

Neither the maximum tumor size nor solid component size is prognostic in part-solid lung cancer: to be ground-glass opacity or not to be, is that really the question?

Kimihiko Shimizu, Yoichi Ohtaki, Seshiru Nakazawa, Akira Mogi, Hiroyuki Kuwano

Division of General Thoracic Surgery, Integrative Center of General Surgery, Gunma University Hospital, Maebashi, Japan

Correspondence to: Dr. Kimihiko Shimizu, MD, PhD. Division of General Thoracic Surgery, Integrative Center of General Surgery, Gunma University Hospital, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan. Email: kmshimizu@gmail.com.

Submitted Jul 10, 2016. Accepted for publication Jul 19, 2016.

doi: 10.21037/jtd.2016.08.32

View this article at: <http://dx.doi.org/10.21037/jtd.2016.08.32>

Hattori *et al.* (1) retrospectively analyzed the oncologic outcomes of 1,181 patients with surgically resected clinical N0 M0 non-small cell lung carcinoma (NSCLC). They reported that maximum tumor size was a significant prognostic factor in patients with all T stages of solid tumors without a ground-glass opacity (GGO) component. Moreover, there were significant differences in 5-year overall survival (OS) among each tumor size group. In contrast, patients with pure GGO tumors had a 5-year OS rate of 100%. Patients with part-solid lung cancers had a 5-year OS of more than 90%, and additionally, maximum tumor size, solid component size, and consolidation tumor ratio (CTR) were not prognostic factors. Based on these results, the authors concluded that neither the maximum tumor size nor solid component size has any prognostic value in patients with radiologically nonsolid or part-solid lung cancer. Therefore, they recommend classifying pure GGO and part-solid lung cancers independently of the maximum tumor and solid component sizes, and describing them as clinical-Tis and clinical-T1a, respectively.

Based on the pathoradiological correlation results in the Japan Clinical Oncology Group (JCOG) 0201 study (2,3), the radiological criterion to distinguish noninvasive from invasive lung adenocarcinoma is defined as a CTR ≤ 0.50 in c-T1a and c-T1b tumors (< 3 cm), and an excellent prognosis is predicted for such radiologically defined noninvasive adenocarcinomas (2,3). However, in their study, Hattori *et al.* evaluated and compared OS between patients with GGO-dominant ($0 < \text{CTR} \leq 0.50$) and solid-dominant tumors ($0.5 < \text{CTR} < 1.0$) in patients with radiologically part-solid lung cancer (these cases were all adenocarcinomas).

The oncologic outcomes did not differ between these two groups if solid lung cancer cases were excluded from the cohort.

We were interested in the differences between the results of these two studies, both of which analyzed a patient cohort with adenocarcinoma. We have three comments for the study by Hattori *et al.* concerning this point.

- We have concerns related to their radiological evaluations on thin-section CT. They defined a pure GGO tumor as a lung tumor without a solid component (i.e., CTR = 0), a part-solid tumor as a lung tumor with both GGO and a solid component (i.e., $0 < \text{CTR} < 1.0$), and a solid tumor as a tumor showing only consolidation without GGO (i.e., CTR = 1.0). We occasionally encounter tumors with a GGO component that is difficult to judge, even if the tumor histology indicates non-adenocarcinoma (4). How did the authors distinguish between tumors with slight GGO component (e.g., $0.95 < \text{CTR} < 1.0$) and those without a GGO component (e.g., CTR = 1.0)? We believe that these radiological evaluations can be subjective and can affect the outcomes of such studies directly. Our main concern is that radiological evaluations may result in discrepancies in outcomes among studies, including those of this study (1-3,5). Therefore, we support the classical radiological definition used in JCOG 0201, which does not distinguish tumors only by the presence or not of a GGO component;
- In this study, the median follow-up period was too short (median: 43 months) to determine the actual

Table 1 Survival and recurrence of postoperative patients according to *EGFR* mutation status

No. of patients (WT/mutant)	<i>EGFR</i> -WT	<i>EGFR</i> -mutant	Refs.
307 non-Sq (245/62)	Recurrence rate 21.6%; median DFS 7.0 yr; 5 yr OS 73%	Recurrence rate 9.7%; median DFS 8.8 yr; 5 yr OS 98%	(10)
58 adenocarcinoma (32/26)	2 yr PRS 47%	2 yr PRS 81%	(11)
172 adenocarcinoma (86/86); matched pair analysis	3/5 yr RFS 74/60%; 3/5 yr OS 80/72%	3/5 yr RFS 85/78%; 3/5 yr OS 92/87%	(12)

EGFR, epidermal growth factor receptor; Sq, squamous cell carcinoma; OS, overall survival; PRS, post-recurrence survival; RFS, recurrence-free survival; DFS, disease free survival.

oncologic outcomes for stage I or GGO tumors due to their indolent nature. Maeda *et al.* (6) reported that 21 of 519 patients with stage IA NSCLC who underwent complete resection developed a late recurrence >5 years after resection (recurrence was locoregional in 9 patients and distant in 12). Furthermore, Yoshida *et al.* (7) reported three cases of delayed cut-end recurrence after limited resection of GGO adenocarcinomas that had been intraoperatively diagnosed as Noguchi Type B. All three cases developed a cut-end recurrence >5 years after resection. Noguchi Type B is equivalent to adenocarcinoma in situ (AIS) according to the new classification for adenocarcinoma (IASLC/ATS/ERS 2011) (8). Therefore, the median follow-up time used by Hattori *et al.* was too short to confirm their conclusion regarding the importance of the GGO component as a significant clinical T descriptor. Moreover, the patient sample size was too small to conclude an outcome. The authors concluded that neither the maximum tumor size nor CTR was prognostic in 448 patients with part-solid lung cancer. Although the differences reported were not significant, a larger tumor size and higher CTR were related to a poorer outcome. The limited tumor sample size and retrospective nature of their study should be taken into consideration;

- The prognosis of patients with adenocarcinoma largely depends on the presence of driver gene mutations, including mutations in the epidermal growth factor receptor (*EGFR*) gene (9) (Table 1). This is because tyrosine kinase inhibitors (TKIs) markedly prolong the OS of patients with *EGFR*-mutant tumors (13,14). We must consider driver gene mutations in the assessment of OS as an oncologic

outcome. Besides, the subgroups with radiologically nonsolid or part-solid lung cancers in this study included high proportions of AIS, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma. Therefore, the *EGFR* mutation rate is also significantly higher in these subgroups than in the other subgroups, such as those with solid or other histological types (15). Therefore, *EGFR* mutation must be considered a significantly favorable prognostic factor before and after recurrence. Thus, this study's outcome may be related more to the *EGFR* mutation status than the clinical T factor.

Lung cancer staging classification has a strong effect on the management and treatment strategies for NSCLC. However, the recent development and validation of a new generation of *EGFR*-TKIs and immune checkpoint inhibitors have greatly prolonged the survival of patients with advanced lung cancer, even after recurrence (9,13,14,16,17). Because such new treatments affect both OS and progression-free survival (PFS), they will influence forthcoming TNM classifications. We should reconsider whether OS or PFS is more adequate to evaluate the outcome of a new treatment. Furthermore, the *EGFR* mutation status should be considered in TNM classification in this molecular-based therapeutic era.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Feichao Bao (Department of Thoracic Surgery, The First Affiliated Hospital, Zhejiang University,

Hangzhou, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Hattori A, Matsunaga T, Takamochi K, et al. Neither Maximum Tumor Size nor Solid Component Size Is Prognostic in Part-Solid Lung Cancer: Impact of Tumor Size Should Be Applied Exclusively to Solid Lung Cancer. *Ann Thorac Surg* 2016;102:407-15.

References

- Hattori A, Matsunaga T, Takamochi K, et al. Neither Maximum Tumor Size nor Solid Component Size Is Prognostic in Part-Solid Lung Cancer: Impact of Tumor Size Should Be Applied Exclusively to Solid Lung Cancer. *Ann Thorac Surg* 2016;102:407-15.
- Asamura H, Hishida T, Suzuki K, et al. Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201. *J Thorac Cardiovasc Surg* 2013;146:24-30.
- Suzuki K, Koike T, Asakawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). *J Thorac Oncol* 2011;6:751-6.
- Watanabe Y, Tsuta K, Kusumoto M, et al. Clinicopathologic features and computed tomographic findings of 52 surgically resected adenosquamous carcinomas of the lung. *Ann Thorac Surg* 2014;97:245-51.
- Tsutani Y, Miyata Y, Nakayama H, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. *J Thorac Cardiovasc Surg* 2012;143:607-12.
- Maeda R, Yoshida J, Ishii G, et al. Long-term outcome and late recurrence in patients with completely resected stage IA non-small cell lung cancer. *J Thorac Oncol* 2010;5:1246-50.
- Yoshida J, Ishii G, Yokose T, et al. Possible delayed cut-end recurrence after limited resection for ground-glass opacity adenocarcinoma, intraoperatively diagnosed as Noguchi type B, in three patients. *J Thorac Oncol* 2010;5:546-50.
- Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244-85.
- Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* 2014;311:1998-2006.
- Izar B, Sequist L, Lee M, et al. The impact of EGFR mutation status on outcomes in patients with resected stage I non-small cell lung cancers. *Ann Thorac Surg* 2013;96:962-8.
- Ohtaki Y, Shimizu K, Kakegawa S, et al. Postrecurrence survival of surgically resected pulmonary adenocarcinoma patients according to EGFR and KRAS mutation status. *Mol Clin Oncol* 2014;2:187-196.
- Matsumura Y, Owada Y, Yamaura T, et al. Epidermal growth factor receptor gene mutation as risk factor for recurrence in patients with surgically resected lung adenocarcinoma: a matched-pair analysis. *Interact Cardiovasc Thorac Surg* 2016;23:216-22.
- Takano T, Fukui T, Ohe Y, et al. EGFR mutations predict survival benefit from gefitinib in patients with advanced lung adenocarcinoma: a historical comparison of patients treated before and after gefitinib approval in Japan. *J Clin Oncol* 2008;26:5589-95.
- Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141-51.
- Yoshizawa A, Sumiyoshi S, Sonobe M, et al. Validation of the IASLC/ATS/ERS lung adenocarcinoma classification for prognosis and association with EGFR and KRAS gene mutations: analysis of 440 Japanese patients. *J Thorac Oncol* 2013;8:52-61.
- Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:123-35.
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* 2015;373:1627-39.

Cite this article as: Shimizu K, Ohtaki Y, Nakazawa S, Mogi A, Kuwano H. Neither the maximum tumor size nor solid component size is prognostic in part-solid lung cancer: to be ground-glass opacity or not to be, is that really the question? *J Thorac Dis* 2016;8(9):2334-2336. doi: 10.21037/jtd.2016.08.32

Implication of ¹⁸F-fluorodeoxyglucose uptake by affected lymph nodes in cases with differentiated thyroid cancer

TAKAAKI FUJII, REINA YAJIMA, HIRONORI TATSUKI and HIROYUKI KUWANO

Department of General Surgical Science, Graduate School of Medicine, Gunma University, Maebashi, Gunma 371-8511, Japan

Received November 20, 2015; Accepted March 16, 2016

DOI: 10.3892/mco.2016.958

Abstract. In this study, we evaluated the usefulness of positron emission tomography using ¹⁸F-fluorodeoxyglucose (FDG-PET) to detect metastatic lymph nodes in differentiated thyroid cancer. We also investigated whether certain factors, including the size of the metastasis to the lymph nodes, are associated with FDG avidity. A total of 22 consecutive patients with differentiated thyroid cancer who underwent FDG-PET preoperatively were enrolled in this study. Lymph node metastasis was diagnosed in the final pathology in 10 of the 22 patients (45.5%). The mean maximum standardized uptake value of the metastatic lymph nodes was 4.53 (range, 0-23.5). The 22 cases with differentiated thyroid cancer were divided into two groups based on lymph node metastasis. Clinicopathological variables other than FDG uptake of metastatic lymph nodes were not predictors of lymph node metastasis of thyroid cancer. The sensitivity, specificity, overall accuracy and false-negative rates of preoperative FDG-PET in the prediction of lymph node status were 40.0, 100, 72.7 and 60.0%, respectively. The false-positive rate of FDG-PET evaluation was 0%. The mean largest dimension of metastasis was 23.0 mm for FDG-positive cases and 10.9 mm for FDG-negative cases. There was a marked difference in the size of metastases between FDG-positive and -negative cases; however, even in patients with node metastasis >10 mm, the false-negative rate was 50.0%. Therefore, FDG-PET imaging was not found to be sufficient for the evaluation of lymph node status, particularly in cases with small metastases. Our findings indicate that preoperative FDG-PET evaluation of the lymph nodes cannot be considered predictive of the final pathology.

Introduction

The presence of lymph node metastasis is considered a risk factor for lymph node recurrence or distant metastasis in patients

with thyroid cancer (1). The success of surgery for thyroid cancer depends on accurate preoperative imaging, which enables complete clearance of metastatic lymph nodes (2,3). Ultrasound remains the most important imaging modality in the evaluation of thyroid cancer (3). In recent years, the clinical applications using positron emission tomography (PET) have increased significantly. PET with ¹⁸F-fluorodeoxyglucose (FDG) is a non-invasive whole-body imaging technique used to evaluate various types of malignancies, including thyroid cancer (1,3-7), in terms of tumor staging, restaging, detection of recurrence and monitoring treatment response (8,9). However, there are limited data regarding the role of FDG-PET in preoperative staging of thyroid cancer (3,7,10). Only a limited number of previous studies have evaluated the accuracy of PET in detecting preoperative lymph node metastasis, and it has been reported that PET does not improve the management or outcome of thyroid cancer (3,11-13). For the evaluation of affected lymph nodes in thyroid cancer, an understanding of FDG avidity is important. Several studies evaluated factors associated with the FDG avidity of the primary thyroid tumor in cases with thyroid cancer, and the thyroid tumor size has been reported to be associated with a higher likelihood of positive FDG uptake (14,15). However, to date, there has been no study assessing the factors associated with FDG avidity of the affected lymph nodes. The aim of this study was to evaluate the usefulness of FDG-PET for detecting metastatic lymph nodes in differentiated thyroid cancer. Furthermore, we investigated whether certain factors, including the size of metastasis to the lymph nodes, were associated with FDG avidity.

Patients and methods

Patients. A total of 22 consecutive patients with differentiated thyroid cancer who underwent FDG-PET preoperatively were enrolled in this study. All the patients underwent thyroidectomy at the Department of Surgical Science, Graduate School of Medicine, Gunma University (Maebashi, Japan) from January 2008 to December 2014. Patients with incomplete clinical information were excluded. None of the patients had distant metastasis.

Correspondence to: Dr Takaaki Fujii, Department of General Surgical Science, Graduate School of Medicine, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
E-mail: ftakaaki@gunma-u.ac.jp

Key words: thyroid cancer, ¹⁸F-fluorodeoxyglucose-positron emission tomography, lymph node metastasis, tumor size, maximum standardized uptake value

Thyroid cancer detection and evaluation. Most cases of thyroid cancer in this study were detected by PET during evaluation for other cancers. PET images were qualitatively examined by expert nuclear radiologists. Maximum standardized uptake

values (SUVmax) were calculated according to a routine clinical method. Thyroid nodule size, size of metastatic foci to the lymph nodes, age, and serum levels of thyroid-stimulating hormone (TSH), thyroglobulin and C-reactive protein (CRP) were investigated as possible predictors of lymph node metastasis.

Statistical analysis. The Fisher's exact test, χ^2 test and Student's t-test were used to compare benign and malignant groups. Differences were considered to be statistically significant when $P < 0.05$.

Results

Measures of the effectiveness of preoperative FDG-PET in the prediction of lymph node status. The mean SUVmax of metastatic lymph nodes was 4.53 (range, 0-23.5). As shown in Table I, the sensitivity, specificity, overall accuracy and false-negative rates for FDG uptake in the prediction of lymph node status were 40.0, 100, 72.7 and 60.0%, respectively. The false-positive rate of FDG-PET evaluation for lymph node status was 0%.

Patient and clinicopathological characteristics associated with lymph node metastasis and FDG uptake. The mean age of the patients was 58.6 ± 13.8 years and 4 of the 22 patients were men. The mean size of the thyroid nodules was 15.8 ± 8.3 mm. Lymph node metastasis was diagnosed in the final pathology in 10 of the 22 patients (45.5%). The 22 cases with differentiated thyroid cancer were divided into two groups based on lymph node metastasis. The patient characteristics and the results of the univariate analysis conducted to determine the association between the clinicopathological variables and lymph node metastasis are shown in Table II. These clinicopathological variables, apart from the FDG uptake of metastatic lymph nodes, were not predictors of lymph node metastasis from thyroid cancer. The 10 cases with lymph node metastasis were divided into two groups based on the presence of FDG uptake in the lymph nodes (Fig. 1). The patient characteristics and the results of the univariate analysis conducted to determine the association between the clinicopathological variables and FDG uptake in the lymph nodes are shown in Table III. None of the clinicopathological characteristics of the primary tumor, including size and SUVmax, were significantly associated with FDG uptake. However, the clinicopathological characteristics of the metastatic lymph nodes were significantly associated with FDG uptake in the lymph nodes. The analysis revealed that the size of the node metastasis was a statistically significant factor, although the number of lymph node metastases was not statistically significant.

FDG-PET results and size of lymph node metastasis. The association of metastatic tumor size in the lymph nodes and FDG-PET evaluation results (i.e., positive or negative) is shown in Fig. 2. The mean largest dimension of metastatic tumors was 23.0 mm for FDG-positive and 10.9 mm for FDG-negative cases. Thus, a significantly larger size of metastatic tumors was observed in FDG-positive nodes compared with that in FDG-negative nodes ($P < 0.01$). However, despite this marked difference in the size of the metastases, the false-negative rate was still 50.0% in patients with node metastases sized > 10 mm.

Table I. Measures of the effectiveness of preoperative positron emission tomography with ^{18}F -fluorodeoxyglucose in the prediction of lymph node status.

Measures	No./total (%)
Sensitivity	4/10 (40.0)
Specificity	12/12 (100.0)
Accuracy	16/22 (72.7)
False-negative rate	6/10 (60.0)

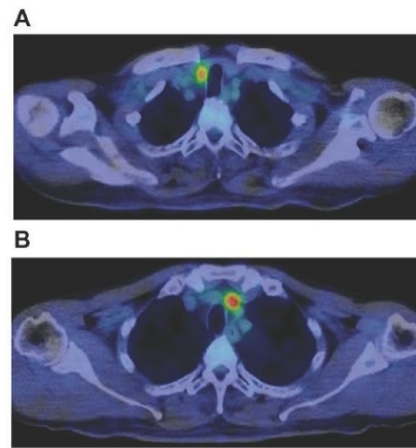


Figure 1. Examples of focal ^{18}F -fluorodeoxyglucose (FDG) uptake by lymph nodes on positron emission tomography-computed tomography in a 61-year-old male patient. FDG uptake in a (A) thyroid nodule [maximum standardized uptake value (SUVmax) = 4.7] and (B) lymph node (SUVmax = 6.6). Papillary carcinoma with lymph node metastasis was histopathologically confirmed.

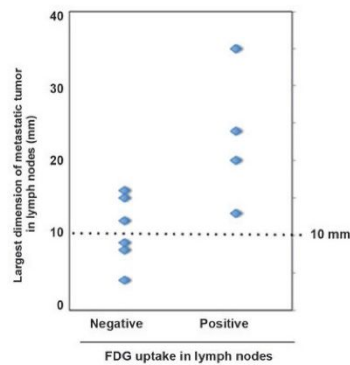


Figure 2. Comparison of the results of ^{18}F -fluorodeoxyglucose (FDG) uptake-positive and -negative cases regarding the size of lymph node metastasis. The mean largest dimension of metastatic tumors was 23.0 mm for FDG-positive and 10.9 mm for FDG-negative cases ($P < 0.01$). In the patient group with node metastasis > 10 mm as the cut-off point, the false-negative rate was 50%.

Table II. Patient and clinicopathological characteristics associated with lymph node metastasis.

Characteristics	Lymph node metastasis		P-value
	Absent (n=12)	Present (n=10)	
Age, years	59.0±14.5	58.1±13.1	0.792
Gender			0.956
Male	1	3	
Female	11	7	
Primary tumor size, mm	18.7±7.8	15.8±8.3	0.311
SUVmax of primary tumor	12.5±12.9	4.4±4.4	0.634
FDG uptake in lymph nodes, n (%)	0 (0.0)	4 (40.0)	0.157
TSH	1.25±0.47	1.81±1.00	0.224
Tg	170.9±421.9	109.1±134.5	0.450
CRP	0.10±0.21	0.17±0.35	0.721

Values are expressed as mean ± standard deviation. SUVmax, maximum standardized uptake value; FDG, ¹⁸F-fluorodeoxyglucose; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; CRP, C-reactive protein.

Table III. Patient and clinicopathological characteristics associated with FDG uptake in the lymph nodes.

Characteristics	FDG uptake in axillary lymph nodes		P-value
	Present (n=4)	Absent (n=6)	
Age, years	67.8±15.4	51.7±6.5	0.024
Gender			0.333
Male	2	1	
Female	2	5	
TSH	1.67±1.08	1.81±1.04	0.637
Tg	145.4±176.6	84.9±110.0	0.259
CRP	0.06±0.04	0.22±0.42	0.723
Primary tumor			
Histology			-
Papillary carcinoma	4	9	
Tumor size, mm	12.5±10.7	18.0±6.3	0.834
SUVmax	5.8±6.7	3.6±2.2	0.236
Extrathyroidal extension, n	1	1	0.667
Lymph node metastasis			
Tumor size, mm	23.0±9.2	10.7±4.5	0.011
Number of node metastases	3.8±2.8	5.2±2.9	0.717

Values are expressed as mean ± standard deviation. SUVmax, maximum standardized uptake value; FDG, ¹⁸F-fluorodeoxyglucose; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; CRP, C-reactive protein.

Discussion

FDG-PET has been widely used for diagnosing, staging, or detecting recurrence in various types of cancer; however, its diagnostic usefulness for thyroid cancer is controversial (1,3-8,14,15). Regarding thyroid nodules, there are several reports of preoperative evaluation with FDG-PET, and it is generally considered that FDG-PET is of limited value in

predicting thyroid cancer outcome (3-8,14,15). Furthermore, there are limited data regarding the role of FDG-PET in detecting preoperative lymph node metastasis of thyroid cancer (3,11-13). Clinically, FDG-PET is not generally used for the primary diagnosis of thyroid cancer. However, as FDG-PET is becoming a commonly used imaging modality, the number of thyroid lesions incidentally detected by FDG-PET is increasing. We previously demonstrated that the risk of thyroid cancer

in patients with PET incidentaloma was relatively high (5). Previous studies evaluated the factors associated with the FDG avidity of the primary tumor in thyroid cancer (14,15), but there has been no study assessing the factors associated with FDG avidity of the affected lymph nodes. Thus, the present study was undertaken to assess the accuracy of FDG-PET evaluation of lymph node metastases for patients with thyroid cancer. The key observations made in this study may be summarized as follows: i) The sensitivity, specificity, overall accuracy and false-negative rates of preoperative FDG-PET evaluation in the prediction of lymph node status were 40.0, 100, 72.7 and 60.0%, respectively; ii) the size of node metastasis, but not their number, was associated with FDG uptake in the lymph nodes; and iii) the false-positive rate of FDG-PET evaluation of lymph node metastasis was 0%; however, even in the patient group with node metastasis sized >10 mm, the false-negative rate was 50%.

SUVmax is used as a semi-quantitative indicator of FDG uptake, but it is sometimes difficult to obtain a reliable value with only one FDG-PET imaging, as SUVmax is affected by several factors, including glucose transporter expression, viable cell number, tumor perfusion and inflammatory cells (5,16,17). Several studies have reported that SUVmax is correlated with the size of the thyroid nodule to a certain extent (14,15), according to the resolution of the PET scanner, known as the partial volume effect (14,18). However, there has been no study assessing the factors associated with FDG avidity of affected lymph nodes. A few previous studies have evaluated the diagnostic accuracy of PET in lymph node metastasis. In this study, we evaluated the association between the size of lymph node metastasis and the FDG avidity of lymph nodes. There was a significant correlation between FDG uptake and the size of lymph node metastasis; however, even in the patient group with node metastasis >10 mm, the false-negative rate was 50%. Therefore, FDG-PET evaluation of lymph node metastasis is not predictive of small metastasis or micrometastasis.

On the other hand, in the present study, the false-positive rate of FDG-PET evaluation of lymph node metastasis was 0%. Thus, in cases with FDG uptake by the lymph nodes, macrometastasis to the lymph node is highly suspected. However, the size of lymph node metastases does not always reflect lymphatic spread; thus, FDG-PET imaging was not sufficient for the evaluation of lymphatic spread. This study has potential limitations, the major one being that it was a retrospective analysis and the number of cases was relatively small. However, the clinical implications of the data we obtained on FDG avidity are very important. However, additional research is required to elucidate this putative association between FDG-PET evaluation and lymph node metastasis.

Inflammation also increases FDG uptake and, therefore, SUVmax (14). CRP is an acknowledged marker of inflammation reflecting a systemic inflammatory response, and the measurement of serum CRP levels is an easily available test. However, recent clinical evidence suggests that FDG-PET is more accurate in detecting thyroid cancer at high rather than at low TSH levels (19). In this study, there was no correlation between SUVmax and either CRP or TSH level in lymph node metastasis.

In conclusion, we demonstrated that preoperative FDG-PET evaluation of lymph nodes is not effective in predicting node status. Even in cases with relatively large (>10 mm) node

metastases, FDG-PET imaging was not sufficient for the evaluation of lymph node status. The positive predictive value is high, but our findings suggest that preoperative FDG-PET evaluation of lymph node is not predictive of the final pathology.

Acknowledgements

The authors would like to thank Saitoh Y, Yano T, Matsui Y, Ishida A and Yamamoto A for their secretarial assistance.

References

1. Byun BH, Jeong UG, Hong SP, Min JJ, Chong A, Song HC and Bom HS: Prediction of central lymph node metastasis from papillary thyroid microcarcinoma by ¹⁸F-fluorodeoxyglucose PET/CT and ultrasonography. *Ann Nucl Med* 26: 471-477, 2012.
2. Yeh MW, Bauer AJ, Bernet VA, Ferris RL, Loevner LA, Mandel SJ, Orloff LA, Randolph GW and Steward DL: American Thyroid Association Surgical Affairs Committee Writing Task Force: American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. *Thyroid* 25: 3-14, 2015.
3. Pak K, Kim SJ, Kim JJ, Kim BH, Kim SS and Jeon YK: The role of ¹⁸F-fluorodeoxyglucose positron emission tomography in differentiated thyroid cancer before surgery. *Endocr Relat Cancer* 20: R203-R213, 2013.
4. Kresnik E, Gallowitsch HJ, Mikosch P, Stettner H, Igerc I, Gomez I, Kummig G and Lind P: Fluorine-18-fluorodeoxyglucose positron emission tomography in the preoperative assessment of thyroid nodules in an endemic goiter area. *Surgery* 133: 294-299, 2003.
5. Fujii T, Yajima R, Yamaguchi S, Tsutsumi S, Asao T and Kuwano H: Is it possible to predict malignancy in cases with focal thyroid incidentaloma identified by ¹⁸F-fluorodeoxyglucose positron emission tomography? *Am Surg* 78: 141-143, 2012.
6. Wu YJ, Wu HS, Yen RF, Shen YY and Kao CH: Detecting metastatic neck lymph nodes in papillary thyroid carcinoma by ¹⁸F-2-deoxyglucose positron emission tomography and Tc-99m tetrofosmin single photon emission computed tomography. *Anticancer Res* 23: 2973-2976, 2003.
7. Marcus C, Whitworth PW, Surasi DS, Pai SI and Subramaniam RM: PET/CT in the management of thyroid cancers. *AJR Am J Roentgenol* 202: 1316-1329, 2014.
8. Liu Y: Clinical significance of thyroid uptake on F18-fluorodeoxyglucose positron emission tomography. *Ann Nucl Med* 23: 17-23, 2009.
9. Fletcher JW, Djulbegovic B, Soares H, Siegel BA, Lowe VJ, Lyman GH, Coleman RE, Wahl R, Paschold JC, Avril N, *et al.*: Recommendations on the use of ¹⁸F-FDG PET in oncology. *J Nucl Med* 49: 480-508, 2008.
10. Urhan M, Velioglu M, Rosenbaum J, Basu S and Alavi A: Imaging for the diagnosis of thyroid cancer. *Expert Opin Med Diagn* 3: 237-249, 2009.
11. Choi JW, Yoon YH, Yoon YH, Kim SM and Koo BS: Characteristics of primary papillary thyroid carcinoma with false-negative findings on initial ¹⁸F-FDG PET/CT. *Ann Surg Oncol* 18: 1306-1311, 2011.
12. Jeong HS, Baek CH, Son YI, Choi JY, Kim HJ, Ko YH, Chung JH and Baek HJ: ¹⁸F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. *Clin Endocrinol (Oxf)* 65: 402-407, 2006.
13. Morita S, Mizoguchi K, Suzuki M and Iizuka K: The accuracy of [¹⁸F]-fluoro-2-deoxy D-glucose-positron emission tomography/computed tomography, ultrasonography, and enhanced computed tomography alone in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid carcinoma. *World J Surg* 34: 2564-2569, 2010.
14. Ohba K, Nishizawa S, Matsushita A, Inubushi M, Nagayama K, Iwaki H, Matsunaga H, Suzuki S, Sasaki S, Oki Y, *et al.*: High incidence of thyroid cancer in focal thyroid incidentaloma detected by ¹⁸F-fluorodeoxyglucose [corrected] positron emission tomography in relatively young healthy subjects: Results of 3-year follow-up. *Endocr J* 57: 395-401, 2010.
15. Bae JS, Chae BJ, Park WC, Kim JS, Kim SH, Jung SS and Song BJ: Incidental thyroid lesions detected by FDG-PET/CT: Prevalence and risk of thyroid cancer. *World J Surg Oncol* 7: 63, 2009.

16. Choi JY, Lee KS, Kim HJ, Shim YM, Kwon OJ, Park K, Baek CH, Chung JH, Lee KH and Kim BT: Focal thyroid lesions incidentally identified by integrated ¹⁸F-FDG PET/CT: Clinical significance and improved characterization. *J Nucl Med* 47: 609-615, 2006.
17. Matsuzaki K, Segade F, Matsuzaki U, Carter A, Bowden DW and Perrier ND: Differential expression of glucose transporters in normal and pathologic thyroid tissue. *Thyroid* 14: 806-812, 2004.
18. Hoffman EJ, Huang SC and Phelps ME: Quantitation in positron emission computed tomography. 1. Effect of object size. *J Comput Assist Tomogr* 3: 299-308, 1979.
19. Deichen JT, Schmidt C, Prante O, Maschauer S, Papadopoulos T and Kuwert T: Influence of TSH on uptake of [¹⁸F]fluorodeoxyglucose in human thyroid cells in vitro. *Eur J Nucl Med Mol Imaging* 31: 507-512, 2004.

CASE REPORT

Lung adenocarcinoma with anomalous bronchi and pulmonary veins preoperatively identified by computed tomography

Kouhei Tajima^{1,2}, Nobuyuki Uchida², Hajime Sasamoto², Toshiyuki Okada², Takayuki Kohri³, Akira Mogi⁴ & Hiroyuki Kuwano⁴

1 Department of Thoracic Surgery, Kiryu Kosei General Hospital, Kiryu, Japan

2 Department of Surgery, Haramachi Red Cross Hospital, Haramachi, Japan

3 Department of Surgery, Tone Chuo Hospital, Numata, Japan

4 Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi, Japan

Keywords

Abnormal distribution of the pulmonary vein; bronchial anomaly; lung cancer.

Correspondence

Kouhei Tajima, Department of Thoracic Surgery, Kiryu Kosei General Hospital, 6-3 Orihime-cho, Kiryu 376-0024, Japan.
Tel: +81 27 744 7171
Fax: +81 27 744 7170
Email: k-tajima@kosei-hospital.kiryu.gunma.jp

Received: 15 March 2016;

Accepted: 5 April 2016.

doi: 10.1111/1759-7714.12362

Thoracic Cancer 7 (2016) 599–601

Abstract

A 69-year-old woman visited our hospital complaining of right chest pain. Chest computed tomography showed a 55 × 45 mm tumor in the right upper lobe. Bronchoscopy revealed displaced anomalous B¹ and B²⁺³ arising from the right main bronchus, and the patient was diagnosed with lung adenocarcinoma by transbronchial lung biopsy from the displaced B²⁺³. Three-dimensional computed tomography with multiplanar reconstruction revealed a displaced anomalous B¹ and B²⁺³ branching directly from the right main bronchus, respectively, and abnormal distribution of the aberrant pulmonary vein (V²) descended dorsally to the right main bronchus and emptied into the left atrium. Video-assisted right upper lobectomy with nodal dissection was successfully performed. Attention should be paid to the anomalous bronchus and pulmonary vessels for safer lung cancer operations, especially for video-assisted thoracic surgery.

Introduction

With the widespread use of bronchoscopy and the remarkable progress of recent three-dimensional-computed tomography (3DCT), identification of bronchial abnormalities has become quite common, while variant pulmonary veins are relatively rare.¹ Preoperative recognition of anomalous bronchi or pulmonary vessels is very important for a safe operation, because anatomical variations can cause difficulty, especially in video-assisted thoracic surgery (VATS). This report documents the surgical case of a 69-year-old woman suffering from lung cancer who demonstrated an anomalous bronchi (B¹ and B²⁺³) branching from the right main bronchus and whose pulmonary vein (V²) independently drained directly into the left atrium. To the best of our knowledge, six reported cases of lung cancer, including the present case, have been associated with this type of pulmonary vein anomaly. This report profiles the third case accompanied by bronchial variations.

Case report

A 69-year-old woman visited our hospital complaining of right chest pain. CT showed a pulmonary tumor of 55 × 45 mm in the right upper lobe (Fig 1). Bronchoscopy revealed displaced anomalous B¹ and B²⁺³ arising from the right main bronchus, and a transbronchial lung biopsy from the displaced bronchus was diagnosed as adenocarcinoma. 3DCT with multiplanar reconstruction also revealed displaced anomalous B¹ and B²⁺³ branching directly from the right main bronchus (Fig 2), and an abnormal distribution of the aberrant pulmonary vein (V²) descended dorsally to the right main bronchus and emptied into the left atrium (Fig 3). No abnormal distribution was found in the pulmonary artery. The patient was diagnosed with primary lung adenocarcinoma (c-T2bN1M0) located in the right S³ with displaced B¹ and B²⁺³ and abnormal distribution of the aberrant pulmonary vein. A video-assisted right upper lobectomy was performed with a 7 cm access window and

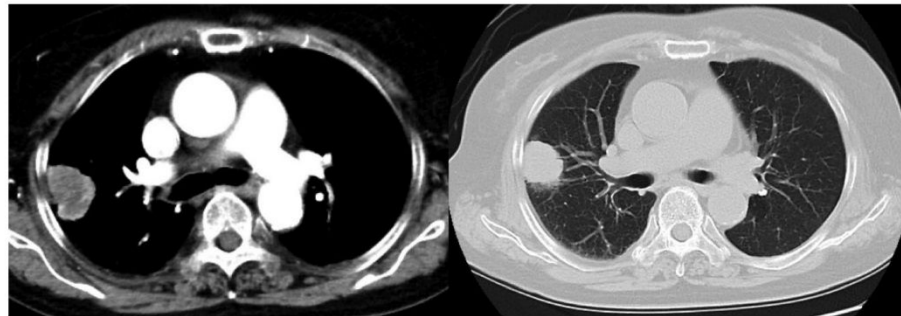


Figure 1 Chest computed tomography shows a 55 × 35 mm tumor in the right upper lobe.



Figure 2 Three-dimensional computed tomography revealed a displaced anomalous B¹ and B²⁺³, branching directly from right main bronchus.

three ports. From the anterior aspect of the hilum, V¹⁺³ without the central vein (V²) was divided using a vascular endostapler. An anomalous vein (V²) was identified behind the right main bronchus at the posterior aspect of the hilum that independently drained directly into the left

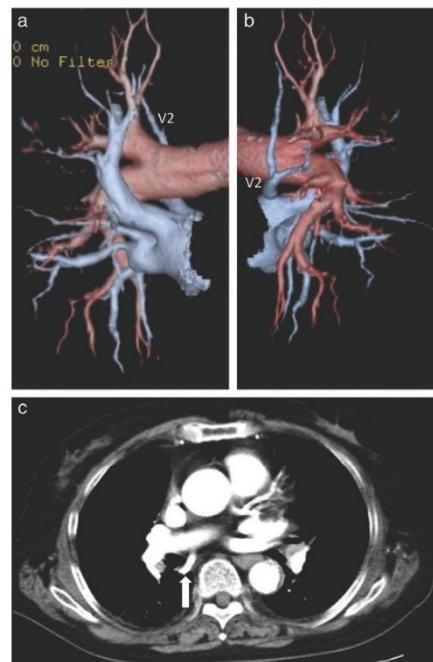


Figure 3 Abnormal distribution of the aberrant pulmonary vein (V²) descended dorsally and emptied into the left atrium. (a) Front view; (b) right side view. (c) V2 (white arrow) behind the right main bronchus independently drained directly into the left atrium, observed on two-dimensional computed tomography.

atrium and was divided using a vascular endostapler. The displaced B¹, B²⁺³, A², A¹⁺³, and interlobar fissure were sequentially divided, and the right upper lobe was removed. Hilar and mediastinal lymph node dissection was performed. The postoperative course was uneventful. Pathological diagnosis was adenocarcinoma with a maximal diameter of 55 mm with #4R and #12u node metastases (pT2bN2M0).

Discussion

Recently, VATS has become a widespread procedure among thoracic surgeons as a potential alternative to conventional thoracotomy because of its clinical benefits, less postoperative pain, and quicker recovery following surgery.² However, the vessels, bronchi, and interlobar fissures are dissected using a thoracoscope with less tactile feedback with a two-dimensional vision, which occasionally might lead to serious complications, especially in patients with anomalous pulmonary vessels, as bleeding from an unknown origin could cause a critical situation. Tsuboi *et al.* reported that one of the causes of conversion to thoracotomy during VATS could be an anomalous hilar structure, as well as dense pleural adhesion, difficulty in safely dissecting the interlobar pulmonary artery, or bleeding from vessels.³ Indeed, Asai *et al.* reported that one of nine right thoracotomy patients with a right upper lobe vein posterior to the bronchus intermedius suffered venous injury, and the patient's anomalous vein was not identified either preoperatively or intraoperatively.¹ They further demonstrated that in 5.7% of the patients studied, the pulmonary vein branch of the right upper lobe posterior to the bronchus intermedius was observed. According to the five previous case reports with anomalous V², it was recognized preoperatively in only two cases.³⁻⁷ Akiba *et al.* reported the importance of preoperative 3D imaging for a safe operation because variations in pulmonary vessels can have a serious impact on patients undergoing lung surgery, especially in VATS.⁸

Moreover, our patient also presented anomalous bronchi (B¹ and B²⁺³) branching from the right main bronchus. Although only a few surgical cases of lung cancer with anomalous vein accompanied by bronchial variations have been reported, as these abnormalities may be complicated, surgeons should pay attention to their possible presence, not only on preoperative images but also intraoperatively.^{5,7}

In this case, one of the important factors in a successful VATS lobectomy is preoperative foreknowledge of anomalous vessels and bronchi. For the safe completion of a VATS lobectomy, a cautious preoperative evaluation of the anatomical structures, as well as of the tumor itself, to identify any abnormal vascular or bronchial distribution is essential.

Disclosure

No authors report any conflict of interest.

References

- 1 Asai K, Urabe N, Yajima K, Suzuki K, Kazui T. Right upper lobe venous drainage posterior to the bronchus intermedius: Preoperative identification by computed tomography. *Ann Thorac Surg* 2005; **79**: 1866–71.
- 2 Yamashita S, Goto T, Mori T *et al.* Video-assisted thoracic surgery for lung cancer: Republication of a systematic review and a proposal by the guidelines committee of the Japanese Association for Chest Surgery 2014. *Gen Thorac Cardiovasc Surg* 2014; **62**: 701–5.
- 3 Tsuboi M, Asamura H, Naruke H, Nakayama H, Kondo H, Tsuchiya R. A VATS lobectomy for lung cancer in a patient with an anomalous pulmonary vein: Report of a case. *Surg Today* 1997; **27**: 1074–6.
- 4 Spaggiari L, Solli P, Leo F, Veronesi G, Pastorino U. Anomalous segmental vein for right upper lobe: An unusual anatomical variation. *Ann Thorac Surg* 2002; **74**: 267.
- 5 Yurugi Y, Nakamura H, Taniguchi Y *et al.* Case of thoracoscopic right upper lobectomy for lung cancer with tracheal bronchus and pulmonary vein variation. *Asian J Endosc Surg* 2012; **5**: 93–5.
- 6 Utsumi T, Sakamoto T, Sakaguchi M *et al.* Preoperative identification of anomalous drainage vein for posterior segment of right upper lobe. *Ann Thorac Surg* 2012; **94**: e127.
- 7 Xu XF, Chen L, Wu WB, Zhu Q. Thoracoscopic right posterior segmentectomy of a patient with anomalous bronchus and pulmonary vein. *Ann Thorac Surg* 2014; **98**: e127–9.
- 8 Akiba T, Marushima H, Harada J, Kobayashi S, Morikawa T. Anomalous pulmonary vein detected using three-dimensional computed tomography in a patient with lung cancer undergoing thoracoscopic lobectomy. *Gen Thorac Cardiovasc Surg* 2008; **56**: 413–6.