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Original Article

Methastatic N2 in T1 Non-small cell lug cancer: Should we go back to invasive staging?

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Abstract

Aim: T1 patients who were operated due to non-small cell lung cancer (NSCLC)were evaluated retrospectively. The objective of this study was to evaluate metastatic lymph node status in T1 tumors and to discuss staging approaches in these tumors.

Material and Methods: A total of 217 patients who met specified criteria between May 2012 and May 2019 were included in the study. Patients operated due to NSCLC who have a tumor size < 3 cm were evaluated in terms of age, gender, preoperative diagnostic methods, thorax CT and PET-CT examinations, size, anatomic localization and histopathologic type of tumors, excised mediastinal lymph nodes and pathology results.

Results: Of total 292 lymph node stations sampled in patients with adenocarcinoma, 257 (89.73%) were reported as benign and 30 (10.27) as malignant according to pathologic results. Of total 316 lymph node stations sampled in patients with squamous cell carcinoma, 298 (94.3%) were benign and 18 (5.7%) were malignant.N2 positivity was found in 40 (18.43%) of the 217 patients.

Conclusion: Mediastinoscopy should be performed for staging in the presence of a tumor size above 2 cm, histopathological type of adenocarcinoma, high mass SUVmax values, lymph node with radiological growth and pathological involvement.

Keywords: Lung cancer; lymph node; mediastinoscopy; PET-CT; staging; T1 tumor; Torax-CT

INTRODUCTION

Lung cancer is one of the most important health problem worldwide with its increasing incidence and mortality rates. It is important to diagnose the disease as soon as possible in order to increase the chance for a successful surgical treatment in non-small cell lung cancer (NSCLC) (1). For a correct staging in NSCLC, localization and size of the primary tumor (T factor), regional lymph nodes (N factor) and distant metastases (M factor) should be determined. Several imaging methods such as computed tomography of the thorax (thorax-CT), bone scintigraphy, magnetic resonance imaging (MRI), abdominal ultrasonography and positron emission tomography (PET-CT) are used for this purpose (2).

Mediastinal lymph node involvement is the most important factor determining treatment method and prognosis in patients without distant metastasis. Therefore, suspicion of mediastinal lymph node involvement should be ruled out in the preoperative period (3).

It is known that a considerable part of patients with clinic stage I NSCLC have N1 or N2 lymph node metastasis. Many studies have investigated the factors increasing the rate of lymph node metastasis. Anatomic localization, size and histological type of the tumor, mass and lymph node SUVmax values are the most commonly investigated parameters (4,5). The importance of lymph node evaluation in determination of treatment and prognosis is beyond controversy.

Therefore, the objective of this study was to evaluate lymph node metastatic status in the preoperative clinical staging with a comprehensive retrospective analysis in patients with T1 tumor diagnosed clinically or pathologically.

MATERIAL and METHODS

Patients diagnosed with pre-perioperative NSCLC who underwent radiologic imaging, surgical intervention and mediastinal lymph node dissection or sampling between May 2012 and May 2019 were retrospectively analyzed. Patients who underwent clinical and radiological examinations and radiologically diagnosed with T1 tumors and those pathologically diagnosed with T1 tumors postoperatively were included in the study. Patients who received neoadjuvant chemotherapy, those with a history of hospitalization due to granulomatous

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disease and patients diagnosed with diabetes mellitus were excluded from the study. This study was conducted in line with the principles of the Declaration of Helsinki.

All patients were evaluated with preoperative anamnesis, physical examination, respiratory function tests, electrocardiography, blood biochemical and hemogram tests, coagulation tests, postero-anterior and lateral X-rays, thorax-CT and PET-CT. Age, gender, preoperative method of diagnosing NSCLC, localization of the mass, intrathoracic lymph nodes that showed pathologic size increase (> 1 cm) on thorax-CT, SUVmax values of the mass and all intrathoracic lymph nodes on PET-CT, the operation performed, sampled/excised lymph nodes during the operation, size of the tumoral lesion, histopathologic results of the sampled lymph nodes and tumor type were recorded to a database in all patients.

Statistical Analysis

Data of the patients were analyzed using SPSS for Windows package software. Descriptive statistics were expressed as mean±standard deviation or median (min-max) for continuous variables, and categorical variables as frequency (n) and percentage (%). Pearson's Chi-Square or Fisher's exact and ROC analysis were used to determine whether thorax-CT and PET-CE results in each lymph node station were significant in distinguishing between metastatic and non-metastatic groups according to histopathological results. Sensitivity, specificity, positive and negative predictive values and accuracy rate were calculated to evaluate diagnostic indicators.

RESULTS

A total of 217 patients with 190 (87.6%) being male and 27 (12.4%) female who were pre- or perioperatively diagnosed with NSCLC, and who underwent thorax-CT, PET-CT, and surgical resection were included in the study based on evaluation criteria. Patients' ages differed between 37 and 87 years with a mean age of 58.2 years. A total of 112 patients (51.6%) were in 46-60 age range and 85 patients (39.2%) in 61-75 age range.

Preoperative diagnosis of NSCLC was established with bronchoscopic biopsy in 107 (49.3%), with transthoracic fine needle aspiration biopsy in 91 (41.9%) and frozen examination in 19 88.8%) patients. None of the patients received neoadjuvant chemotherapy. Of all tumors, 123 (56.7%) were right lung localized and 94 (43.3%) were left lung localized. Forty-eight (22.1%) of the right lung localized tumors were localized in the right upper lobe, 33 (4.3%) in the right hilar, 29 (13.4%) in the right lower lobe and 13 (6%) in the middle lobe. Of the left lung localized tumors, 156 (25.8) were localized in the left upper lobe, 20 (9.2%) in the left lower lobe and 18 (8.3%) in the hilar region. Size of the mass was between 0-1 cm in 6 (2.8 %), 1-2 cm in 69 (31.8%) and 2-3 cm in 142 (65.4%) patients. PET-CT mass SUVmax values varied between 1.26 and 23.33 with a mean value of 10.65. SUVmax values between 0-2.5 were found in 2 (0.9%) patients, 2.5-5 in 18 (8.3%) patients, 5-10 in 82 (37.8%) patients, 10-15 in 80 (36.9%) patients, 15-20 in 28 (12.9%) patients and 20-25 in 7 (3.2%) patients. SUVmax values were in 5-15 range in 74.7% of the patients.

Of 217 patients operated for staging and/or treatment of their preoperative diagnosis of NSCLC, 142 (65.5%) underwent lobectomy, 35 (16.1%) mediastinoscopy alone, 36 (12%) pneumonectomy, 7 (3.2%) mediastinoscopy+lobectomy, 4 (18%) wedge resection, 2 (0.9%) mediastinoscopy+segmentectomy and 1 (0.5%) segmentectomy.

In the evaluation of tumor cell types; the most common type was squamous cell carcinoma in 100 (46.1%) patients followed by adenocarcinoma in 92 (44.1%) patients, adenosquamous carcinoma in 14 (6.5%), large cell carcinoma in 5 (2.3%) patients and pleomorphic carcinoma in 2 (0.9%) patients.

The results of histopathological examination of the mediastinal lymph nodes that showed an increase in size on thorax-CT and the lymph nodes sampled/excised during operation were separately evaluated for each lymph node station. The lymph nodes with a short diameter of ≥ 1 cm that showed an increase in size on thorax-CT were considered as metastatic and the lymph nodes < 1 cm as benign. Following comparison of histopathologically confirmed lymph nodes and the lymph nodes classified as malignant or benign based on the lymph node size on thorax-CT; sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated for each mediastinal lymph node (Table 1). In addition, overall statistical evaluations were made for N2.

There were 527 lymph nodes from the stations that did not show increase in size on thorax-CT images, classified as benign and histopathologically examined. Pathologic examination was reported as benign in 507 and metastatic in 20 lymph node stations. Whereas 115 N2 lymp node stations were classified as metastatic on thorax-CT. Pathology examination was reported as benign in 116 and metastatic in 39 of these lymph nodes. In the evaluation of N2 lymph node stations, sensitivity of thorax-CT in determining the status of the lymph nodes was found as 66.1%, specificity as 81.4%, PPV as 25.2%, NPV as 96.2% and accuracy as 80.1% (Table 1).

Table 1. Diagnostic performance indicators of CT and PET-CT exaaminations in determination of metastatic and non-metastatic N2 lymph node stations according to pathology results

N2 LN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Thorax CT	66.1	81.4	25.2	96.2	80.1
PET-CT	55.9	86.2	27.7	95.4	83.6

LN: Lymph Node; NPV: Negatif Predictive Value
PPV: Positive Predictive Value

The effectiveness of PT-CET in determining the status of lymph nodes and mediastinal staging was separately evaluated for each lymph node station. In addition, overall statistical evaluations were made for N2. There were 563

lymph nodes from the stations that did not show increase in size on thorax PET-CT images, classified as benign and histopathologically examined. Pathologic examination was reported as benign in 539 and metastatic in 26 lymph node stations. Whereas 119 N2 lymph node stations were classified as metastatic on thorax PET-CT. Pathology examination was reported as benign in 86 and metastatic in 33 of these lymph nodes. In the evaluation of N2 lymph node stations, using a SUVmax cut-off value of 2.5, sensitivity of thorax PET-CT in determining the status of the lymph nodes was found as 55.9%, specificity as 86.2%, PPV as 27.7%, NPV as 95.4% and accuracy as 83.6% (Table 1).

Pathologic examination results of all lymph node stations were evaluated in squamous cell carcinoma and adenocarcinoma that were the most commonly found types of tumors. The number of sampled lymph node stations determined as adenocarcinoma in histopathologic examination was 292. Pathology result was reported as benign in 257 (89.73%) and malignant in 30 (10.27%) of these lymph nodes. The number of sampled lymph node stations determined as squamous lymph node in histopathologic examination was 316. Pathology result was reported as benign in 298 (94.30%) and malignant in 18 (5.70%) of these lymph nodes.

Lymph node stations were individually examined based on SUVmax values. SUVmax values were divided into groups and metastatic status of lymph nodes were examined in these groups. SUVmax value was between 5-10 in 82 patients. Of the 254 lymph node stations sampled from these patients, 238 (93.70%) were reported as benign and 16 (16.30%) as malignant. SUVmax value was between 10-15 in 80 patients. Of the 251 lymph node stations sampled from these patients, 220 (87.65%) were reported as benign and 31 (12.35%) as malignant. In the examination based on patients, N2 positivity was found in 40 (18.43%) of the 217 patients. The mean age was 58.4 (42-75) years in these patients. The mean tumoral lesion size was 2.94 cm and 14 of these patients underwent mediastinoscopy, 1 mediastinoscopy + resection, and 25 resection alone. The mean mass SUVmax value was 11.38 (1.6-21.07). Localization of tumor was found as the right hilar in 14, left hilar in 5, right lower lobe in 4, middle lobe in 1, right upper lobe in 7, left lower lobe in 3 and right lower lobe in 6 of these patients. Tumor subtype was squamous cell carcinoma in 14 and adenosquamous carcinoma 7 patients.

N2 positivity was found in 14 of 35 patients who underwent mediastinoscopy alone and resection was not performed in these patients. The remaining 21 patients were referred from the thoracic diseases clinic and did not present for resection after mediastinoscopy staging.

DISCUSSION

As in all oncologic diseases, size and anatomic localization of tumor, lymph node involvement and metastatic status are the factors affecting survival in lung cancers (6). Determination of metastasis in mediastinal lymph nodes is the most important prognostic factor determining R0 resectability. Lymph node metastasis is evaluated with thorax-CT, PET-CT, EBUS and mediastinoscopy. Lymph node metastases that could not be preoperatively detected with clinic and radiologic examinations remain a clinical problem in operable NSCLC patients. It has been reported that N2 positivity could be found with mediastinoscopy in at least 10% of the patients that were considered to have no lymph node metastasis with clinic and radiologic examinations (7). In our study N2 positivity was detected in 40 patients. N2 positivity was confirmed with mediastinoscopy in 14 of these patients. Whereas 26 patients underwent resection and N2 positivity was shown after histopathologic evaluation. Therefore, in our study N2 positivity was detected in 26 (11.98%) patients that were considered to have no lymph node metastasis with clinical evaluation. The rate of false negative results is 0 with mediastinoscopy, while the rate of false negativity is high in the subcarinal region (6%) and low in the paratracheal region at 1-2% (8). Therefore, mediastinoscopy is highly effective in evaluation of lymph nodes especially in the paratracheal region. In our study, in a patient with N2 positivity who underwent mediastinoscopy and resection, lymph stations 2, 4 and 7 were sampled and the operation was converted to resection upon the pathology report was benign. Positivity was found in lymph node station 7 following mediastinoscopy and resection. As specified in the literature, the rate of false negativity in the subcarinal region should not be overlooked.

Hasdiraz et al. reported, N2 positivity was found in 5 (23.8%) of the 21 patients with T1 NSCLC, with 4 of these patients underwent mediastinoscopy alone. In that study with a small number of cases, mediastinoscopy was routinely recommended in T1 tumors because of the high rate of N2 positivity (9).

Meyers and colleagues reported in 248 patients with clinical stage 1, 178 patients (72%) had mediastinoscopy before resection and 5 patients (3%) had N2 disease. N2 metastasis was found in further nine patients after resection, and as a result, mediastinal lymph node metastasis was found in 14/248 (5.6%) patients. The authors reported that mediastinoscopy after thorax-CT and PET-CT has low benefit and brings a serious financial burden (10). In our study, mediastinoscopy was performed in 40 of 217 T1 patients, with 44 underwent mediastinoscopy alone and 9 mediastinoscopy plus resection operation. N2 positivity was found in 14 (31.8%) of the 15 patients who underwent mediastinoscopy, and subcarinal lymph node metastasis was found in one of these patients in histopathologic examination. Meyers et al. performed mediastinoscopy in 72% of their patients, while in our study this operation was performed in %20 of the patients. These authors reported a low (3%) N2 positivity rate despite high rate of mediastinoscopy. They reported the total N2 positivity rate as 5.6% including the patients who underwent resection. In that study, high mediastinoscopy rates may explain financial burden that they reported. However, in our study we could not find a serious financial burden since our mediastinoscopy rates

were not too high. In our study, N2 positivity rate was found as 18.43% after all operations. Herein, our high N2 positivity rate might be attributed to our excess confidence with preoperative non-invasive staging methods and low rate of mediastinoscopy operations. The important detail is to review our criteria for N2 positivity in clinical and radiological examinations and to answer the question that whether mediastinoscopy should be used more commonly in staging despite its serious financial burden, or mediastinal staging should be made with additional minimal invasive methods in the cases evaluated as at limit in patients with T1 tumors.

Lee et al. investigated risk factors that could be used in predicting of N2 lymph node metastasis in 224 patients with clinical stage 1 NSCLC; the rate of pathologic N2 lymph node metastasis was higher in patients with a central tumor and a larger T size. When the authors examined SUVmax value of the primary tumor on PET-CT, they found a higher median SUVmax value (6±3.6) in patients with N2 lymph node metastasis. The authors reported that adenocarcinoma cell type and a high SUVmax value (>4) were risk factors and recommended to direct these patients to mediastinoscopy (11). In our study, the mean tumor size was found as 2.49 cm, the mean mass SUVmax value as 11.38, the rate of central localized lesions as 65%, the rate of adenocarcinomas as 47.5% and the rate of adenosquamous carcinomas involving adenocarcinoma component that should be not neglected as 17.5%. Similarly, in our study tumor size, high SUVmax values, and anatomic localization were shown to be the risk factors in mediastinal lymph node metastasis in T1 NSCLCs.

Staging studies have shown that prognosis is negatively affected by increasing tumor size. The increase in size has been associated with the incidence of mediastinal lymph node metastasis and its effect on a poor prognosis has been studied. In the literature, it has been observed that tumors of 2-3 cm sizes showed clinical features of next stage compared to T1 lesions < 2 cm. Looking at the survival of patients, a breaking point has been reported between the prognoses of T1N0 tumors < 2 cm and T1N0 tumors of 2-3 cm (12). In our study also the mean tumor size was higher than 2 in N2 positive T1 tumors. The incidence of mediastinal lymph node has been reported as 5-15% in peripheral T1N0 tumors (7). Regardless of tumor size, the incidence of mediastinal lymph node involvement has been advocated to be 50% (13). Goldstraw (14) argued that even if resectability is good in patients who are clinically and radiologically considered to have no N2, mediastinoscopy and anterior mediastinotomy or extended mediastinoscopy in the left upper lobe tumors in all patients are the gold standard because survival is poor among patients with N2 detected in the preoperative period.

CONCLUSION

NSCLC patients with the longest survival and highest treatment success rates are those diagnosed at an early stage and underwent surgical resection. Therefore, the basic feature sought in all non-invasive and invasive examination is staging of N factor with the most correct results in the preoperative mediastinal staging.

The nonignorable rate of metastatic lymph nodes in T1 NSCLCs is a clinical problem. Although mediastinoscopy is superior over radiologic methods (Thorax-CT, PET-CT) in the evaluation of lymph nodes, it can not be performed in all patients since it is an invasive procedure. Mediastinoscopy is not cost-effective for all patients without choosing a patient. However, in other staging methods, the detection rate of occult lymph node metastasis is low. Risky groups should be evaluated in detail in terms of the staging method to be selected.

In conclusion, we think that the staging should be made with endobronchial ultrasonographic biopsy or/and mediastinoscopy in the presence of one of the criteria including a tumor size > 2 cm, histopathological subtype compatible with adenocarcinoma, high mass SUVmax values, and the presence of lymph nodes showing pathological involvement even it is radiologically small. Whereas in low-risk patients group, it would be appropriate to avoid additional surgical procedures, to follow a cost effective policy and to prefer minimal invasive staging methods if necessary.

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