Role of PET-CT in the evaluation of early response to neoadjuvant treatment of locally advanced non-small cell lung cancer (NSCLC)

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Purpose

The staging of lung cancer is the most important conditioning factor in the prognosis and therapeutic strategy. Today the surgery is the most effective treatment; nevertheless, it is used as first approach to early stage lung cancer (stage I, II, IIIA-N1). Locally advanced lung cancers (stage IIIA-N2, IIIB) require a multimodal radio-chemotherapy treatment with neoadjuvant finality. Just in this population of patients the assessment of response to treatment is very important. In the case of "down-staging" of the disease or stable disease after treatment (positive response), a surgical approach is indicated in the second instance (1, 2, 3).

In the literature the role of Positron Emission Tomography-Computed Tomography (PET-CT) is known in the evaluation of response to therapy. Some studies reported that alterations in tissue metabolism generally precede anatomic changes and that the 18F-fluorodeoxyglucose (FDG) uptake by the lung tumor tissue after radiotherapy or chemotherapy correlates with the degree of histo-pathological regression of the tumor (4, 5).

The objective of our study is to assess whether the changes in metabolic activity and changes in tumor volume on PET-CT scans are predictive of response to treatment in patients with locally advanced lung cancer, especially in the early phase.
Methods and Materials

From December 2006 to July 2008 10 patients with NSCLC (5 men, 5 women, mean age 64.3 years, range 43-77 years) were enrolled. 7/10 (70%) had locally advanced lung cancer, 3 with stage IIIA (N2) and 4 IIIB. 2/10 patients with stage IIB were included in the study because they could not benefit from surgery in the first step for comorbidities (respiratory failure) and underwent neoadjuvant radio-chemotherapy. One patient is considered stage IV for a supraclavicular lymph node with FDG uptake not confirmed in subsequent histological examination (reactive hyperplastic lymphadenitis).

All patients underwent neoadjuvant treatment (NAD), using the scheme p-GEM-RT (platinum-gemcitabine-radiation therapy) and they underwent PET-CT scans performed before, during and after NAD treatment, respectively. None of the patients had been treated before.

A nuclear medicine physician and a radiology resident analyzed PET-CT images for each patient and each examination. Morphological total volume of tumor was calculated on CT images of PET-CT scans with semi-automatic method by delineating a region of interest (ROI) on each section of lesion and adding all ROI areas obtained. Metabolic total volume was calculated on PET images with semiautomatic qualitative method by delineating a ROI on each section of lesion with increased metabolic activity and adding all ROI areas obtained; the maximum standardized uptake value of tumor (SUVmaxT) is extrapolated from the lesion volume. The cut-off of SUV maxT value to consider a pathological lesion was 2.5.

For each patient the morphological volumes calculated on CT images of PET-CT scans before, during and after NAD treatment were compared by the Anova test. A similar analysis was performed for metabolic volumes and SUV maxT values calculated on PET-CT scans.

Patients were classified as responders (R) on the basis of the pathological stage pT0 or pT1micr, considered as a major pathologic response to NAD treatment. It was calculated the mean of modifications of SUVmaxT values observed during and after NAD treatment.
Results

A statistically significant difference is demonstrated between the tumor volumes calculated on PET-CT scans before therapy and those calculated on examinations performed after treatment (p<0.01).

A statistically significant difference is obtained between the SUVmaxT values calculated on PET-CT scans before therapy and those calculated on examinations during NAD treatment (p<0.001), and between the SUVmaxT values calculated on PET-CT scans before therapy and those calculated on examinations after NAD treatment (p<0.001) (Fig. 1).

After NAD treatment, 7 of 10 patients underwent surgery; on the basis of pathologic response, 4 patients were considered responders (R) (3 pT1micr and 1 pT0) and 3 non responders (NR).

Other three patients not underwent surgery were identified as NR after NAD treatment, because 1 in progression disease and 2 in stable disease but with severe clinical conditions (Fig. 2).

The trend of SUVmaxT values calculated on three PET-CT examinations was graphically represented for each patient of two groups, R and NR (Fig. 3). The mean of reduction of SUVmaxT values, expressed as a percentage, was calculated both during treatment and after treatment. The mean of reduction of SUVmaxT values was 63% and 40% during NAD treatment, and 70% and 56% after treatment, in R and NR patients respectively (Fig. 4). In our study it was observed that the mean percentage of reduction of SUVmaxT values is greater for R compared to NR patients both during treatment and after treatment.
Fig. 1 - Changes in tumor volume and SUVmaxT values at PET-CT scans performed before, during and after NAD treatment.

a) PET-CT before therapy: the presence of large area with increased metabolic activity in the lesion of the right upper lobe with a central area without 18F-FDG uptake as a necrotic colliquative phenomena.
b) PET-CT during therapy: reduction of tumor volume and intensity of uptake.
c) PET-CT after therapy: further reduction of tumor volume and intensity of uptake in the residual tumor.

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<table>
<thead>
<tr>
<th></th>
<th>PET-CT before NAD</th>
<th>PET-CT during NAD</th>
<th>PET-CT after NAD</th>
<th>pTN</th>
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<tbody>
<tr>
<td>1</td>
<td>T2N1M0 (IIB)</td>
<td>T2N0M0 (IB)</td>
<td>T2N0M0 (IB)</td>
<td>T2N0 NR</td>
</tr>
<tr>
<td>2</td>
<td>T4N2M0 (IIIB)</td>
<td>T4N2M0 (IIIB)</td>
<td>T4N2M0 (IIIB)</td>
<td>/ NR</td>
</tr>
<tr>
<td>3</td>
<td>T3N2M0 (IIIA)</td>
<td>T3N2M0 (IIIA)</td>
<td>T3N2M0 (IIIA)</td>
<td>T3N2 NR</td>
</tr>
<tr>
<td>4</td>
<td>T2N2M0 (IIIA)</td>
<td>T1N2M0 (IIIA)</td>
<td>T1N0M0 (IA)</td>
<td>T1micN0 R</td>
</tr>
<tr>
<td>5</td>
<td>T4N0M0 (IIIB)</td>
<td>T4N0M0 (IIIB)</td>
<td>T4N0M0 (IIIB)</td>
<td>T1micN0 R</td>
</tr>
<tr>
<td>6</td>
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<td>T4N2M1 (IV)</td>
<td>T4N0M0 (IIIB)</td>
<td>T1micN0 R</td>
</tr>
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<td>T4N0M1 (IV)</td>
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<td>T2N2M0 (IIIA)</td>
<td>T2N0M0 (IB)</td>
<td>T2N1 NR</td>
</tr>
</tbody>
</table>

Fig. 2– Staging of lung cancer in 10 patients at PET-CT scans before, during and after NAD treatment and pathologic staging (pTN) in 7/10 patients underwent surgery. Correlation with response to therapy.

Fig. 2

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**Fig. 3**

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**Fig. 4**

Mean % ΔSUV\text{max} in the two groups of patients, R and NR, both during and after NAD treatment.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>NR</th>
</tr>
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<tbody>
<tr>
<td>During NAD</td>
<td>63%</td>
<td>40%</td>
</tr>
<tr>
<td>After NAD</td>
<td>70%</td>
<td>56%</td>
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Conclusion

The accurate assessment of response to therapy is essential in the management of patient both to determine the efficacy of treatment and to eventually change the therapy. In the follow-up of patients treated for lung cancer, conventional imaging techniques (radiography, CT and MRI) provides only morphological informations, often not sufficient to differentiate between residual/recurrent disease and post-treatment alterations. In assessing response to therapy, the advantage of PET is to differentiate between metabolically active tumor tissue and fibrosis post-therapy, metabolically inactive. Many studies demonstrated that 18F-FDG uptake (measured with a semiquantitative method in terms of SUVmax), closely related to the amount of viable tumor cells, represents a significant independent prognostic factor both in the assessment the response to therapy and in the assessment of the recurrences (6). In our study the response to therapy was assessed in terms of changes in volume of lesions and in intensity of uptake. For the assessment of response to neoadjuvant treatment, according to our data, changes in SUVmaxT values were more significant compared to the changes in the tumor volume, particularly in early phase of treatment. According to the results of this study, patients that showed a decrease of SUVmaxT values during treatment greater than 63% can be considered as R patients, whereas patients with a reduction of SUVmaxT values less than 40% can be considered as NR. In conclusion, PET-CT may be considered useful in assessing early response to NAD treatment, and in particular the changes in SUVmaxT values could be predictive of pathologic response.
References

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