Significance of a new fluorodeoxyglucose-positive lesion on restaging positron emission tomography/computed tomography after induction therapy for non-small cell lung cancer

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Abstract

Objectives: Restaging of patients with locally-advanced NSCLC is of paramount importance, since only patients with down staging after induction therapy will benefit from surgery. In this study, we assessed the aetiology of new FDG-positive focal abnormalities on restaging PET/CT in patients with a good response after induction chemotherapy in the primary tumor and lymph nodes.

Methods: Between 2004 and 2008, 31 patients with histological proven stage III NSCLC had a PET/CT prior and after induction chemotherapy. Their medical charts were retrospectively reviewed.

Results: Restaging PET/CT revealed a new FDG-positive lesion in 6/31 (20%) patients. Initial clinical stage of the disease was IIIA N2 in 4 and IIIB T4 in 2 patients. The maximal standard uptake value (SUV max) in the primary tumor (p=0.043) and in the initially involved mediastinal nodes (p=0.068) decreased after induction treatment in all patients. The new PET/CT findings were located in an ipsilateral cervical in 2, a contralateral mediastinal in 1 and an ipsilateral mammary internal lymph node in 1 patients. Two other patients had a lesion on the contralateral lung. Malignant lymph node infiltrations were excluded following fine-needle punction, intraoperative biopsy or follow-up PET/CT. Contralateral pulmonary lesions were diagnosed as benign following mini thoracotomy and pulmonary wedge resection.

Conclusions: New solitary FDG-positive lesions on restaging PET/CT after induction chemotherapy for NSCLC are not rare in good responders to chemotherapy. In our experience, all these lesions were not associated with malignancy.

Key words: Lung, Cancer, Positron emission tomography, Imaging, Adjuvant/neoadjuvant therapy

Introduction

Patients with clinical stage III-N2 or -T4 non-small cell lung cancer (NSCLC) have a poor prognosis when treated with surgery alone. In order to improve outcome, the concept of preoperative induction therapy was introduced. It has been shown that induction chemotherapy (or radiochemotherapy) combined with surgery is effective in selected subgroups of patients such as patients with IIIA N2 disease [1, 2]. Recent studies suggested that mediastinal down staging and complete resection after induction are significant factors for better outcome in cases of stage IIIA or IIIB disease. But several reports have also described an increased perioperative morbidity and mortality for surgical resection following induction therapy compared with resection without induction treatment [3]. Therefore, restaging after induction therapy plays a central role in selecting candidates for resection.

^{18}Fluoro-2-deoxy-D-glucose positron-emission tomography with integrated computed-tomography (FDG-PET/CT) has become widely adopted as a major tool for the staging of NSCLC and has been increasingly incorporated into the routine work-up for restaging after induction therapy. However, due to a poor sensitivity of 50% to 60%, PET scan for mediastinal restaging is not as accurate as prior to induction [4-8].

In this study, we assessed the significance of new solitary FDG-positive lesions on restaging PET/CT located in lymph nodes or in the contralateral lung in patients who showed a good radiological response in the primary tumor and in the mediastinal nodes after induction therapy.

Materials and Methods

Between January 2004 and March 2008, an integrated whole-body PET/CT was performed in a consecutive series of 603 patients with potentially operable NSCLC. Conventional staging by means of a history, physical findings, blood test, bronchoscopy and contrast medium-enhanced CT scan of the chest and upper abdomen was performed in all patients. Hundred and forty-five (24%) of these patients with clinical stage III disease underwent induction chemotherapy or radiochemotherapy. Restaging was performed by use of CT-scan. Patients without evidence of disease progression after restaging underwent surgery. Anatomical resection of the primary tumor combined with a mediastinal lymph node dissection was performed whenever possible according to the lung function test after induction and to the intraoperative findings.

In 31 patients, additional restaging PET/CT was performed 4 weeks after induction therapy. Stage IIIA was observed in 26 patients and stage IIIB in 5 patients. Stage IIIA included T1N2, T2N2, T3N1, and T3N2 in 2, 16, 1, and 7 patients, respectively, whereas stage IIIB included T4N0, T4N1, and T4N2 in 1, 2, and 2 patients. In patients with stage IIIA N2, suspected tumor involvement of the mediastinal lymph nodes on PET/CT had been confirmed histologically by use of videomediastinoscopy before induction treatment. In patients with clinical stage IIIB T4, PET/CT demonstrated several positive satellite nodes in the same lobe in 3 patients and suspicion of infiltration of the superior vena cava in 2 patients. All patients underwent induction chemotherapy alone, consisting of a combination of platinum (100mg/m^2) and gemcitabine (1000 mg/m^2) in 13 patients and of platinum and taxotere (85 mg/m^2) in 18 patients. Stable disease, partial and total remissions occurred in 9 (29%), 21 (68%) and 1 (3%) patients. The data of the pre- and post-induction PET/CT examinations were reviewed in these 31 patients. Patient informed consent was obtained prior to surgery for performing this analysis.

Results

Restaging PET/CT revealed a new solitary focal abnormality in 6/31 (20%) patients after induction therapy. Characteristics of these 6 patients, histology, clinical stage of the disease and location of the primary are shown in Table 1. Induction treatment could be completed in all patients. Transient neutropenia and gastroenteritis were observed in one patient.

In all patients, restaging PET/CT showed an important decrease of the FDG-uptake in the primary tumor as well as in the mediastinal lymph nodes which were strongly PET-positive before induction treatment. Despite the small number of patients, the decrease of SUV max was significant for the primary tumor (non parametric Wilcoxon test). Table 2 gives the values of SUV max in the primary and in the lymph nodes before and after induction therapy. This radiological response to chemotherapy could be confirmed histopathologically by the presence of necrosis in the operative specimen. Median necrosis values for the primary tumor and for the lymph nodes were 45% and 20%, respectively.

The 6 new focal abnormalities revealed at restaging PET/CT after induction chemotherapy were located in an ipsilateral cervical lymph node in 2 patients, in the contralateral upper lobe in 2 patients and in a contralateral paratracheal lymph node and an ipsilateral mammary internal lymph node in 1 patient, respectively (Table 3). These new PET-positive lesions showed a high maximal standard uptake value (SUV max), with a mean value of 5.8 ± 2.2. Diagnostic procedures were performed in 5/6 patients. Two patients underwent a mini thoracotomy followed by a wedge resection of the contralateral left upper lobe without postoperative complication. Histopathological diagnosis revealed aspergilloma in the first (Figure 1.) and pneumonia in the second patient. Both patients could undergo complete lung resection consisting of right pneumonectomy and right upper lobectomy.

Two patients had pre-operative fine-needle punctions of cervical lymph node (Figure 2.) and one had intraoperative resection of a mammary internal lymph node. Histological/cytological examination revealed benign reactive lymph nodes in all patients. In the last patient, follow-up PET/CT at one month showed no focal abnormality anymore and could exclude therefore tumor involvement of the contralateral mediastinal lymph node.

Discussion

In the nineteens, induction therapy including preoperative radiochemotherapy or chemotherapy alone has been increasingly used for locally advanced stage III NSCLC in order to downstage tumors and render them completely resectable [9, 10]. Several studies have shown a strong survival benefit in patients with stage IIIA-N2 disease who have been down staged by induction therapy in comparison with patients with residual N2 disease [1, 2]. It has also been shown that surgery can be performed in a curative intent in highly selected patients with stage IIIB-T4 disease within a multimodality therapy concept. The most important prognostic factors are complete resection and the absence of mediastinal lymph node involvement. As a consequence, accurate restaging after induction therapy is of a paramount importance in these subgroups of patients. The difficulty is to assess the pathologic response after induction treatment. In many centers re-staging CT alone is performed despite its low accuracy in restaging the mediastinum. Its sensitivity varied from 41% to 59% and its specificity from 75% to 62% with an accuracy of 58% and 60% [11, 12]. More invasive techniques such as endoesophageal ultrasound-guided fine needle aspiration (EUS-FNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy offer the advantage of providing cytological/histological evidence of response after induction treatment. Both endoscopic techniques have until yet poorly been studied in restaging N2 patients. In a pioneer study, Annema and collaborators assessed the accuracy of EUS-FNA for restaging the mediastinum after induction chemotherapy in 19 patients with proven N2-disease. The positive predictive value, negative predictive value, sensitivity, specificity and diagnostic accuracy of EUS-FNA in this small group of patients were 100%, 67%, 75%, 100% and 83%, respectively [13]. More recently, Herth et al. published the results of a large trial evaluating EBUS-TBNA in restaging the mediastinum after induction chemotherapy in 124 patients with NSCLC. Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were 76%, 100%, 100%, 20% and 77%. Therefore, the authors recommended the need to confirm EBUS-FNA tumor-negative mediastinal nodes by surgical staging before thoracotomy [14]. Repeated mediastinoscopy, although technically more difficult than the first procedure due to adhesions and mediastinal fibrosis is technically feasible in experienced hands [15]. In different series, its sensitivity after induction therapy

for mediastinoscopy proven N2 disease was reported from 70% to 78% except in one prospective study with a reported sensitivity to detect mediastinal disease of 29% [11, 12, 16-18]. This low sensitivity was largely explained by the fact that biopsy of the subcarinal nodes was not adequately performed in 2/3 of patients.

In our study, we used whole body integrated PET/CT for restaging in 31 patients. Accuracy of PET/CT was assessed in different settings related to induction protocol (chemotherapy or chemoradiotherapy), timing of imaging (from one to ten weeks post-induction) and interpretation of imaging (visual or standardized uptake value). Its sensitivity and specificity in three different studies were 77 and 92%, 73 and 89%, 62 and 88%, respectively [12, 19, 20]. Although accuracy of PET/CT in restaging is lower than for staging untreated patients, it enables the direct correlation of FDG-accumulating lesions with morphologic structures throughout the body. It has also been showed that the comparison of SUVmax values before and after induction treatment allowed prediction of histopathologic response in the primary tumor and in the mediastinal lymph nodes, therefore carrying an important prognostic value [19, 21]. In the present study, restaging PET/CT showed a marked response in primary tumor ($p=0.043$) and in mediastinal nodes ($p=0.068$) after induction chemotherapy for all patients, indicating a favourable outcome. Surprisingly, restaging PET/CT revealed new solitary high FDG-positive lesions in cervical or contralateral mediastinal lymph nodes as well as in the contralateral lung. There was a discrepancy since FDG uptake had strongly decreased in the primary and in the involved lymph nodes. The clinical significance of these new findings was unclear. Was it a metastasis or a second tumor resistant to the induction treatment? Further management of the patient would strongly differ according to the neoplastic or inflammatory nature for the lesions. Cyto/histopathologic diagnosis was then mandatory. We performed pre-operative fine-needle punctions for cervical lymph nodes as well as an intraoperative resection of the mammary interna lymph node. These procedures revealed inflammatory reactive lymph nodes. The same diagnosis could be deducted in a mediastinal contralateral lymph node from the disappearance of the lesion's high FDG-uptake on follow-up PET/CT. Regarding FDG- positive lesions in the contralateral lung, histopathological examination revealed an aspergilloma and pneumonia.

New solitary high FDG accumulation in lymph node or contralateral parenchymal lung on restaging PET-CT after induction chemotherapy in good responders with locally advanced NSCLC were not rare (6/31 or 20%). In our experience, these FDG-positive lesions did not imply progression of the disease since they were diagnosed as benign lesions in all 6 patients. Therefore extensive diagnostic procedures for these lesions could be avoided in the future if larger studies confirm our findings.

Tables

Table 1. Patient and tumor characteristics.

Patient	Gender	Age (y)	Histology	cStage	Location of the primary
1	w	44	adeno	T1N2	left upper lobe
2	m	61	large cell	T2N2	left upper lobe
3	m	58	squamous cell	T2N2	middle lobe
4	w	51	adeno	T2N2	right upper lobe
5	m	62	large cell	T4N0	left upper lobe
6	m	60	squamous cell	T4N1	right lower lobe

Table 2. Values of SUVmax before and after induction treatment in the primary lung tumor and in the mediastinal lymph nodes.

Patient	**Primary tumor**		**Mediastinal lymph nodes**	
	SUVmax pre-induction	**SUVmax post-induction**	**SUVmax pre-induction**	**SUVmax post-induction**
1	7.3	2.7	6.6	0.1
2	10.7	4.4	8.4	3.8
3	7.9	4.8	4.3	2.8
4	16.8	6.4	16.7	3.2
5	10.4	1.2		
6	9.6	5.7		
	p*=0.043		p*=0.068	

*non parametric Wilcoxon test

Table 3. Characteristics of the new focal abnormalities revealed on restaging PET/CT after induction chemotherapy.

Patient	New focal post-induction abnormality (SUVmax)	Diagnostic procedure	Diagnosis
1	ipsilateral cervical LN (5.4)	FNP	reactive LN
2	ipsilateral cervical LN (7.2)	FNP	reactive LN
3	contralateral LN ATS 2L (5.7)	follow-up PET/CT	reactive LN
4	contralateral LUL (3.8)	wedge resection LUL	pneumonia
5	ipsilateral mammary internal LN (3.1)	intraoperative resection	reactive LN
6	contralateral LUL (9.6)	wedge resection LUL	aspergilloma

LN=lymph node, LUL=left upper lobe, FNP=fine-needle punction

Figure legends

Figure 1.

A 60-year-old man with a central squamous cell carcinoma coming from the right lower lobe. (A) Axial PET/CT scan showed the high FDG primary tumor before induction therapy. (B) Restaging axial PET/CT scan demonstrated the partial response of the primary tumor after induction therapy. (C) Restaging axial PET/CT scan revealed the new solitary PET-positive lesion in the contra lateral upper lobe. (D) Histopathology of the lung parenchyma FDG-positive lesion revealed an aspergilloma.

Figure 2.

A 61-year-old man with a large cell carcinoma of the left upper lobe and ipsilateral mediastinal lymph node invasion. (A) Axial PET/CT scan showed the high FDG activity within the ipsilateral mediastinal lymph node. (B) Restaging axial PET/CT scan demonstrated the partial response of the mediastinal lymph node after induction therapy. (C) Restaging axial PET/CT scan revealed the new solitary PET-positive lesion in the cervical lymph node. (D) Cytology after fine-needle punction revealed a reactive lymph node.

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