Thoracic lymph node recurrence of non-small cell lung cancer (NSCLC) surgically treated: is PET-CT accuracy higher than that of MDCT?

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Lung cancer is the leading cause of cancer-related deaths in the Western world, and non-small cell lung cancer (NSCLC) accounts for 85% of the cases (1). For most NSCLC patients at an early stage (stages I and II) and selected patients at a locally advanced stage (stage IIIA), curative resection is the most appropriate treatment for a cure (1). Although advancements in the early diagnosis and treatment have been made in the hope of improving survival (2), recurrence remains a major obstacle to achieving a complete cure for NSCLC patients. Reported recurrence rate after complete resection ranges from 30 to 75% (3-5), depending on the final pathologic stage. Although no conclusive data support the survival benefits of earlier detection of recurrence or start of treatment for recurrent disease, early and accurate diagnosis of recurrence is relevant for selecting optimal therapy (6).

Imaging techniques such as chest radiography, computed tomography (CT), ultrasonography (US) and, when requested, Magnetic Resonance (MR), provide morphological information and are essential for the diagnosis, staging and follow-up of patients with lung cancer. In contrast to these techniques, \(^{18}\)F-2-deoxy-fluoro-D-glucose (\(^{18}\)F-FDG) Positron Emission Tomography integrated with Computed Tomography (PET/CT) provides metabolic information and allows differentiation between malignant and benign lesions based on differences in glucose metabolism between normal and cancer tissues (7). FDG-PET/CT has rapidly become accepted as the standard non invasive modality for staging lung cancer (7). On the other hand, the need of performing FDG-PET/CT for surveillance in postoperative NSCLC patients is controversial. Recent studies have demonstrated the usefulness of FDG-PET/CT for the detection of postoperative recurrence in NSCLC patients (8-9), however it is currently not recommended for routine follow-up. Usually, patients are followed up with chest CT examinations every 3-6 months in the first year after surgery and less frequently later, using FDG-PET/CT to evaluate equivocal CT findings or to answer clinical needs. The anatomic site of recurrence is associated with post-recurrence survival (9). Recurrence in the regional lymph nodes of the initial primary lung cancer is considered local. A study by Sugimura et al. (10) demonstrated that 1-year post-recurrence survival rates were 50% for patients with local recurrence, 26% for extrathoracic recurrence, and 28% for combined local and extrathoracic recurrences.

While FDG-PET/CT accuracy in the assessment of nodal recurrence in patients who underwent surgical intervention after induction therapy has been already evaluated, as reported in a review of ten studies by Vansteenkiste et al. (11), to our knowledge no study has established FDG-PET/CT accuracy in patients undergoing radical surgery alone. The purpose of our study was to evaluate if FDG-PET/CT has a higher accuracy than Multidetector CT (MDCT) in diagnosing thoracic lymph node recurrence in patients undergoing radical surgery for early stage NSCLC.
Methods and Materials

255 consecutive patients with NSCLC treated between January 2008 and April 2012 with radical surgery were retrospectively evaluated. Patients were eligible for this study if they had undergone MDCT and FDG-PET/CT during follow-up after surgery. Both examinations had to be performed within 2 months each other. The final analysis included 75 patients (55 males and 20 female) with mean age of 72 years (range: 38-87 years). The histotypes included 53 adenocarcinomas, 19 squamous cell carcinomas, 2 large cell carcinomas and 1 adenosquamous cell carcinoma. According to the TNM classification, the pathological stage of tumors was stage IA in 32 patients, IB in 16, IIA in 15, IIB in 7 and IIIA in 5, with 53 patients classified as N0, 8 as N1 and 14 as N2. In all cases, a complete resection of tumor could be performed.

Two chest radiologists in consensus identified a total of 346 measurable lymph nodes (short axis > 4mm) at the follow-up MDCT scans. Lymph nodes were considered positive when short axis was > 1cm on MDCT. One nuclear medicine physician considered positive lymph nodes those with a FDG uptake higher than the physiological mediastinal uptake assessed at visual analysis on FDG-PET/CT images.

Biopsy or imaging follow-up (from 12 to 48 months) were considered as the reference standard. When technically feasible and clinically relevant, the diagnosis of lymph node recurrence was histologically confirmed by using endoscopic or surgical biopsies or fine-needle aspiration cytology (FNAC). If the suspected nodal relapse at imaging could not be confirmed histologically, lymph nodes which grew in size during follow-up or which decreased in size after antineoplastic treatment were considered positive for recurrence, while lymph nodes which had not changed in size during follow-up or treatment period were considered normal. Results of pathology or follow-up were compared to the assessment of each lymph node measurable at imaging. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CT and FDG-PET/CT were calculated.
Results

30 out of 346 thoracic lymph nodes demonstrated recurrent disease, with a prevalence of 8.6%. Positive lymph node have a short axis diameter ranging from 0.7 cm to 3.5 cm. Lymph node recurrent sites were the following: 13 mediastinal lymph nodes, 9 hilar, 7 supraclavicular and 1 axillary. Recurrence was confirmed by cyto-histological examination in 10 lymph nodes and by imaging follow-up in 20 lymph nodes.

36 out of 346 thoracic lymph nodes were considered positive at MDCT scans (mean short axis: 1.8 cm; range: 1.1-3.5 cm); 26 were true positive and 10 were false positive (Fig. 1). Positive predictive value of MDCT was 72.2% (26/36). 310 out of 346 thoracic lymph nodes were considered negative at MDCT scans. False negative results were found in 4/310 lymph nodes, among which 3 grew over time and 1 was biopsied (Fig. 2). The remaining 306 lymph nodes were true negative, with a negative predictive value of MDCT of 98.7% (306/310). MDCT showed a sensitivity, specificity and accuracy of 86.7% (26/30), 96.8% (306/316) and 96% (332/346) respectively.

On FDG-PET/CT scans 42/346 thoracic lymph nodes showed an FDG uptake higher than the physiological mediastinal uptake; 30 out of 42 were true positive with a PPV for diagnosing lymph node recurrence of 71.4% (30/42) (Fig. 2). FDG-PET/CT false-positive results were found in the remaining 12 lymph nodes: histological examination showed that 8/12 were benign inflammatory processes (Fig. 3) and 4/12 disappeared spontaneously, and were therefore considered reactive lymph nodes. All 304 lymph nodes without FDG uptake were true negative at follow-up (NPV 100%). The sensitivity, specificity and accuracy of FDG-PET/CT for diagnosing lymph node recurrence were 100%, 96.2% and 96.5% respectively (Tab. 1).
**Fig. 1:** False positive lymph node recurrence at MDCT. A 78-year-old patient underwent RUL lobectomy for a pT1N0 adenocarcinoma. A CT scan performed after 2 months (A) demonstrated a 2R node with a short-axis diameter of 1.2 cm (arrow), considered as positive for recurrence. FDG-PET/CT scan (B) demonstrated no nodal FDG uptake. Endobronchial ultrasound-guided needle aspiration (EBUS-NA) was negative for neoplastic recurrence (reactive 2R lymph node at cytology). A CT scan performed 12 months later (C) demonstrated no nodal size change (arrow).

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**Fig. 2:** False negative lymph node recurrence at MDCT and true positive at FDG-PET/TC. A 72-year-old patient underwent LUL lobectomy for a T1bN1 adenocarcinoma. A CT performed after 3 months (A) demonstrated a 2R node with a short-axis diameter less than 1 cm (arrow), considered as negative for recurrence. Follow-up FDG-PET/CT (B) demonstrated high nodal FDG uptake. Endobronchial ultrasound-guided needle aspiration (EBUS-NA) was positive for the presence of malignant cells.

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Fig. 3: False positive lymph node recurrence at FDG-PET/TC. A 61-year-old patient underwent RLL atypical resection for a T1a adenocarcinoma. 5-month-follow-up CT scan (A) demonstrated nodes with a short-axis diameter less than 1 cm at 7 and 10R stations (arrows). FDG-PET/CT scan demonstrated high nodal FDG uptake in both stations (B). Endobronchial ultrasound-guided needle aspiration (EBUS-NA) demonstrated anthracotic lymph nodes.

Table 1: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of MDCT and FDG-PET/CT are reported.

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<td>CT</td>
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<td>FDG-PET/CT</td>
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Conclusion

FDG-PET/CT showed an overall accuracy as high as MDCT in diagnosing thoracic lymph node recurrence of NSCLC surgically treated, even if FDG-PET/CT showed a better sensitivity, as expected. MDCT may be considered a reliable tool for following up patients surgically treated for early stage NSCLC. In this context, FDG-PET/CT scan may be reserved to cases with specific radiological or clinical suspicion of recurrence.
References


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