M	6x5	Epidermoid	2.48	N2 (+)	1.86	N2(+)(1.42) N3(+)(1.64)	N2(+), N3(+)	-
23	72/F	3x2	Adeno	2.61	0	2.65	1	A	A
24	59/M	3x3	Epidermoid	1.96	N2(+)	2.31	1	R	R
25	52/M	7x5	Adeno	1.85	0	1.62	1	R	R
26	61/M	3x3	Adeno	2.74	0	3.06	1	R,A	R,A
27	75/M	3.5x2	Epidermoid	2.32	0	2.18	1	R	R
28	62/M	7x6	Adeno	2.17	N2(+)	2.18	1	R	R
29	45/F	3x3	Adeno	1.84	0	1.5	1	N3(+)	-
30	66/M	4x3	Adeno	1.89	N2(+)	2.68	N2(+)(1.46)	R,A	R
31	58/M	10x10	Basal cell	1.34	0	1.55	1	R	R
32	47/M	4x4	Epidermoid	1.45	0	2.19	1	R	R
33	59/M	4x3	Epidermoid	2.14	0	1.84	1	R	R
34	70/M	7x5	Epidermoid	2.79	N2(+)	3.5	N2(+)(1.61)	N2(+)	-
35	56/M	3x3	Epidermoid	1.72	0	1.81	1	R	R
36	55/M	8x7	Adeno	1.9	0	1.75	1	R,A	R,A
37	67/M	3.5x3	Epidermoid	3.3	0	3.48	1	R	R
38	46/M	3x3	Epidermoid	2.23	0	1.82	N3(+) (2.0)	N3(+)	-
39	44/M	4x3	Epidermoid	3.51	0	3.38	1	R	R
40	65/M	6x5	Epidermoid	3.24	0	2.7	1	R	R
Total					8(+)		7(+)	6(+)	0

CT: computed tomography; T/N: tumor/normal lung involvement rate; MLN/Nm: mediastinal lymph node/normal mediasten involvement rate; VM: video-mediastinoscopy; R: reactive; A: anthracotic

clinical importance for numerous neoplasms including lung cancer (12, 14, 15). 99mTc-MIBI is used mostly in myocardial perfusion imaging (16). 99mTc-MIBI reuptake is correlated with the high metabolic activity in neoplastic cells, increased blood flow, and capillary permeability (17). Nosotti et al. (18) reported that 99mTc-MIBI SPECT was able to detect MLN metastasis in 12 out of 22 patients. Also the authors observed no false positive results with 99mTc-MIBI. In the study conducted by Santini et al. (12), it was specified that positive results were obtained via 99mTc-MIBI SPECT in 2 out of 3 patients with MLN metastasis, and there was no involvement determined by SPECT in the patients with negative MLN. Nosotti et al. (18) and Santini et al. (12) both specified that 99mTc-MIBI SPECT had 100% specificity and PPV in determining the malignancies and was more specific than CT in determining N2-3 disease. Also, they argued that mediastinoscopy may not be necessary in patients with 99mTc-MIBI SPECT positive results. The results of 99mTc-MIBI SPECT in the literature regarding the determination of MLN metastasis are presented in Table 3. In this study, MLN metastasis was detected correctly in 5 out of 6 patients with 99mTc-MIBI SPECT. The reason for the determination of low specificity and PPV was that 2 patients diagnosed with right-upper-lobe adeno carcinoma in this study had false positive results. Right upper lobectomy and MLN dissection were applied in these patients. However, the pathology reports of the MLN were as reactive as anthracotic lymph nodes. False positive results were obtained by MIBI SPECT in these patients (Figure 1). MLNs sometimes become larger or hyper-activated due to inflammation, and the accumulation of Tc-99m MIBI can also be detected in these inflammatory areas (22, 23). However, benign nodes may also be enlarged because of reactive hyperplasia, anthracosis, inflammation, or infection (9). The false positive results detected in 2 patients were based on the inflammation in reactive and anthracotic lymph nodes. Tc-99 m MIBI uptakes in MLN were calculated, and the mean MLN/Nm ratio was 2.1±0.66 SD (range 1.06–3.5). These values were containing MIBI uptake in all metastatic, reactive, and anthracotic lymph nodes. Because of this involvement, we analyze the MIBI SPECT results by semi-quantitative analysis according to the value of bilateral MLN ratio to exclude the Tc-99 m MIBI uptakes in reactive and anthracotic lymph nodes. There was only one 99mTc-MIBI SPECT false negative result in a 45-year-old female patient who was diagnosed with adeno carcinoma in the left lower lobe (Figure 2). Right no.2 MLN (N3) metastasis was determined through mediastinoscopy. Also MLN did not have pathological size in thoracic CT. The cause of errors in the scintigraphy assessment was investigated. Even though 99mTc-MIBI SPECT is an easily applied method, its interpretation is not always easy. It was very difficult to determine the number of MLNs showing the exact involvement, although 3D sections can be taken. There was no difficulty in determining an increased 99mTc-MIBI reuptake in various areas of mediastinum. However, it was not always possible to evaluate its correlation with the surrounding vein structures. Because anatomic margins cannot be exactly selected via SPECT, contrary to CT, lesion and large vein structures can be confused and thus false interpretations may occur.

In a meta-analysis including 5.687 cases, the sensitivity of VM was 84%, specificity 100%, false positive 0%, and false negative 9% (24). The results of VM from this study are given in Table 2. The most important factor that contributed to such high rates was that there was no false negative results in case of mediastinoscopy. The reason for this was that utmost effort was shown for taking biopsies from all the MLNs that can be seen by dissecting all the MLN stations routinely that can be reached during mediastinoscopy.

Table 2. Comparative evaluation of CT, 99mTc-MIBI SPECT, and VM results in detecting MLN metastases

	CT	99mTc-MIBI SPECT	VM
Sensitivity	(2/6) 33%	(5/6) 83.3%	(6/6) 100%
Specifity	(28/34) 82.3%	(32/34) 94.1%	(34/34) 100%
PPV	(2/8) 25%	(5/7) 71.4%	(6/6) 100%
NPV	(28/32) 87.5%	(32/33) 96.9%	(34/34) 100%
Accuracy	(30/40) 75%	(37/40) 92.5%	(40/40) 100%

NPV: negative predictive value; PPV: positive predictive value; CT: computed tomography; VM: video-mediastinoscopy

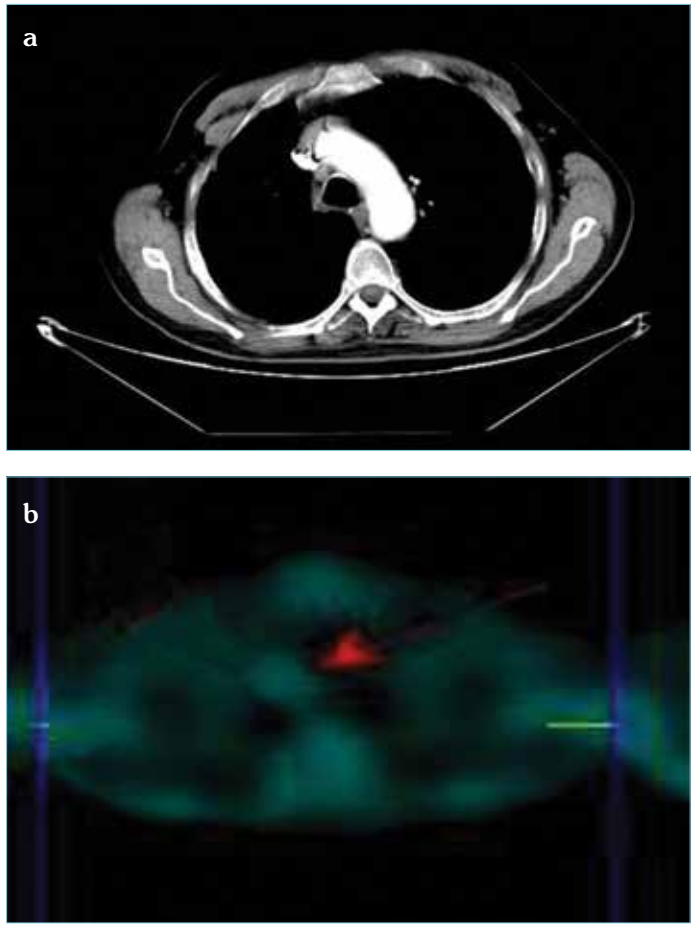

Figure 1. a, b. Image of 63-year old man with adenocarcinoma of the right upper lobe. (a) Contrast material-enhanced CT scan shows a right paratracheal node. (b) 99mTc-MIBI SPECT shows increased abnormal accumulation corresponding to the mediastinal lesion (MIBI MLN ratio =1.45) (red arrow). Reactive and anthracotic lymph node was determined by mediastinoscopy. False positive result was detected with 99mTc-MIBI SPECT

Table 3. Detecting of MLN metastases with 99mTc-MIBI SPECT (a literature review)

Authors	Patients (n)	Sensitivity %	Specifity %	PPV %	NPV %	Accuracy %
Chiti[4]	36	91	84	71	95	86
Santini[12]	57	66.7	100	100	97.9	-
Nosotti[18]	116	54.5	100	100	86.6	88.5
Nagamachi[19]	46	62.5	84	-	-	-
Komori[20]	37	85.7	100	-	-	-
Miziara[21]	41	14.3	97.1	50	84.6	-
Onal	40	83.3	94.1	71.4	96.9	92.5

MLN: mediastinal lymph node; NPV: Negative predictive value; PPV: positive predictive value

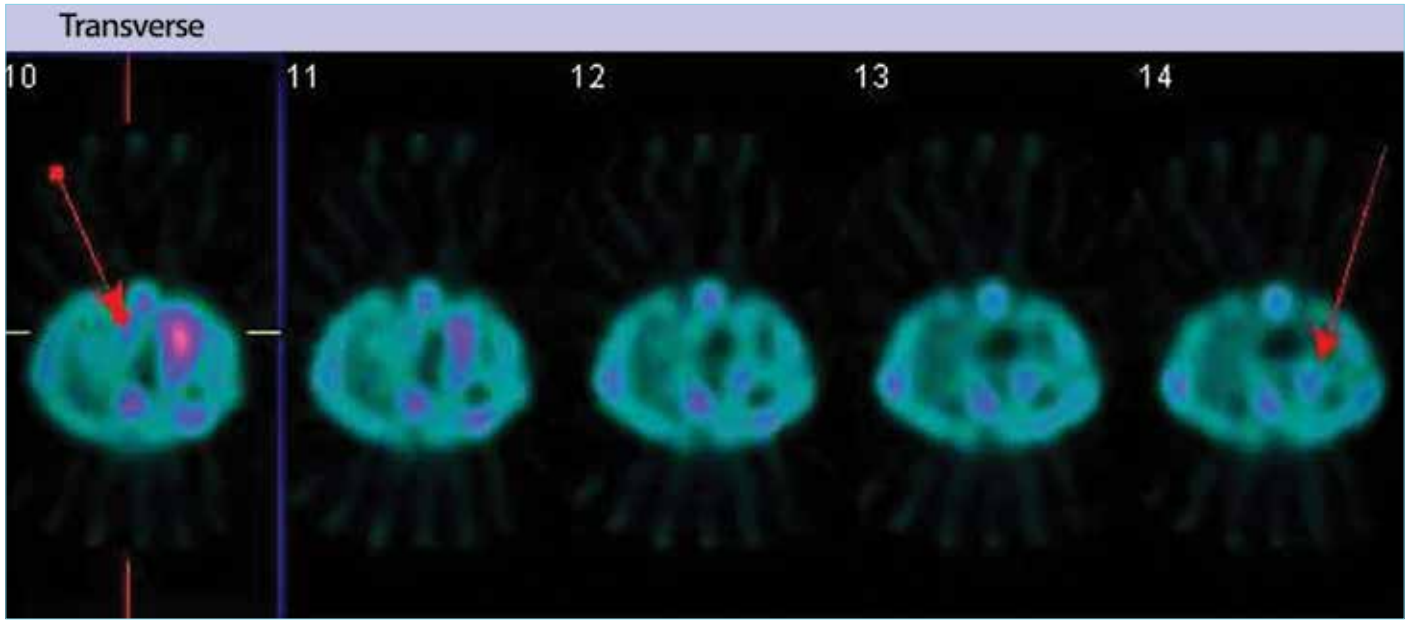

Figure 2. Demonstrates transverse sections of 99mTc-MIBI SPECT in a 45 years old woman diagnosed with adeno carcinoma. Transverse 10: Right paratracheal LN with (MLN/Nm) =1.5 and MIBI MLN ratio=1. Transvers 14: Left lower lobe mass with T/N= 1.84. Right no.4 MLN (N3) metastasis was determined through mediastinoscopy. False negative result was detected with 99mTc-MIBI SPECT

Study limitations

The main limitation of this study was the low number of patients. This prospective study was planned as an expertise thesis. The time for the recruitment of patients was limited to only 1 year. Planning a long-term study can lead to wider outcomes, including subgroups of lung cancer, by increasing the number of patients.

CONCLUSION

Considering the results of this study and those described in the literature, despite the improvements in technology, the accuracy of thoracic CT in mediastinal staging of NSCLC patients has not reached the desired level. Although 99mTc-MIBI SPECT has high NPV, specificity, and sensitivity, considering the studies conducted until now, it is incorrect to assert that it will supersede mediastinoscopy. Even though mediastinoscopy is invasive, it is still the gold standard in staging MLN due to its high accuracy rates, easy application, and minimal morbidity and mortality rates.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethics committee.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: OO., OFD. Performed the experiments or case: OO., OFD. Analyzed the data: OO., OFD. Wrote the paper: OO., OFD. All authors have read and approved the final manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

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