Lymph node involvement in T1 non-small-cell lung cancer: could glucose uptake and maximal diameter be predictive criteria?

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Abstract

Objective: The introduction of modern staging systems such as computed tomography (CT) and positron emission tomography/CT (PET/CT) with fluorodeoxyglucose ([18F]FDG) has increased the detection of small peripheral lung cancers at an early stage. We analyzed the behavior of pathological T1 non-small-cell lung cancer (NSCLC) to identify criteria predictive of nodal involvement, and the role of cancer size in lymph node metastases.

Methods: We retrospectively analyzed 219 patients with pathological T1 NSCLC. All patients were staged by high-resolution CT and PET as stage I, and underwent anatomical resection and radical lymphadenectomy. Our data were collected based on pathological nodule size (0—10 mm; 11—20 mm; and 21—30 mm); morphological features of lung nodule and FDG uptake of the tumor measured by standardized uptake value (SUV).

Results: A total of 190 patients (87%) were pN0, 14 (6%) pN1, and 15 (7%) pN2. No nodal involvement was observed in any of the 62 patients with nodule size less than 10 mm, in 20 out of 120 patients (17%) with nodule size 11—20 mm, and in nine out of 37 tumors (28%) 21—30 mm in size ($p = 0.0007$). All 55 patients with nodule SUV < 2.0 and all 26 non-solid lesions were pN0 (respectively, $p = 0.0001$ and $p = 0.03$). All nodal metastases occurred among the group of 132 patients with size larger than 10 mm and SUV higher than 2.0 with a 22% rate of nodal involvement of (29 patients) ($p < 0.0001$).

Conclusions: The low probability of lymph node involvement in NSCLC < 1 cm or showing glucose uptake < 2 suggests lymphadenectomy could be avoided. A randomized trial should be performed to validate our data.

Keywords: Lung cancer; Lymph node involvement; Tumor size; SUV; Positron emission tomography; Fluorodeoxyglucose

1. Introduction

The introduction of modern staging systems such as computed tomography (CT) and positron emission tomography/CT (PET/CT) with fluorodeoxyglucose (FDG) has increased the detection of small peripheral lung cancers at an early stage [1].

Stage I non-small-cell lung cancers (NSCLCs) are confined to the lung without lymph node involvement, and surgical resection is currently considered the standard therapeutic approach.

In 2007, according to the new TNM (tumor, node, metastasis) classification (seventh edition), the International Association for the Study of Lung Cancer Lung Cancer Staging Project reported 5-year survival rates for early stage NSCLC of 77% and 71% after radical excision of pathological T1N0 (stage IA) tumors of 2 cm or smaller (T1a) and 2—3 cm (T1b), respectively, and 5-year survival rates of 58% and 49% for pathological T2N0 (stage IB/IIA) tumors measuring 3—5 cm (T2a) and 5—7 cm (T2b), respectively [2]. Findings to date demonstrate that primary tumor size has a direct effect on prognosis, which is consistently better for patients with resected stage IA disease (tumor ≤ 3 cm) compared with resected stage IB disease (tumor > 3 cm but ≤ 7 cm) [3].

Lobectomy with radical lymphadenectomy is currently considered the treatment of choice for early-stage lung cancer, irrespective of tumor size or its metabolic features on PET. However, the new TNM classification recently demonstrated that very small lung cancers may be less aggressive than others [2], suggesting a less aggressive surgical approach to reduce morbidity. A recent trial demonstrated that both sampling and systematic lymph node dissection could be associated with an increased incidence of complications (38%) such as atrial arrhythmias, prolonged air leaks, and excessive chest tube drainage [4].
A preoperative diagnostic determination to establish the size and correct staging of the tumor is mandatory for appropriate selection of candidates for surgical treatment. Data have demonstrated that PET-FDG is a reliable tool versus CT in evaluating both solitary pulmonary nodules and lymph node involvement [5].

We analyzed the behavior of pT1 NSCLC to identify predictors of nodal involvement and to establish criteria to avoid radical lymphadenectomy and related subsequent morbidity. The present study describes our experience in a series of 219 consecutive patients with pT1 NSCLC preoperatively evaluated by morphologic and metabolic imaging, who underwent radical surgical excision of the primary tumor and loco-regional lymph nodes.

2. Materials and methods

2.1. Patients

Between June 2000 and June 2009, we retrospectively evaluated 219 pT1 NSCLC patients referred to our Surgical Division for a single pulmonary nodule. A total of 146 patients were male with a median age of 64 years (range 34—84). None had received prior treatment or had a history of lung cancer. All patients underwent total body CT scan (chest, abdomen, and brain) and total body PET/CT-FDG that determined the clinical stages using the TNM classification (seventh edition) [2]. After morphologic and metabolic imaging evaluation, all patients, were classified as clinical T1 or T2 (pleura) N0M0.

2.2. Diagnostic imaging

The maximal diameter of the lung nodules was measured on axial CT images classifying three tumor size groups: 0—10 mm; 11—20 mm, and 21—30 mm. In addition, lung nodules were defined as ground glass opacity (GGO) type (tumors showing >50% of GGO area on CT) or solid-type lesions (tumors showing <50% of GGO area on CT).

In 20 out of 219 patients, the lung nodule was CT-guided marked using technetium (TC99) radiotracer within 24 h from surgery because considered not palpable: 10 patients had GGO nodules, five had a nodule size less than 1 cm, and five patients had the nodule distant from the pleura more than 1 cm.

The mean time between PET and surgery was 28 days (range 1—102 days). All tumors had a maximal diameter larger than 8 mm. The maximal standardized uptake value, corrected for body weight (SUVbwmax), was measured on axial PET images by an experienced nuclear radiologist, who was informed of the location of the lung nodule. When the lung nodule was recognized on the axial low-dose CT image, the radiologist analyzed the corresponding PET images to detect any focal increase in glucose uptake, and collected the data. Tumors with SUV < 2.0 were considered negative and lesions with SUV ≥ 2.0 were considered positive.

2.3. Surgery

All patients underwent anatomical lung resection and radical lymphadenectomy via muscle-sparing lateral thoracotomy. Systematic lymph node dissection according to the classification of the American Thoracic Society was performed in all patients removing all lymphatic tissue from stations 2R, 4R, 7, and 10R for right-sided tumors and from stations 5, 6, 7, and 10L for left-sided tumors. Patients treated with resection of primary tumor without mediastinal lymph node dissection were not included.

2.4. Histology

All surgical specimens were analyzed at our institute. A total of 3944 lymph nodes were examined. The mean number of nodes removed per patient was 10 (range 0—27) for N1 station and eight (range 2—23) for N2 station. Although all the lymphatic tissue had been removed, only in one patient was no lymph node found after the pathologist analyzed all the specimens.

2.5. Statistical analysis

The Fisher exact test and the Mantel—Haenszel chi-square test for trend were used to assess the association between, categorical (sex, type of intervention, laterality, tumor site, clinical stage, and SUV) and ordinal variables (classes of tumor size: <10 mm, 11—20 mm, and >20 mm), respectively, and lymph node status. We then combined information from selected features of the nodules, which were significantly associated with lymph node status at univariate analysis (tumor size and nodule SUV ≥ 2) to assess their joint predictive value. The diagnostic accuracy of the combination of tumor size and SUV was evaluated by sensitivity, specificity, positive predictive value, and negative predictive value; 95% confidence intervals for proportions were calculated according to the efficient-score method (corrected for continuity). Overall survival plots according to selected patient/tumor characteristics were drawn using the Kaplan—Meier method. The log-rank test was used to assess the survival difference between strata. All analyses were performed with SAS software, version 8.2 (Cary, NC, USA).

3. Results

Patient characteristics and pathological features of nodal involvement are listed in Table 1. The clinical size of the primary tumor was 0—10 mm in 57 patients (26%), 11—20 mm in 121 (55%), and 21—30 mm in 41 (19%). A total of 190 patients (87%) had solid tumors and 26 patients (13%) had GGO type nodules. All lymph nodes measuring <10 mm were clinically considered non-pathologic. Fifty-five lesions (25%) had SUV < 2.0 and 164 (75%) ≥ 2.0. All lymph nodes had SUV < 2. A total of 188 patients (86%) were cT1NO stage and 31 (14%) were cT2NO stage. Lobectomy was performed in 202 patients (92%), bilobectomy in six (3%), typical wedge resection in nine (4%), and pneumonectomy in two (1%). All primary tumors were NSCLC pT1a or pT1b. Tumors were located on the right side in 138 patients (63%), in the upper
lobe in 148 cases, in the lower lobe in 59, and in the middle lobe in 12. Tumors consisted of squamous carcinoma in 34 patients (15.6%), adenocarcinoma in 135 (61.6%), bronchoalveolar in four (1.8%), large cell in five (2.3%), adenosquamous in one (0.4%), and adenocarcinoma mixed with bronchioloalveolar subtype in 40 (18.3%). The pathological size of the primary tumor was 0—10 mm in 62 patients (28.3%), 11—20 mm in 120 (54.7%), and 21—30 mm in 37 (17%).

A total of 190 patients (87%) were pN0, 14 (6%) pN1, and 15 (7%) pN2. The pathological status of loco-regional lymph nodes in cT1 was pN0 in 169 (90%), pN1 in 10 (5%), and pN2 in nine (5%), whereas the pathological status of loco-regional lymph nodes in cT2 was pN0 in 21 (68%), pN1 in four (13%), and pN2 in six (19%). No nodal involvement was observed in any of the 62 patients with pathological node size < 10 mm, in 20 out of 120 patients (17%) with node size 11—20 mm, and in nine out of 37 tumors (24%) 21—30 mm in size ($p < 0.0007$). All 55 patients with node SUV < 2.0 and all 26 patients with non-solid lesions were pN0 ($p = 0.0007$ and $p = 0.0008$, respectively). All nodal metastases occurred among the group of 132 patients with tumor size > 10 mm and SUV > 2.0 with a 22% rate of nodal involvement of (29 patients) ($p < 0.0001$) (Table 2).

Postoperative morbidity and mortality was 12% and 0%, respectively. After a mean follow-up of 38 months, 188 patients (86%) were alive without evidence of disease, whereas 18 patients had died (8%) from disease.

The overall survival of patients with tumor size < 1 cm or tumors with low FDG uptake (SUV < 2) was compared with that of patients with nodules > 1 cm and with higher FDG uptake (SUV ≥ 2) (Fig. 1). Overall survival based on size, SUV, and nodule type are listed in Fig. 2. Our selection criteria, based on tumor size and SUV, have a sensitivity of 100% (85—100%), specificity of 46% (39—53%), positive predictive value of 22% (15—30%), and negative predictive value of 100% (95—100%) to identify positive node tumors.

4. Discussion

Stage I NSCLC is confined to the lung without lymph node involvement. Lobectomy with radical lymphadenectomy is usually accepted as the standard therapeutic treatment in patients with an early stage lung cancer [6].

According to the new TNM classification (seventh edition), the overall 5-year survival rate for pathological stage IA NSCLC was 73%, ranging from 71% to 77% for T1a and T1b tumors respectively, compared with 58% for stage IB tumors [2]. Among patients with stage I cancer, tumor size may affect outcome and drive survival [7], as confirmed by different studies. In 1995, Martini et al. found that patients with tumor diameter < 1 cm had a better prognosis than those with tumor diameter > 1 cm but < 3 cm [8]. Gajra et al. analyzed 246 patients treated over 10 years, and demon-
Stratified that the 5-year survival was significantly higher in patients with tumor size ≤1.5 cm compared with larger tumors [9,10].

Several studies demonstrated that primary invasive non-small-cell lung carcinomas >2.0 cm were twice as likely to have nodal metastases as carcinomas ≤2.0 cm, emphasizing that small lung cancers had less lymph node involvement, and confirming a better survival [11—14]. In Ishida’s study, 17% of 1—2-cm tumors were also associated with occult lymph node involvement, whereas none of the tumors <1 cm had lymph node metastases [15]. Lastly, Konaka et al. reported the absence of lymph node metastases in sub-centimeter lung cancer [16].

A preoperative diagnostic determination to establish the size and correct staging of the tumor is mandatory for appropriate selection of candidates for surgical treatment. Data have demonstrated that PET/CT-FDG is a reliable tool, compared with CT alone, to evaluate both solitary pulmonary nodules (when their size is superior to 8 mm, which is the spatial resolution of the device) and lymph node involvement [5,17]. Divisi et al. recently demonstrated that PET/CT-FDG improves the identification and characterization of potentially malignant pulmonary nodules with a diameter less than 1 cm using an SUVmax cut-off of 2.5 [18]. PET-FDG will estimate intratumoral lymphatic vessel invasion and the aggressiveness of T1 NSCLC nodules [19,20]. Higashi et al. demonstrated that pulmonary nodules with more FDG uptake than mediastinal background presented intratumoral vessel invasion and were more frequently related to nodal involvement and worse survival [20]. A recent study by Pastorino et al. demonstrated that the 5-year survival of lung cancer patients was 100% for nodules with SUV level < 2.5, confirming the clinical value of PET-FDG in discriminating undetermined lung nodules and its ability to use SUV to predict long-term survival [1].

Our study retrospectively studied 219 pathological T1 NSCLC patients to demonstrate the true behavior and aggressiveness of early stage lung cancer, and to fathom predictors of nodal involvement, thereby avoiding unnecessary radical lymphadenectomy. No nodal involvement was observed in any of the patients with pathological nodule size <10 mm or SUV <2.0 or GGO lesions. Patients with any of these three features had a 5-year survival of 100% (Fig. 2), confirming these variables as predictors of long-term survival.

In addition, we matched SUV and tumor size, and compared patients with tumor size <1 cm or tumors with low FDG uptake (SUV <2.0) to patients with nodules >1 cm and with higher FDG uptake (SUV ≥2.0), showing an overall survival of 100% and 79% (95% confidence intervals 70—88%), respectively (Fig. 1). GGO lesions were also associated with negative lymph node status but did not represent an independent risk predictor: 20 of the 26 GGO lesions had SUV <2.0 and 13 had a size <10 mm, leaving only three GGO lesions >10 mm with SUV ≥2.0. Analyzing these results, we confirmed the ability of PET-FDG to use SUV to predict tumor biology prior to surgery, and we showed the relation of nodule size and morphology to tumor aggressiveness and subsequent lymph node involvement.

Fig. 2. The 5-year overall survival of 219 patients was 86% (95% confidence intervals 80—93%) (a). Five-year survival of patients with SUV ≥2 was 83% (95% confidence intervals 75—91%) (b), 85% in patients solid nodules (95% confidence intervals 78—92%) (c), and 82% in patients with nodule size >10 mm (95% confidence intervals 74—90%) (d).
There was a good correlation between lesion size measured preoperatively on CT and the pathological evaluation ($R^2 = 0.46$) (Fig. 3). When at least one of the variables (SUV or size) was below cut-off, the rate of pathological nodal involvement was 0% versus 22% (29/219) for patients with both variables above the cut-off, confirming that they are reliable predictors of nodal involvement.

Ishida and then Konaka have already demonstrated the absence of lymph node involvement in sub-centimeter lung cancers [15,16] and the feasibility to omit lymph node dissection in those cases. By contrast, Zhoua et al. recommended systematic nodal dissection in the presence of sub-centimeter disease, finding nodal metastases in 15% of NSCLC < 1 cm, but also including higher tumor stages such as stage II and III in their study without performing PET scan as part of the preoperative staging [21].

Radical lymph node dissection has been associated by many authors with lower risk of local recurrence and with a better prognosis because of an improved staging [22–25]. Even a recent randomized trial, proposed by Allen et al., showed that the complete mediastinal lymphadenectomy could be spared radical lymph node dissection if deemed not essential, thereby reducing operative risks, postoperative morbidity, and surgery time. Based on our findings, we adopted cut-offs of 10 mm for nodule diameter and 2.0 as peak SUV to distinguish patients with nodal involvement from those without. These patients could be spared radical lymph node dissection if deemed not essential, thereby reducing operative risks, postoperative morbidity, and surgery time.

In conclusion, our study confirms literature reports suggesting that tumor size and SUV could be reliable independent predictors of tumor aggressiveness and lymph node involvement. Radical lymphadenectomy could be omitted in patients with stage I NSCLC tumors < 1 cm or SUV < 2.0. A randomized trial should be performed to validate our data.

### References


