Technical note

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Targeted lymph node biopsy in mediastinoscopy using 3D FDG-PET/CT movies: a feasibility study

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In non-small-cell lung cancer, positive lymph nodes with increased fluorodeoxyglucose (FDG) uptake may be missed by mediastinoscopy. Lack of pathological confirmation may lead to radical, but unnecessary lung surgery. To minimize these false-negative results, the feasibility and potential value of three-dimensional (3D) FDG-PET/computed tomography (CT) movies were investigated to improve targeted lymph node biopsy during mediastinoscopies. PET/CT images were rendered in 3D volumes with multiplanar reconstructions and maximum intensity projections and reviewed in 3D 'fly-through' and 'fly-around' movies. These movies were developed and optimized by the Departments of Surgery and Nuclear Medicine. Twenty-two consecutive patients with non-small-cell lung cancer were included, of whom eight were FDG-PET positive for mediastinal lymph nodes. 3D FDG-PET/CT movies were presented to surgeons before mediastinoscopy. Surgical consequences were investigated, including sensitivity and the negative predictive value of mediastinoscopy. Results were compared with those of a retrospective study in which 3D techniques were not used. During mediastinoscopies, the 3D-PET/CT movies were found to be helpful in the surgical localization of FDG-positive lymph nodes. It led to more confidence in the surgical approach. The sensitivity and negative predictive value were 86 and 94%, respectively. Although not statistically significant, these results were higher compared with those of the retrospective study (75 and 92%, respectively). 3D FDG-PET/CT guidance during mediastinoscopy is feasible. The movies seem to lead to targeted biopsy of lymph nodes. They may reduce false-negative mediastinoscopies and improve staging of lung cancer. 3D FDG-PET/CT can be seen as a promising tool for further implementation of image-guided surgery. *Nucl Med Commun* **33:439–444 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

In non-small-cell lung cancer (NSCLC) staging, fluorodeoxyglucose PET/computed tomography (FDG-PET/CT) is an important diagnostic tool to determine tumor spread as it combines functional FDG-PET information with morphological CT information [1–4]. An FDG-positive N2 lymph node on PET/CT needs to be confirmed by biopsy, followed by pathological analysis to establish a patient's diagnosis and subsequent treatment. Several invasive staging biopsy techniques are available [5–10]. The choice of the technique depends on the location of the suspicious lymph node [11–13]. A mediastinoscopy is performed to reach right and left high and low paratracheal nodes, pretracheal nodes, and anterior subcarinal nodes [13,14]. When N2 lymph nodes are found to be pathological, it usually implies that curative surgery is not applicable because of lymph node involvement [11].

For mediastinoscopy, the sensitivity to detect mediastinal lymph node involvement from cancer ranges from 72 to 89%, with an average of 81% [15]. The negative predictive value (NPV) is typically 91% [15]. Missing a positive lymph node may lead to radical, but unnecessary lung surgery indicated by false-negative mediastinoscopies.

The surgeon aims to collect information on the status of several lymph node stations, particularly the suspicious nodes. However, lymph node stations are located near each other and are sometimes difficult to distinguish during mediastinoscopy. During the procedure, important structures may also be damaged such as the azygos vein, aorta and superior vena cava, the first branch of the right pulmonary artery, or the innominate artery [16]. Hence, accurate guidance in the mediastinoscopical examination is essential for localizing mediastinal lymph nodes.

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Evaluation of lesions in transversal planes only on standard PET/CT may result in an underestimation of the craniocaudal extent of a lesion and inadequate display of structures that are oriented oblique to the transversal plane [17]. These FDG-PET/CT images lack anatomic information on volume-rendered three-dimensional (3D) images provided by CT [18]. CT scanners produce 3D volume datasets and enable the creation of additional 2D-multiplanar and 3D images from the original transversal CT data. Multiple viewing formats for rendering of PET/CT images in 3D volumes can be applied such as internal views through lumina (flying through) and external views around anatomical structures (flying around) [11,18].

It is hypothesized that targeted biopsy in mediastinoscopical procedures can be improved using PET/CT image information in a dedicated manner. An added value may be achieved in the surgical guidance as depiction of mediastinal lymph nodes within an anatomical landscape may provide a useful roadmap for surgeons. This study therefore aims to assess the feasibility and subsequently the potential added value of 3D FDG-PET/CT movies in mediastinal lymph node localization and their use in the surgical approach during mediastinoscopy.

Materials and methods

Imaging

Using a Biograph 40 TrueV PET/CT system (Siemens, Knoxville, Tennessee, USA), FDG-PET/CT imaging was performed in 22 consecutive patients with NSCLC who later underwent a mediastinoscopy. The patient group included 14 men and eight women and their ages ranged from 50 to 76 years, with a mean of 66 years. None of the patients showed metastases outside the thorax, but all were suspected for lymph node metastases on the basis of CT and/or FDG-PET. Eight patients had FDG-positive mediastinal lymph nodes that could be reached with mediastinoscopy (stations 2L, 2R, 4L, 4R, and 7). In the case of pathological negative biopsies, only patients who underwent radical lung surgery were included. Staging was performed using the lymph node map with the nomenclature introduced by the International Association for the Study of Lung Cancer in 2009 [14].

CT was acquired with the following scanning parameters: 120 kV, 30 mAs, and 3.0 mm slice thickness. FDG-PET of the central body was performed 60 min after an intravenous injection of 2.3 MBq/kg FDG. The acquisition time was 4 min per bed position. PET image reconstructions were performed using Fourier rebinning and two-dimensional ordered-subset expectation maximization, including both CT-based scatter and attenuation correction.

Before mediastinoscopies, FDG-PET/CT images were rendered in 3D and displayed. In collaboration with nuclear medicine physicians, the resulting movies were presented to surgeons before and during surgery to achieve the targeted lymph-node biopsy and hence more accurate staging. During the development of the viewing method, FDG-PET/CT images of all patients were used. To study the added value of these movies during mediastinoscopy, only PET/CT images with FDG-positive lymph nodes are relevant.

The image processing starts by 3D rendering of PET/CT images using maximum intensity projection (MIP) and multiplanar reconstruction (MPR). MIP projects voxels in the visualization plane, providing a direct overview of the body parts and FDG-PET-positive lesions. In the case of MPR, a clip plane is used to look at different slides step by step, an option available in all directions through the subject. An advantage of MIP is that all FDG-PET/CT information is acquired in one view, which is not possible in MPR. However, MIP does not provide a good sense of depth of the original data.

To increase spatial awareness, additional 3D FDG-PET/CT movies were developed on the basis of the 3D rendering methods. The movies were loaded and viewed using the Siemens Syngo 2009B (Siemens AG, Medical Solutions, Erlangen, Germany) and the Osirix V3.7.1 software (Osirix, Los Angeles, California, USA). The last program allows 3D volume rendering of structures, for example, of the lungs and trachea. PET information of a positive lymph node was added to the CT volume-rendered images. Several viewing formats were applied such as 'flying around' the thorax and 'flying through' a body cavity, in particular simulating the pathway of a videoscope [18]. After collaborating and discussing with the surgeons, the 3D FDG-PET/CT movies were improved to serve as a useful tool during the mediastinoscopy. Items that were reviewed included level of contrast detail, color intensity, zoom level, specific visibility of other structures in the body (e.g. veins and arteries), 3D flight distances to, for example, the trachea, etc.

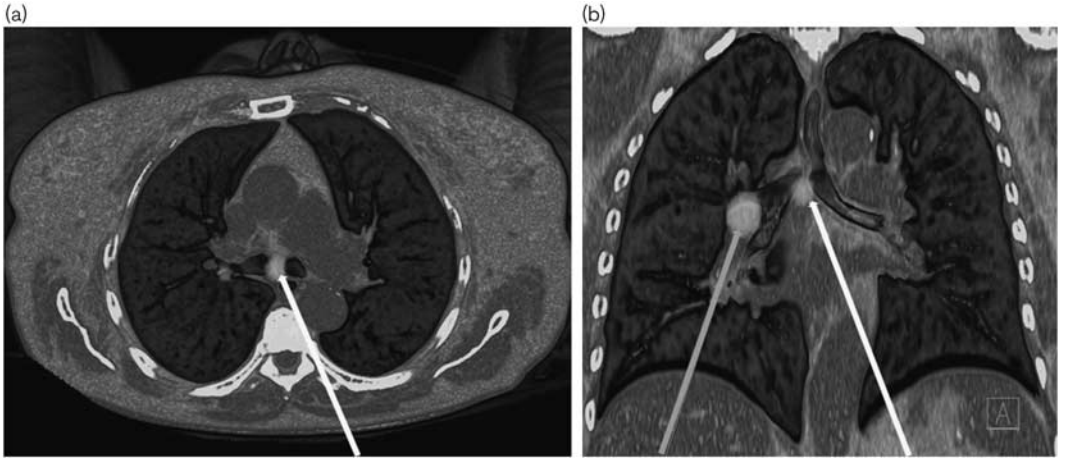
Movies were presented on a dedicated notebook and using the hospital's picture archiving and communications system (PACS; Synapse, Fujifilm Medical Systems, Stamford, Connecticut, USA) to increase its acceptance for clinical use. Mediastinoscopies were performed by five different surgeons. After the lymph nodes were biopted, they were sent for pathology assessment (PA).

Analysis

The value of 3D FDG-PET/CT mapping of lymph nodes was partially determined from discussions with the surgeons after performing a mediastinoscopy. Particularly, the surgeon's confidence in the movies was reviewed. The performance was analyzed in terms of sensitivity, specificity, NPV, and positive predictive value (PPV), including 95% confidence intervals (CIs), for both FDG-PET and mediastinoscopy.

FDG-PET and mediastinoscopy were verified using PA. PA was used as the gold standard for the presence or

Fig. 1



(a) An MPR image of a transversal plane through the thorax. The white arrow indicates an FDG-PET-positive subcarinal lymph node in station 7. (b) An MPR image of a coronal plane through the thorax. The light purple arrow indicates a primary process in the lung (location 11R) as seen on PET and the white arrow again indicates the subcarinal FDG-PET-positive lymph node. FDG-PET, fluorodeoxyglucose PET; MPR, multiplanar reconstruction.

absence of malignancy. If lymph nodes in the mediastinum were found to be PA negative, the PA of the subsequent lung surgery was used as the gold standard. The comparison of FDG-PET and mediastinoscopy with PA was made at the patient level and not at the lymph-node level, as not all individual lymph nodes were removed for PA during surgery.

To gain more insight into the added value of 3D FDG-PET/CT mapping, the results of mediastinoscopies along with 3D FDG-PET/CT were compared with those of a retrospective study, in the same institute, in which FDG-PET/CT images were used in a conventional way, which basically implies viewing of the images in three orthogonal planes (transversal, sagittal, and coronal). In this retrospective study, data of 64 patients (31 men and 33 women, mean age 67 years) with NSCLC who received FDG-PET/CT and mediastinoscopy were analyzed. FDG-PET and mediastinoscopy were compared with PA results using the same procedure as described above.

Results

Imaging

In the process of developing 3D FDG-PET/CT movies, surgeons indicated that two types of movies were of added value during mediastinoscopy. The first movie was based on sequential transversal MPR images through the thorax of the patient. An example of a screenshot of such a movie is shown in Fig. 1a. Figure 1b shows a coronal view of the same patient with a primary process and a suspected subcarinal lymph node, indicated by an increased FDG uptake. The second movie is based on 3D volume rendering of structures along with PET information (see Video, Supplemental digital content 1, which demonstrates the supporting 3D-PET/CT information during a mediastinoscopy) when going through the mediastinum. Four images in different stages of the second type of movie are shown in Fig. 2.

Both movies were based on the same strategy as that followed by the surgeon during mediastinoscopy. They show a 'fly' through the mediastinal region. Using the trachea as a reference, several lymph node stations were approached until finally reaching the suspected lymph node.

Analysis

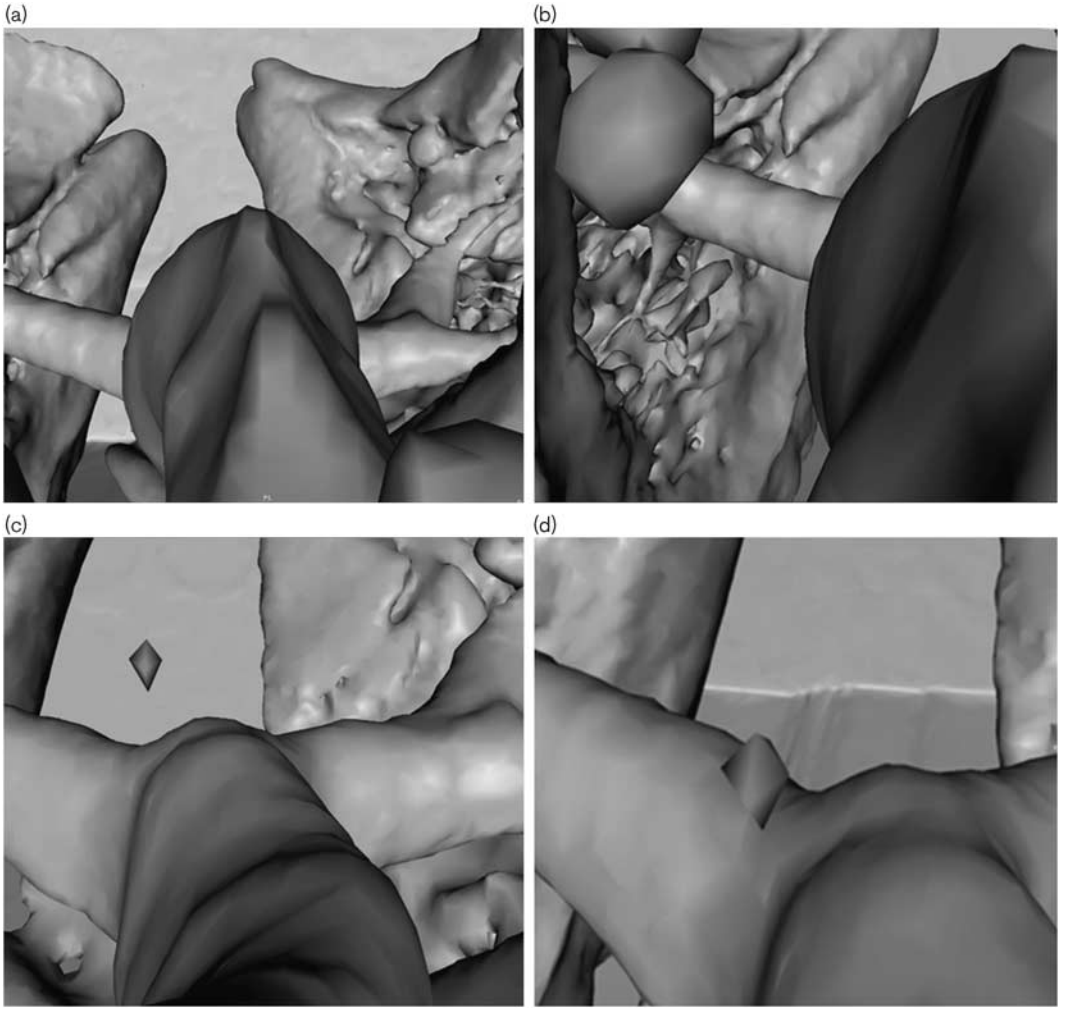
Table 1 summarizes the advantages of using 3D PET/CT movies compared with the conventional approach. The increase in knowledge of the location of the suspected lymph node provided more confidence in the surgical approach, specifically for targeted biopsy of the node. The surgeons indicated that the movies provided more guidance during surgery as well as more input in the presurgery planning process. The trachea as a reference through the mediastinum and a greater awareness of distances contributed to the guidance and were considered as beneficial to the procedure and the patient.

NPV, PPV, sensitivity, and specificity for both FDG-PET and mediastinoscopy are shown in Table 2. The PPV and specificity of the mediastinoscopy are 100% by definition. The results of the retrospective study of 64 patients in whom FDG-PET/CT was used in a conventional manner, which is where 3D techniques were not used, are shown in Table 3. Within statistical uncertainties, the results from Tables 2 and 3 are consistent with each other.

Discussion

The possibility of generating 3D PET/CT images for fly-through and fly-around viewing has been previously

Fig. 2



Images of a movie presented to the surgeon before mediastinoscopy to localize an FDG-PET-positive lymph node in station 4L. The trachea is followed (a) and a left view (b) shows the suspected tumor. The trachea rings were followed and the FDG-PET-positive lymph node is visible (c). Next, the movie turns in the caudal direction and shows the suspected lymph node close to the branching of the trachea, which has to be biopted (d).

Table 1 Summary of the advantages of mediastinoscopy with 3D FDG-PET/CT movies

Mediastinoscopy with 3D FDG-PET/CT movies
Increased knowledge of location of the suspected lymph node
More guidance
Trachea as a reference
Greater awareness of distances
More confidence for the surgeon
More input during the pre-surgical-planning process

3D, three dimensional; FDG-PET/CT, fluorodeoxyglucose PET/computed tomography.

Table 2 Results of the study ($n=22$) when using 3D FDG-PET/CT movies

	FDG-PET	Mediastinoscopy
PPV (%)	63 (31–86)	100 (NA)
NPV (%)	86 (60–96)	94 (72–99)
Sensitivity (%)	71 (36–92)	86 (49–97)
Specificity (%)	80 (55–93)	100 (NA)

95% confidence intervals are shown within brackets.
3D, three dimensional; FDG-PET/CT, fluorodeoxyglucose PET/computed tomography; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

demonstrated for several applications such as virtual bronchoscopy, colonoscopy, and mediastinoscopy [18, 19]. The current study primarily focused on accurate staging of patients with NSCLC using FDG-PET/CT movies as a surgical guidance during mediastinoscopy.

The 3D PET/CT movies cannot be considered as 'standalone'. Conventionally acquired PET/CT images remain important for optimal interpretation and recognition of artefacts [17]. 3D PET/CT movies can be seen as additional tools, particularly for guidance during surgery to localize FDG-positive lymph nodes. This aspect is

Table 3 Results of the retrospective study ($n=64$) without using 3D imaging techniques

	FDG-PET	Mediastinoscopy
PPV (%)	67 (47–82)	100 (NA)
NPV (%)	100 (91–100)	92 (82–97)
Sensitivity (%)	100 (81–100)	75 (51–90)
Specificity (%)	83 (70–91)	100 (NA)

95% confidence intervals are shown within brackets.
3D, three dimensional; FDG-PET, fluorodeoxyglucose PET; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

illustrated in Fig. 2, in which information on the location of an FDG-positive lymph node is provided but where detailed information on its metabolic characteristics is lacking. Rendering of lymph nodes in 3D PET/CT imaging must be performed with caution because noise can be represented and highlighted as being suspicious. It may also diminish or remove true FDG-positive lymph nodes. Therefore, in all cases, the creation and interpretation of the 3D images was carried out in close cooperation between nuclear medicine physicians and surgeons.

Part of the optimization process was performed while the next step, presenting the movies to the surgeon, was initiated. Surgeons gave recommendations toward improvement of the movies while performing a mediastinoscopy under the guidance of 3D PET/CT. It is expected that this might only result in a negative bias in the sensitivity and NPV of mediastinoscopy.

Furthermore, as FDG-PET/CT diagnosis is independent of the use of 3D movies during mediastinoscopy, it is expected that the corresponding quantitative FDG-PET results in Tables 2 and 3 are similar. This appears to be the case within statistical uncertainties. Furthermore, these quantitative results correspond to those of studies performed previously [20–23]. The difference in sensitivity (71% in the study with PET/CT movies and 100% in the retrospective analysis) seems to be large but occurs because of only two patients with a false-negative FDG-PET result. The limited number of patients causes a large 95% CI, but it is still within the CI of the retrospective study and is statistically within established limits. In addition, the 3D movies of these two patients were analyzed. One of the cases showed a slight increase in FDG uptake of a lymph node that was reported to be negative using the conventional PET/CT images. This implies that the additional movies were supportive in the targeted biopsy of this specific lymph node during mediastinoscopy.

Inclusion of 3D FDG-PET/CT movies in PACS was a part of the strategy to introduce them in clinical practice. The availability of the generated 3D movies in PACS increases acceptance in clinical use. The Synapse PACS (Fujifilm Medical Systems) that was used in this study enabled adequate visualization of movies. However, hospital PACS does not always provide adequate and reliable tools for visualization of 3D images and movies [24]. It is expected that this issue will be solved by PACS vendors, as the demand for these tools will increase with the increasing use of multimodality imaging.

In the initial optimization phase of this study, the PET/CT image rendering and surgical use of the movies were quite time consuming. As the study progressed, it took approximately half an hour per patient to render PET/CT images in 3D volumes with MIP and MPR, including reviewing patient history. The workload is expected to reduce further both in terms of rendering time and surgical use when use of 3D FDG-PET/CT movies becomes more routine. An improvement in the hospital PACS system will also increase the availability of the 3D movies.

The evaluation of PA was performed at the patient level and not at the lymph node level, as not all individual lymph nodes were removed for PA during surgery. Moreover, lymph nodes cannot always be accurately localized, either on PET/CT or during mediastinoscopy. Hence, an FDG-positive lymph node does not necessarily have to correspond to a PA-confirmed positive lymph node. However, in the case of FDG-positive and PA-positive nodes, there is a positive match in 80% of the cases between the location of the corresponding lymph node station as observed on PET and during mediastinoscopy. This implies that the principle of targeted biopsy is reasonably justified.

A limitation of this study is the size of the patient group. A longer study with more patient data may provide statistically significant evidence for the added value of 3D FDG-PET/CT movies. Despite this limitation, the feasibility of the technique was shown and a positive trend in added value of the new 3D FDG-PET/CT movies was achieved.

Targeted lymph node biopsy using 3D PET/CT movies is not limited only to mediastinoscopy. The movies can also be applied to endobronchial ultrasound or endoesophageal endoscopic ultrasound with fine-needle aspiration and other types of interventions by which lymph nodes can be reached and biopted. This is relevant as mediastinoscopy is being replaced by these less invasive techniques [25,26]. Instead of using standard surgical-intervention procedures, based on practical surgical performance, combined with knowledge of general anatomy and pathophysiology, 3D multimodality imaging and movies may facilitate dedicated individualized patient treatment.

Conclusion

3D FDG-PET/CT guidance during mediastinoscopy is feasible. Especially, 3D FDG-PET/CT ‘fly-through’ and ‘fly-around’ movies were found to be of added value in targeted lymph node biopsy. They seem to have potential

value in reducing false-negative mediastinscopies and hence in the staging of NSCLC patients. To prevent suboptimal and incorrect usage of the movies, a close collaboration between the nuclear medicine physicians and surgeons is essential in the process of creating and interpreting 3D FDG-PET/CT. The use of 3D FDG-PET/CT movies can be seen as promising for further implementation of image-guided surgery.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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