The maximum standardized $^{18}\text{F}$-fluorodeoxyglucose uptake on positron emission tomography predicts lymph node metastasis and invasiveness in clinical stage IA non-small cell lung cancer

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Abstract

In patients with clinical stage IA non-small cell lung cancer (NSCLC), we investigated whether the maximum standardized uptake value (SUV$_{\text{max}}$) of $^{18}\text{F}$-fluorodeoxyglucose (FDG) by the tumor correlated with lymph node metastasis, intratumoral lymphatic and vascular invasion of tumor cells, and pleural invasion. From April 2005 to November 2008, 58 patients underwent a lobectomy with systematic hilar and mediastinal lymph node dissection for clinical stage IA NSCLC. All patients had integrated FDG positron emission tomography (PET)/computed tomography (CT) performed in our center as part of the preoperative workup within one month of resection. The relationships between the SUV$_{\text{max}}$ and pathologic results of lymph node metastasis, intratumoral lymphatic and vascular invasion of tumor cells, and pleural invasion were examined. Compared with tumors with an SUV$_{\text{max}} \leq 2.0$, tumors with an SUV$_{\text{max}} > 2.0$ had a higher local or regional recurrence rate after a limited resection, such as a wedge resection or a segmentectomy, which quantifies the proliferative activity of tumors and is an independent prognostic factor in patients with lung cancer [7, 9]. The objective of this study was to assess whether the maximum SUV normalized to body weight (SUV$_{\text{vmax}}$), which is less variable than the mean SUV [10], correlates with lymph node metastasis, intratumoral lymphatic and vascular invasion of tumor cells, and pleural invasion in patients with clinical stage IA NSCLC.

Keywords: Non-small cell lung cancer; FDG-PET; SUV; Thoracic surgery

1. Introduction

With the advancement of diagnostic techniques, small lung tumors are detected more frequently and surgery is performed more often [1]. However, there are still two unresolved issues regarding operations for patients with clinical stage IA non-small cell lung cancer (NSCLC). One issue is to what extent the lymph node area should be dissected [2], and the other issue is the volume of lung parenchyma that should be resected [3].

A lobectomy with systematic hilar and mediastinal lymph node dissection has become the standard treatment for clinical stage IA NSCLC, because a wedge resection or a segmentectomy results in more frequent local or regional recurrence than a lobectomy [4]. A higher local or regional recurrence rate after a limited resection, such as a wedge resection or a segmentectomy, was observed even though a negative surgical margin had been confirmed pathologically [4]. This finding was probably because of micrometastasis in local or regional lymph nodes, pulmonary parenchyma, or microscopic occult lymphatic invasion [5].

In recent years, the use of positron emission tomography (PET) with $^{18}\text{F}$-fluorodeoxyglucose (FDG) as a non-invasive diagnostic test has become more widespread. FDG-PET has been shown to be useful for the evaluation of an indeterminate pulmonary nodule, the staging of mediastinal lymph nodes and the evaluation of local nodal and distant metastases [6–9]. FDG-PET measures the standardized uptake value (SUV) of a pulmonary mass, which quantifies the glucose avidity of the tumor. The FDG uptake correlates with the proliferative activity of tumors and is an independent prognostic factor in patients with lung cancer [7, 9].

The database of our thoracic surgery department was searched for all patients who underwent a major lung resection (a lobectomy, a bilobectomy, or a pneumonectomy) with systematic hilar and mediastinal lymph node dissection for clinical stage IA NSCLC, and who had inte-
grated FDG-PET/computed tomography (CT) performed in our center as part of the preoperative workup within one month of resection from April 2005 to November 2008. We excluded tumors <1 cm in diameter because the spatial resolution of the current-generation PET scanners is 0.7–0.8 cm, making it difficult to image pulmonary nodules <1 cm. Therefore, we selected clinical stage IA NSCLC with a size of 1–3 cm measured in the preoperative chest CT. The clinical TNM stage was determined based on the findings of FDG-PET/CT and brain magnetic resonance imaging (MRI). A mediastinoscopy was not routinely used for the preoperative clinical staging and lymph node metastases are examined by FDG-PET/CT.

The medical records of each patient were examined to obtain information on age, sex, SUV\textsubscript{max}, preoperative serum level of carcinoembryonic antigen (CEA) and cytokeratin fragment (CYFRA) 21, pathological stage, actual maximum tumor diameter after resection, histology, lymph node metastasis, intratumoral vascular and lymphatic invasion of tumor cells and pleural invasion.

2.2. FDG-PET scanning

FDG-PET/CT scans were carried out on an integrated PET/CT scanner (Siemens, Bigograph, LSO2). The patients were requested to fast for 4 h and then intravenously received 185 MBq (5 mCi) of FDG, followed by PET scanning after 60 min. Interactive reconstruction with CT attenuation correction was performed. In addition, chest CT scans were available for visual correlation. The SUV\textsubscript{max} was established by drawing regions of interest on attenuation-corrected FDG-PET images around the tumor and calculated by the software within the PET/CT scanner using the following formula: Maximum SUV=[C(\mu Ci/ml)/ID(\mu Ci)]/w, where C is defined as activity at a pixel within the tissue identified by regions of interest and ID is defined as the injected dose per kilogram of the patient’s body weight (w). We adopted SUV\textsubscript{max} in the present analysis because it is less variable than mean SUV in measuring.

2.3. Pathological examination

After localization and size measurement, the specimens were planed with a cryostat, serially sectioned (3–4 mm) and embedded, and then stained by standard hematoxylin and eosin. To identify tumor involvement in the intratumoral vessels or pleura, we routinely performed elastica-van Gieson staining.

The histological classification was based on the current World Health Organization (WHO) classification guidelines [11]. Pleural invasion was subdivided into: p0 (no invasion), p1 (invasion into the visceral pleura), or p2 (invasion beyond the visceral pleura).

2.4. Statistical analysis

Continuous variables were analyzed by Student’s t-test, categorical variables by the \chi\textsuperscript{2}-test using Stat View 5.0 (SAS Institute Inc, Cary, NC). The differences were considered to be statistically significant when the P-value was <0.05.

3. Results

3.1. Patient characteristics (Table 1)

Our cohort consisted of 34 men and 24 women. All patients underwent a lobectomy with systematic hilar and mediastinal lymph node dissection for clinical stage IA NSCLC. Video-assisted thoracoscopic (VATS) lobectomy was performed in 46 patients and conventional lobectomy via open thoracotomy was performed in the remaining 12 patients. Age ranged from 43 to 86 years with a median of 67 years. Actual tumor size of the resected specimens ranged from 1 to 4 cm with a median 2 cm. According to the new TNM staging system for lung cancer [12], 28, 26 and 4 patients were classified as T1a, T1b and T2a, respectively. The pathological tumor stage was stage IA in 36, stage IB in 10, stage IIA in 2, stage IIB in 7, stage IIIA in 2 and stage IIIB in one patient. Lymph node metastasis was seen in 12 patients. Twenty-one patients were up-staged after the operation because of lymph node metastasis in 12, actual tumor size >3 cm in four and pleural invasion in five patients. Lymphatic invasion within the tumor was seen in 26, vascular invasion within the tumor in 30 and pleural invasion in 16 patients. A summary of patient characteristics and pathological characteristics is presented in Table 1.

3.2. The SUV\textsubscript{max} and tumor stage (Table 2)

Table 2 shows the values of SUV\textsubscript{max} that were obtained and their relation to pathological tumor stage, lymph node metastasis, intratumoral lymphatic and vascular invasion of tumor cells and pleural invasion. Compared with tumors with an SUV\textsubscript{max} ≤2.0, tumors with an SUV\textsubscript{max} >2.0 had more frequent lymph node metastasis, intratumoral lymphatic and vascular invasion of tumor cells and pleural invasion. Therefore, medical records were compared between the 20 NSCLCs with an SUV\textsubscript{max} ≤2.0 and the 38 NSCLCs with an SUV\textsubscript{max} >2.0.

3.3. Relationship between the SUV\textsubscript{max} and patient characteristics, tumor size, serum level of CEA and CYFRA and histology (Table 3)

None of the 20 NSCLC patients with an SUV\textsubscript{max} ≤2.0 had increased serum levels of CEA, and this was significantly lower than the incidence (10/38) of increased CEA in patients with SUV\textsubscript{max} >2.0 (P=0.01). Adenocarcinoma subtype had a lower SUV\textsubscript{max} than non-adenocarcinoma (P=0.02). There was no significant difference between the two groups in mean age, sex ratio, tumor size (T1a or others) or serum levels of CYFRA.

3.4. Relationship between the SUV\textsubscript{max} Pathological stage and tumor invasion into intratumoral vessels or pleura (Table 4)

Lymph node metastasis was not seen in any of the 20 patients with an SUV\textsubscript{max} ≤2.0, whereas metastasis was observed in 12/38 patients with an SUV\textsubscript{max} >2.0 (P=0.0005). Intratumoral vascular invasion of tumor cells
was seen in only 2/20 patients with an SUVmax ≤2.0, whereas it was observed in 24/38 patients with an SUVmax >2.0 (P < 0.0001). Intratumoral lymphatic invasion of tumor cells was seen in 3/20 patients with an SUVmax ≤2.0 compared with 27/38 patients with an SUVmax >2.0 (P < 0.00001). Pleural invasion was seen in only 2/20 patients with an SUVmax ≤2.0 compared with 14/38 patients with an SUVmax >2.0 (P = 0.03).

4. Discussion

In recent years, many small-sized NSCLCs have been detected as a result of the introduction of CT screening for lung cancer and surgery is performed more often [1]. However, there are still two unresolved issues regarding operations for patients with clinical stage IA NSCLC. One issue is to what extent the lymph node area should be dissected [2], and the other issue is the volume of lung parenchyma that should be resected [3].

Many surgeons still advocate that systematic nodal dissection should be routinely performed to secure complete local control of an NSCLC, even if a patient’s disease is classified as clinical stage IA, because even small NSCLC lesions have considerable potential for lymph node metastasis [4]. Small tumor size alone cannot be a reason for omitting lymph node dissection. The accurate preoperative determination of the lack of necessity of systematic lymph node dissection in patients with clinical stage IA disease could have an effect on reducing operation time, degree of invasiveness, and perhaps rapidity of patient recovery.
Although clinically reliable predictors of pN0 disease would eliminate unnecessary lymph node dissection, no criteria permitting such a determination have yet been established. Major lung resections, a lobectomy, or a pneumonectomy, combined with systematic hilar and mediastinal lymph node dissection, are the standard treatments for clinical stage IA lung cancer, and this is supported by the results of the LCSG trial [4]. Although a segmentectomy was reported to be preferred to a wedge resection of the lung because of its presumed lower recurrence rate, even a segmentectomy resulted in more frequent local or regional recurrence than a lobectomy [4]. The higher local or regional recurrence rate after a limited resection was observed even though a negative surgical margin had been confirmed pathologically. This finding was probably due to tumor involvement of intratumoral vessels, even for pathologic N0 disease, with the spread of tumor cells into lymphatic vessels outside the primary tumor leading to local recurrence [5]. Some successful results regarding limited surgery for clinical stage IA tumors were published [3, 13]. A limited surgical resection might have some advantages over a standard operation for selected patients. However, the preoperative patient selection for a limited surgical resection is difficult. The use of PET with FDG as a non-invasive diagnostic test has become more widespread. Recently, FDG uptake has been reported to be a prognostic factor in patients with lung cancer [7, 9]. Therefore, we examined whether the SUV\(_{\text{max}}\) correlates with lymph node metastasis, intratumoral lymphatic and vascular invasion of tumor cells, and pleural invasion, which might affect tumor invasiveness in patients with clinical stage IA NSCLC. In the current study, clinical stage IA NSCLC with an SUV\$_{\text{max}}\leq2.0$ seldom invaded the intratumoral lymphatic and vascular invasion of tumor cells, and pleural invasion. This type of lung cancer can be cured by means of a limited surgical resection, such as a segmentectomy.

Our results also showed that lymph node metastasis was not seen in patients with an SUV\$_{\text{max}}\leq2.0$ and no lymphatic invasion of the tumor cells was seen in the patients with an SUV\$_{\text{max}}\leq1.0$. Therefore, lymph node dissection could be reduced for clinical stage IA NSCLC with an SUV\$_{\text{max}}\leq1.0$, without using the sentinel lymph node biopsy. In addition, in recent years, VATS lobectomy has been touted to provide superior outcomes, compared with thoracotomy, for selected patients with early-stage NSCLC [14, 15]. Patients with an SUV\$_{\text{max}}\leq2.0$ may be good candidates for VATS lobectomy. However, there are several limitations to the current study. The biggest limitations were the small size of the study and the short length of the follow-up periods. Therefore, a large-scale prospective study and the longer length of the follow-up periods are absolutely required to confirm the results of the current study.

5. Conclusions

In patients with clinical stage IA NSCLC, SUV\$_{\text{max}}$ is an important predictor of tumor invasiveness and thus could be a useful index for planning a limited surgical resection or eliminating unnecessary lymph node dissection or a mediastinoscopy.

References