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Virtual bronchoscopy using FDG-PET/CT images for the evaluation of lung cancer

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Abstract. – PURPOSE: We aimed to put forward the contribution of virtual bronchoscopy in the determination and diagnosis of tracheobronchial system pathologies. We compared the data obtained from PET/CT and virtual bronchoscopy (VB) with the fiberoptic bronchoscopy (FOB) data of the cases with a diagnosis or prediagnosis of lung tumor.

MATERIALS AND METHODS: A total of 261 (male=238, female=23) lung cancer cases with a mean age of 53±7.3 years (range =35-77 years), who had undergone FOB and had bronchoalveolar lavage and/or biopsy results, were included in this multicenter, prospective study conducted between 2006 and 2008. FOB data confirmed with cytohistopathology were considered as the gold standard. Five cases that had peripheral lesions, with negative cytopathological results were excluded from the study. Positron emission tomography images were fused with 16/slice multi-detector computed tomography system images (Discovery ST PET/16 slice CT fusion system HPOWER 60; General Electric Medical Systems, Milwaukee, WI, USA). Thereafter, all of the cases were evaluated with virtual bronchoscopy, using a special multidisplay workstation with multiplanar reformatting (MPR) and minimum intensity projection (MINIP) to see the fused images simultaneously. The data obtained with both virtual bronchoscopy (PET/CT VB) and FOB in different centers were recorded, and the evaluation and comparison of these data were done by an independent researcher. The sensitivity, specificity, and positive and negative predictive values of making an accurate diagnosis and defining concomitant pathologies by both methods, were calculated.

RESULTS: The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy values of VB and PET/CT-VB in determining the segment involved by malignancy were as follows, 91%, 83%, 94%, 77%, and 89%, and 95%, 97%, 99%, 87%, and 96%, respectively.

CONCLUSIONS: The sensitivity of PET/CT-VB in determining the involved tracheobronchial segment(s) in malignancy and concomitant pathologies in cases with lung tumor was remarkably higher than that with CT-VB. Therefore, PET/CT-VB is recommended to be included in routine lung cancer examinations since it provides similar outcomes to that of FOB+cytohistopathological examination.

Key Words:
Virtual Bronchoscopy, FDG-PET/CT, Lung cancer.

Introduction

Lung cancer is the second most common cancer after prostate cancer in males and breast cancer in females. However, it is the leading cause of cancer deaths in both genders[1,2]. Lung cancer, which is in close relation with smoking, has even left the deaths from cardiac-related diseases behind in the recent times[2,3].

Although the incidence of lung cancer varies in different geographical areas, it is known to be responsible for 1-1.5 million deaths annually all over the world[1]. Annually 200.000 cases are diagnosed in the Unites States of America, Five-year survival of this disease with a quite high mortality is generally lower than 15%[1]. Lung cancer affects the population at the age of 40 years and over.

The factor initiating the main pathology is the negative effects of carcinogenic agents (environmental pollution, chemicals, and tobacco smoke) on the mucosal cells, particularly located at bifurcations[1,6]. The pathophysiology initiated by the carcinogenic agents leads to a process that extends up to atypia and malignant degeneration in the vicious circle of inflammation and irritation[7].

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Lung cancers are divided into two major groups. Non-small cell lung cancers (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) account for 85%, whereas small cell lung cancers account for 15% of all lung cancers[4-6].

Adenocarcinoma, which is located peripherally, is the type that is least related to smoking, whereas bronchoalveolar carcinoma usually has an interstitial pattern leading to confusion in diagnosis[1,6,7]. Squamous cell carcinomas that are usually located proximally, present as cavitary masses, whereas large cell tumors tend to form giant peripheral masses with focal necrosis[6]. The type of treatment is associated with the stage of disease at the time of hospital presentation. However, chemotherapy, rather than surgery, is in the forefront in small cell lung cancers, which arise in peribronchial locations, rapidly extend to the mediastinal lymph nodes and coincide with paraneoplastic syndromes during the course of disease[6].

Seven to ten percent of lung cancer cases are incidentally found during radiological examinations. In general, direct X-rays (because of high error probabilities – 40%) and Computed Tomography (CT) (because of relatively high exposure to radiation) are not used in routine screening[8]. Small-scale screenings conducted to date showed no decrease in deaths from lung cancer at the end of the therapeutic period beginning from the detection of cancer by direct X-rays and CT[8].

In lung cancer, in which the screening tests are meaningless and a small proportion is detected incidentally, various symptoms including cough and hemoptysis, which may be associated with the primary tumor or might have occurred due to a paraneoplastic syndrome, may be in question[9]. In cases, in which a mass has been detected either incidentally or after presenting with the above-mentioned symptoms, evaluation is made directly by fluorine-18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) rather than cross-sectional anatomical imaging. Thus, FDG-PET/CT has become the most preferred method in the recent years since it provides both anatomical and functional information at the same time[10]. The next step in lung cancer cases is the evaluation of the tracheobronchial tree and further evaluation for diagnostic sampling and the general tendency is to perform fiberoptic bronchoscopy (FOB) before surgery[1,11].

Along with the advanced technology, tracheobronchial tree can be evaluated by virtual endoscopy after appropriate reconstruction of axial images obtained by multi-slice computed tomography (Figures 1 and 2). In the present study, we aimed to put forward the anatomopathology of the tracheobronchial tree, by virtual bronchoscopy (VB), in addition to PET/CT fusion system that gives both anatomic and metabolic information.

Materials and Methods

Among 396 cases that underwent FDG-PET/CT for the evaluation of a lung mass, totally 256 cases (male=233, female=23) with a mean age of 53±7.3 years (age range=35-77 years) with available histopathology, FOB and VB data, were included in this multicenter prospective study. The remaining 140 cases, which had PET/CT-VB data, were not included in the study as their FOB or cytohistopathology reports were unavailable, or their pathology reports were negative for malignancy five cases that had peripheral lesions, with negative cytopathological results were also excluded from the study.

Imaging Protocol

PET images were fused with 16/slice multidetector CT images (Discovery ST PET/16 slice CT fusion system HPOWER 60; General Electric Medical Systems, Milwaukee, WI, USA).

Prior to the examination, 40 ml of ionic iodinated contrast agent was added into 1-1.5 liters of water and given to the patients via oral route for colonic opacification. Three hundred milliliters of the solution was kept to give the patients just before the examination of the stomach.

Movements (including speaking, chewing, and walking) were tightly restricted 4 to 5 hours before the procedure in order to prevent FDG uptake in the muscles.

The patient was administered 13-15 mCi FDG via intravenous route 45 to 60 minutes before the procedure and was allowed to rest for one hour in the resting room.

Primarily, CT in the craniocaudal projection including proximal half of the femur was initiated by 16/slice multidetector CT and scans were obtained with a 3.75 cm slice thickness, a 1.75 pitch and a beam width of 10 mm, (120 kV peak, and 100 mA).

Thereafter, with using the PET system (which has been fused to the gantry of CT-unit through the posterior pole), emission scans were achieved

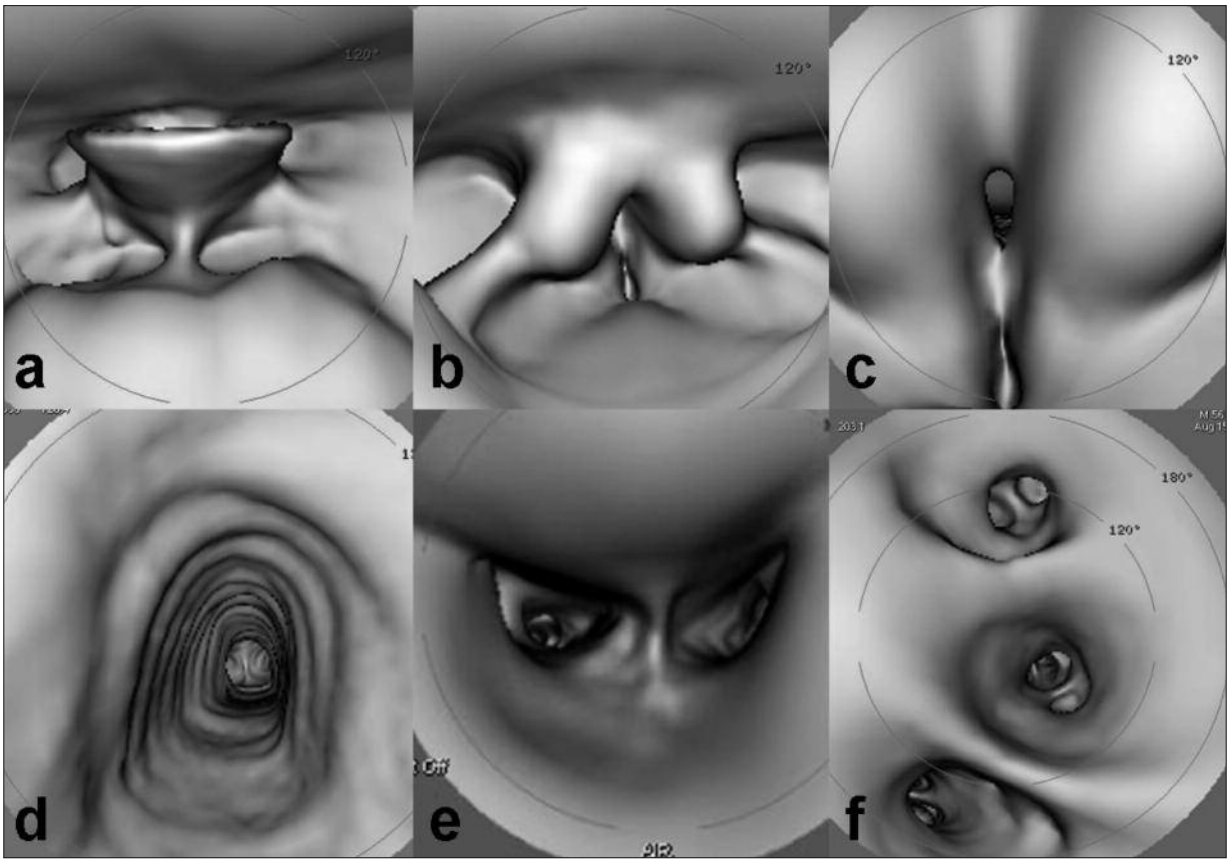

Figure 1. A virtual bronchoscopy examination showing the normal airways. Epiglottis ***(a)***, vocal cords ***(b)***, glottis (from the reverse glance) ***(c)***, trachea ***(d)***, carina ***(e)***, and branching of the branches of the lobar bronchi ***(f)*** are visualized clearly.

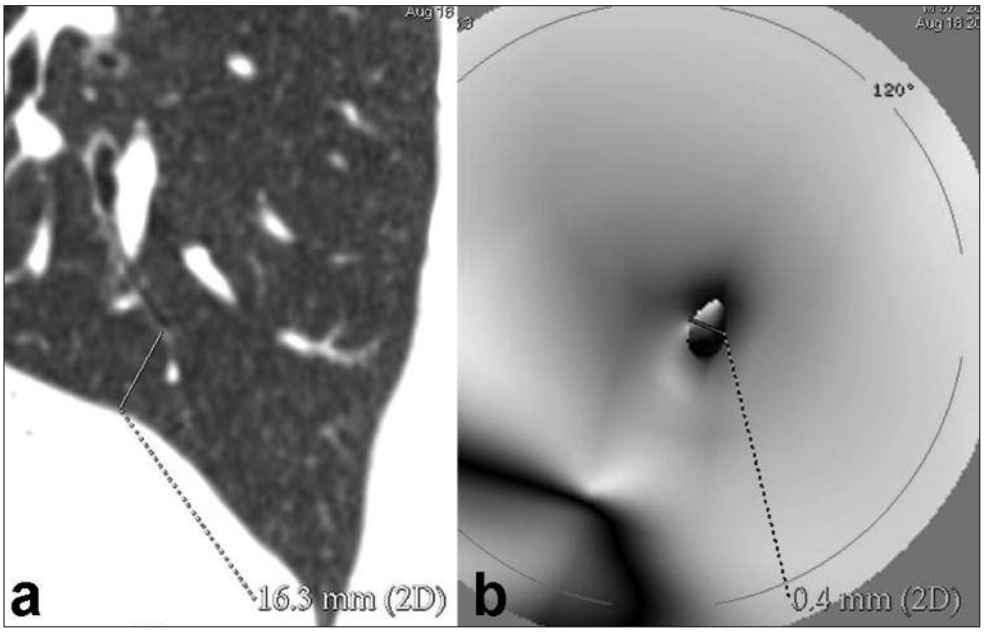

Figure 2. Being 1.5 cm closer to the pleura in the peripheral area, this image obtained via virtual bronchoscopy ***(a)*** raises the thought that bronchi even as thin as 0.4 mm in diameter ***(b)*** can also be evaluated via virtual endoscopy.

in the opposite direction (caudocranial) to CT, before the urine bladder was distended by FDG and displacement activities occur with intestinal motion.

After the images were obtained, the tracheobronchial tree was evaluated via virtual bronchoscopy (VB), on a multidisplay workstation with multiplanar reformatting, minimum intensity projection, in a way that fused PET-CT images were seen simultaneously with VB images. PET/CT-VB examination has been done, and interpreted by a radiologist after the detailed evaluation of PET/CT images with a nuclear medicine specialist.

PET/CT-VB and FOB plus cytohistopathology data were recorded in detail. The pathologies detected by CT-VB, PET/CT-VB, and FOB-bronchoalveolar lavage (BAL)-Biopsy were compared. FOB+BAL+cytohistopathology findings were considered as the gold standard in all examinations.

The sensitivity, specificity, and positive and negative predictive values of CT-VB, PET/CT-VB and FOB examinations in determining the segment involved by malignancy were calculated.

Moreover, based on the results of the present study, a summary table concerning advantages and disadvantages of PET/CT-VB and FOB was created (Table I).

The patients and their legal representatives were informed about the characteristics and requirements of the bronchoscopy examination, and the procedure was performed after obtaining verbal and written consents. Fiber-optic bronchoscopy was performed at three different Centers. According to the routine procedure of the Centers, the procedure was performed providing sedation following decongestant and anticholinergic medication (except for four cases that required general anesthesia) after 4- to 6-hours fasting. FOB data (256 cases) regarding sputum cytology (256 cases), brush cytology (256 cases) and biopsy (108 cases) findings as well as the information about caliber of the bronchial lumen and pathological changes in the mucosa were recorded.

Likewise, findings determined during CT/VB such as stenosis of the relevant bronchial lumen, endoluminal irregularity and vegetation, scalloping and extensions were considered positive for the cases that underwent VB, and all data was recorded.

Determination of the following findings, including acute stenosis of the bronchial lumen, obliteration, irregularity, demarcated lesion vegetating into the lumen, irregularity of the luminal surface, obliteration of normal planes between the bronchus and the related mass, was considered positive for the involvement of the lobe of the related segment or trachea. Those findings were taken into consideration in CT-VB and PET/CT-VB samely in reports as well. In PET/CT-VB, additionally, co-existent FDG uptake thorough the abnormally reported airways has been used an ancillary criteria and has helped focusing to the abnormal-involved segment(s) (Figures 3 to 6).

Both the CT-VB and PET/CT-VB findings of the involved segments were recorded in comparison with FOB findings (Table II).

Statistical Analysis

For statistical evaluation, the data were transferred to the computer and analyzed using SPSS [SPSS 15.0 version for Windows (SPSS Inc., Chicago, IL, USA)] program. The data were an-

Table I. Comparative characteristics of Virtual (VB) and Fiber-Optic Bronchoscopy (FOB).

FOB	VB
• *In vivo*	• *In vitro*
• Appropriate patient and appropriate team	• Appropriate device, appropriate protocol
• Biopsy, lavage, brushing	• Numerous quantitative measurements
• Only frontal inspection	• Controllable, direction of the angle can be changed, repeatable
• Only endoluminal	• Numerous simultaneous images, extraluminal evaluation
• Mucosal surface information	• No information about mucosa, submucosal infiltration. Can it be possible to predict mucosal involvement by adding virtual PET/CT information?
• Low sensitivity in discriminating lesions (carcinoma, polyp, mucus) and in detecting lesions < 5 mm	
• Complications (0.01%-0.5% mortality)	• No complications, the level of exposure to radiation is acceptable
• Time: 20-25 min. + premedication time	
• Total time:10-15 minute	• Premedication is unnecessary

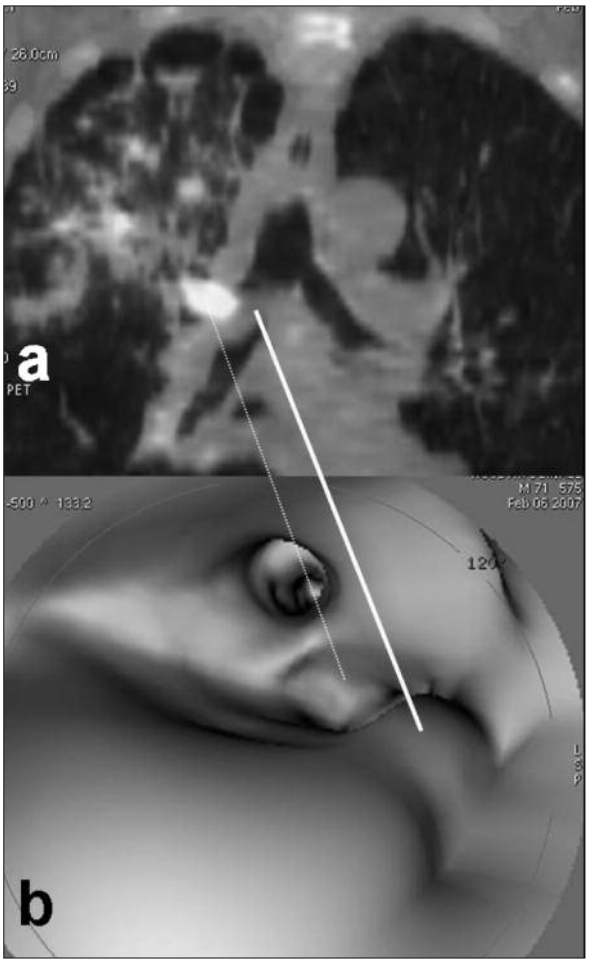

Figure 3. Evaluation of the characteristics of the segment involved by malignancy via VB under the guidance of FDG uptake over the fused images. ***(a)*** The soft tissue mass constricting the upper lobe bronchus shows FDG affinity, whereas the mass constricting the lower lobe bronchus, does not show any uptake. ***(b)*** It is observed that the lesion, which actually do not show FDG uptake on VB attracts more attention in various points of view (*thick line*). However, the pathology that requires biopsy on VB image (*dotted, thin line*) exists in another localization.

alyzed by the Chi-square and independent samples *t*-tests. Mean ± standard deviation, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy values were determined. A p value < 0.05 was considered significant.

Results

FOB plus cytohistopathology was successful in the diagnosis and in the determination of the segments involved by malignancy for all cases (98%), except for five cases with peripherally located lesions smaller than 2.5 cm. The diagnosis in these five cases was made by transthoracic biopsies taken from the lesions and the evaluation after surgery revealed no invasion to the main bronchi. In the present study, data of 256 cases, except for the above-mentioned five cases, were analyzed considering the findings of FOB plus cytohistopathology as the gold standard.

The number of males (n=233) were higher than that of females (n=23); of the cases, 9% were female, whereas 91% were male. The mean age of the participants was 53±7.3 years and no difference was found between males and females in terms of age.

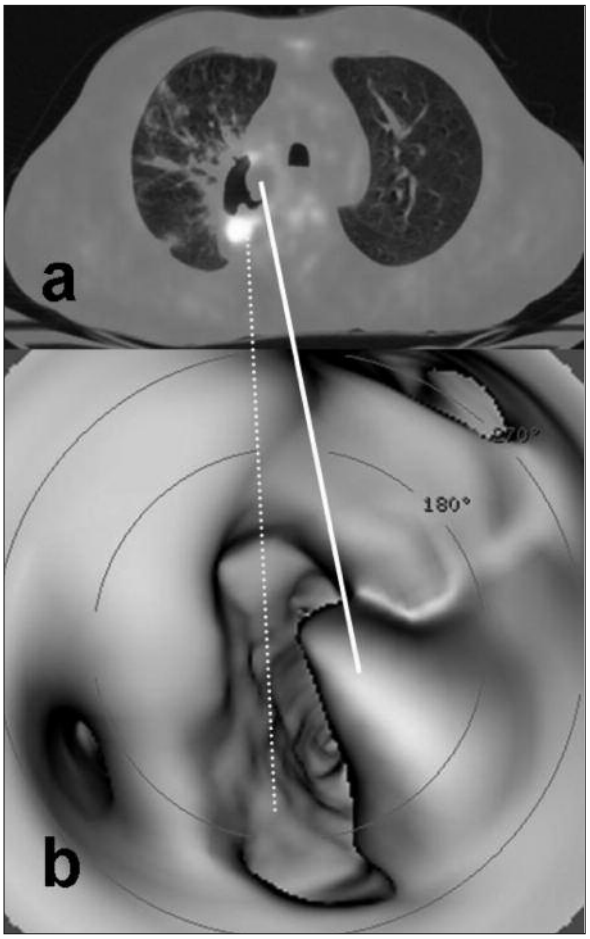

Figure 4. Besides the evaluation of airways, it is possible to use virtual endoscopy for cavitary lesions ***(a)*** fused image, ***(b)*** virtual endoscopy image). There are nodular areas with and without FDG uptake on the wall of the cavitary mass lesion. It is seen that the mass showing vegetation into the lumen (*thick line*) is necrotic in nature (FDG negative) and the area that require biopsy or histopathological examination (*dotted, thin line*) shows high affinity for FDG.

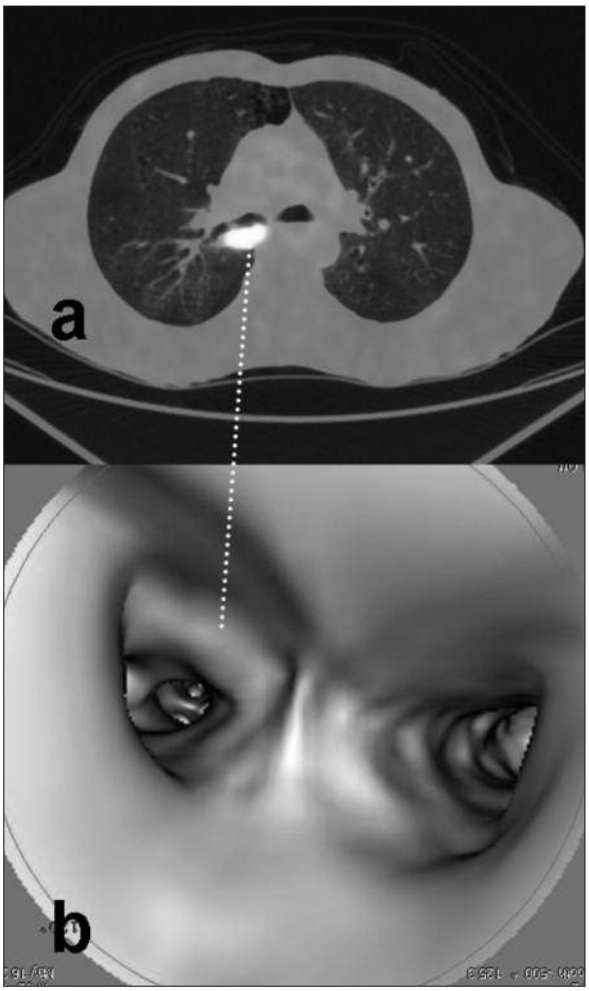

Figure 5. In fused images, ***(a)*** although the lumen is not significantly constricted due to submucosal infiltration, ***(b)*** the pathology can easily be detected with VB performed under the guidance of FDG uptake (*white line*). The depth of the lesion from the surface, extensions, and configuration can also be investigated, if needed.

CT/VB was unable to detect the pathology reported in the FOB plus cytohistopathology results of 17 cases and these cases were reported to be normal (false negative). Moreover, FOB plus cytohistopathology reports showed normal findings in the bronchial walls of 10 cases that were reported abnormal by CT/VB (false positive).

PET/CT-VB was not able to detect the pathology reported in the FOB plus cytohistopathology results of 9 cases (false negative), whereas FOB plus cytohistopathology results of two cases, which showed abnormal bronchial walls, were normal by PET/CT-VB (false positive).

Investigations performed in three different centers showed difference with regard to the involved segments; whereas tumors originating from the right lung were frequent in one center, tumors arising from the left upper lobe were more frequent in the other. As FOB plus cytohistopathological examinations which detected only positive findings associated with malignity were considered as the gold standard, such minor differences were not accepted as significant.

The location of the pathology in the 17 cases detected by CT-VB were as follows; 7 in the right upper lobe, 5 in the left upper lobe, 3 in the right lower lobe, 1 in the lingula, and 1 in the left lower lobe. Except for three, all these tumors, had a peripheral location. Therefore, it was not possible to detect the pathology by CT/VB.

The location of the pathology in the 9 false negative cases in PET/CT-VB were as follows, 2 in the right upper lobe, 3 in the left upper lobe, 2 in the right lower lobe, and 2 in the left lower lobe.

False negativity rate was higher in lesions with a peripheral location and in tumors located in the upper lobes of the lung ($p < 0.05$). While false negativity rate gradually increased towards the periphery, false positivity rate was higher in centrally located lesions (3 in trachea, 3 at carina, 2 in the intermediate bronchus, 1 in the left main bronchus and in the left upper lobe bronchus), and in large size mass lesions (particularly in those > 4 cm) ($p < 0.05$). Although the mean size of the lesions was 3.4±1.9 cm, it was 4.42±1.3 cm in the false positive lesions. These changes were considered in favor of indentation by the space occupying lesion, because any FDG uptake has not been observed on PET/CT-VB at the scalloped borders of the wall, lumen, or surroundings of the related airway. These changes were reported as false positive findings and involvement of the related bronchus was considered as negative in eight of 10 cases.

PET guidance together with CT/VB: As PET directed our examinations to the sites of abnormal FDG uptake, additional 4 bronchi in the right upper lobe, 2 bronchi in the left upper lobe, 1 bronchus in the right lower lobe, and 1 bronchus in the lingula were observed to be involved. Consequently, overall accuracy of VB increased by 7% when PET guidance was added. All the values were summarized in two tables for comparison (Tables III and IV).

Discussion

Lung cancer is associated with smoking, and is the leading type of cancer death all over the world, including the developed countries[1]. Only 15% of

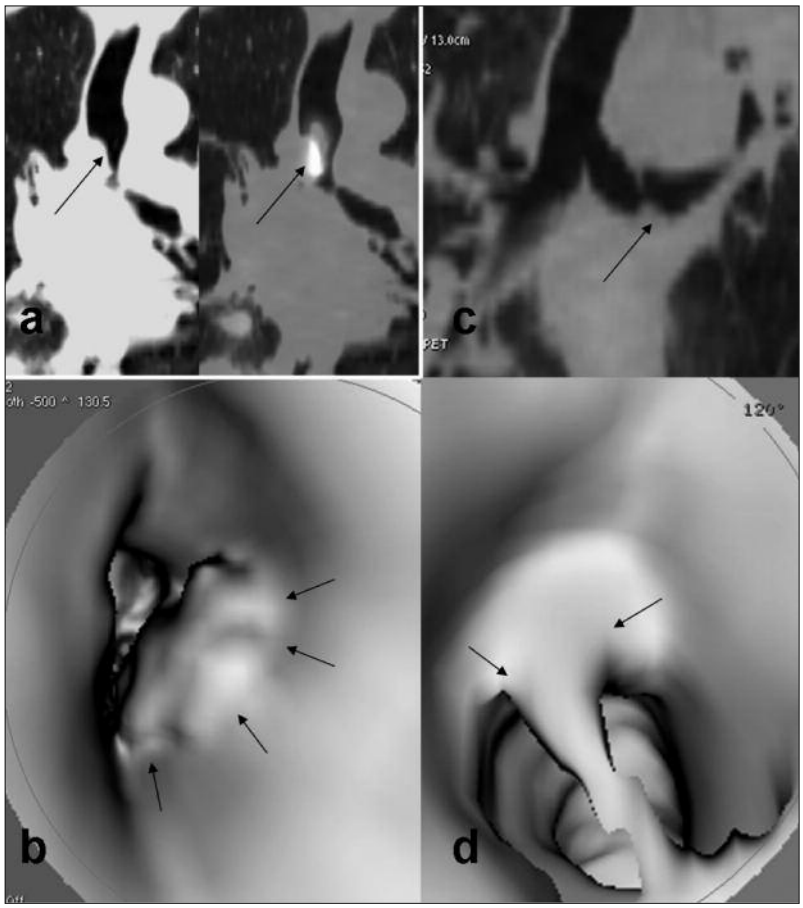

Figure 6. Differentiation of intraluminal filling defects secondary to secretion or malignancy during virtual bronchoscopy: ***(a)*** Coronal reformatted fusion image of an intrabronchial mass lesion. On VB image ***(b)*** Luminal contour deformation due to the mass with positive FDG uptake. ***(c)*** On coronal plane, elongated filling defect that extends from a wall to another ***(d)*** shows no FDG uptake and is seen as a characteristic cone-shaped figure consistent with mucus-secretion.

the patients have the chance of cure and living for a long time[2,6]. Differential diagnosis, histology and staging of the detected mass or nodule, evaluation of therapy response and prognosis at the time of first presentation is important[6,7]. However, appropriate staging is one of the most important parameters in all diagnosis, treatment and follow-up procedures that are successful. Considering staging, FDG-PET/CT is a successful and highly accepted modality in evaluating the tumor and its extensions, as it combines functional and anatomical information. For example, atelectasis, the margins of which may not be differentiated from the true lesion on CT scans, can be more easily detected via PET due to the difference in uptake[6,12]. Again, FDG-PET/CT is superior to CT alone in detecting mediastinal lymph nodes and distant organ metastases[14]. Consequently, FDG-PET/CT has become a preferred method because it gives more information about staging by 27% to 62%, and related to this, gives more information that allows modification of treatment modalities by 19% to 52% as compared to CT[6-14].

Today, along with the fusion of PET and multidetector systems, thin section-high resolution reconstructions are also possible. Reconstruction,

Table II. Segments involved by malignancy (to the fiber-optic bonchoscopy).

Involved segment	N	Involved segment	N
Trachea	11	Right middle lobe	11
Carina	26	Right lower lobe	27
Right hilum	24	Left upper lobe	38
Left hilum	30	Left lingular lobe	18
Right upper lobe	43	Left lower lobe	14
Right intermediate lobar bronchus	14		

Table III. Comparison of CT-VB and FOB plus cytohistopathology results (in the detection of the bronchial segment affected by malignancy).

	FOB+cytohistopathology (+)		FOB+cytohistopathology (–)	
CT-VB (+)	(TP)	177	(FP)	10
CT-VB (–)	(FN)	17	(TN)	52
Total	(TP+FN)		(FP+TN)	
Sensitivity (%)	TP/(TP+FN)		91%	
Specificity (%)	TN/(FP+TN		83%	
Positive Predictive Value (%)	TP/(TP+FP)		94%	
Negative Predictive Value (%)	TN/(FN+TN)		77%	
Accuracy (%)	(TP+TN)/N		89%	

window width adjustments, multiplanar reformatting (MPR), and 3D or virtual endoscopic images are available on CT sections obtained from these systems[13,15,16]. Taking the advantage of the 16-slice multidetector system, we succeeded to form virtual bronchoscopy images that present high-resolution virtual endoscopic-images of the airway mucosa from CT sections. Because of the properties of the workstation, it was possible to see and evaluate the axial images, pilot images, FDG-PET/CT fusion images and virtual bronchoscopy images simultaneously on the multidisplay monitors in real-time[18-23].

Despite all these mentioned benefits, FDG-PET/CT examination is an expensive method with which the patients', relatives' surgeons' and the physicians' exposure to radiation is in question. Thus, the indications for use is identified by multidisciplinary approach[22-24].

Clinically, along with the invention of fiber-optic technology, fiberoptic bronchoscopy, rather than virtual bronchoscopy, is being used in the Pulmonary Diseases and Thoracic Surgery Departments for diagnostic or therapeutic purposes, in relatively ergonomic conditions[25-28]. During FOB, it is possible to obtain samples (brush cytology, punch biopsy, etc.), aspiration, washing, and detection of color changes in the mucosa[29]. However, patients should be well evaluated prior to this invasive diagnostic procedure and their concomitant health problems and risky conditions should be taken into consideration. As in all invasive procedures, here as well, preparation and premedication are required before the procedure[28-30].

Although FOB is a safer method than rigid bronchoscopy, mortality rates ranging between 0.01% and 0.02% and major complication (such as respiratory depression, myocardial infarction, and pneumothorax) rates ranging between 0.08% and 0.3% have been reported[29,30].

Although the field of view and efficiency of FOB has improved, it has limited use particularly in obstructive pathologies, in patients in whom brachytherapy is considered as an alternative[29,30]. However, it is possible to detect the anatomical location and size of the lesion simultaneously with the effects of the lesion on bronchial system by virtual bronchoscopy[28,31,32]. The lumen of the airways up to the segmental bronchi can be evaluated by these non-invasive procedures[28,31]. Such a benefit is useful particularly for patients who cannot tolerate the procedure. However, the major handicaps of this procedure are the impossibility to identify color changes of the mucosal surface and to obtain biopsy[16,32,33]. The compara-

Table IV. Comparison of PET/CT-VB and FOB plus cytohistopathology results (in the detection of the bronchial segment affected by malignancy).

	FOB+cytohistopathology (+)		FOB+cytohistopathology (–)	
CT-VB (+)	(TP)	185	(FP)	2
CT-VB (–)	(FN)	9	(TN)	60
Total	(TP+FN)		(FP+TN)	
Sensitivity (%)	TP/(TP+FN)		95%	
Specificity (%)	TN/(FP+TN)		97%	
Positive Predictive Value (%)	TP/(TP+FP)		99%	
Negative Predictive Value (%)	TN/(FN+TN)		87%	
Accuracy (%)	(TP+TN)/N		96%	

tive properties of both modalities are presented in Table I.

Although virtual bronchoscopy has entered routine clinical use since 2000, it is being used more frequently for the evaluation of the lumen of the tracheobronchial system, for guidance prior to FOB, for the post-treatment evaluation of the stump, and for guidance and measurement (caliber, stent length, etc.) of the airway abnormalities prior to interventions in daily practice[24,28,34,35]. By using VB as a guide during bronchoscopic biopsy, the chance for obtaining appropriate sample is increased while the risk for vascular damage is significantly decreased[24,35,36].

Although the inadequacy of VB, such as inability to evaluate mucosa, low sensitivity for lesions smaller than 5 mm, inability to detect submucosal infiltrations and discoloration, inability in differentiating carcinoma-mucus-benign lesions, can be improved with focused examinations that display FDG uptake, obtaining biopsy remains impossible[36]. Along with advances in technology, progress can be made in the pre-existing quantitative measurements. The areas showing FDG uptake or display surface irregularity in virtual endoscope are likely to be detected by special softwares[36]. Furthermore, again hypothetically, PET/CT-VB can even go further to virtual biopsies with adjustable depth.

The main limitation of the present study was the fact that examination conditions of CT could not be changed in order to be consistent with PET images. Thus, CT images were obtained during Tidal breathing. Although we thought that obtaining scans in this way would lead to severe respiratory artifacts particularly during VB, we obtained quite regular-surfaced images after thin section reconstructions. Because the protocol was the same for all patients, and considering it would provide the same outcomes for all cases, it was thought that this limitation did not affect the overall outcome of the study. Only the reports and the name of the physicians who applied the endoscopic evaluations in the centers were available, whereas, image records and digital photograph records could not be obtained. Although the procedures applied were operator-dependent, this was not thought as a limitation, since it was valid for all of the cases.

Conclusion

PET/CT-VB is as accurate as FOB plus cytohistopathology in the detection of the degree of tracheobronchial system involvement by malignant lung tumors. It can determine the level of involvement in the tracheobronchial system with similar specificity and sensitivity to those of FOB, particularly in patients in whom FOB is contraindicated and who cannot tolerate or refuse the procedure. Although VB alone is not sufficient for the differentiation of intraluminal filling defects (mucus? mass?), it is possible with PET/CT-VB, with the visualization of the fused images along with FDG uptake on the multidisplay monitors during VB. Because it enables the orientation of the VB angle by the guidance of shining areas caused by FDG uptake thorough the involved airways, PET/CT-VB may significantly lower the likelihood of false positive or false negative diagnosis.

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