L-3-[^{123}\text{I}]iodo-alpha-methyl-tyrosine SPECT in non-small-cell lung cancer - preliminary observations.

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9.1 SUMMARY

L-3-[^{123}\text{I}]iodo-alpha-methyl-tyrosine (IMT) is a modified amino acid which is avidly taken up in many tumors. Uptake is based on the increased transmembrane transport of amino acids in malignancies. IMT is the only amino acid tracer suitable for SPECT imaging.

The aim of this study was to determine the feasibility of IMT SPECT in the detection, staging and treatment evaluation of non-small cell lung cancer.

Methods: We evaluated 44 IMT SPECT studies in 17 patients with histologically proven non-small cell lung cancer stage III. IMT SPECT and planar imaging of the chest were performed before, 2 weeks after and 3 months after 60 Gy radiotherapy. Staging was based on bronchoscopy, chest CT scanning, mediastinoscopy or explorative thoracotomy. After radiotherapy, CT and bronchoscopy were repeated to assess tumor response.

Results: In 15/16 evaluable primary tumors avid IMT uptake was present (sensitivity 94%), with a mean tumor to background ratio (TB ratio) of 2.95 ± 0.78 (range 1.7 - 4.9). In 12/14 patients (86%) with mediastinal involvement IMT SPECT detected one or more mediastinal metastases. However, only 13 of 20 mediastinal metastases were detected in lesion analysis (lesion-based sensitivity 65%). For lesions < 2 cm diameter sensitivity was 42%. FDG PET (available in 5 patients) detected more known and unknown lesions than IMT.
SPECT. After radiotherapy, TB ratios had fallen to 1.84 ± 0.29 (p<0.001 vs baseline) and three months later to 1.61 ± 0.41 (NS vs second study). Considerable non-specific uptake was found in irradiated normal lung tissue (mean ratio to non-irradiated tissue 1.79 ± 0.53), persisting for over three months. No relation was observed between various IMT uptake parameters and presence of residual viable tumor tissue or survival.

**Conclusion:** IMT SPECT has a high sensitivity for the detection of primary non-small cell lung cancer. Although patient-based sensitivity to detect mediastinal spread was adequate, sensitivity for individual lesions, especially for small metastases (< 2 cm diameter) was too low to be clinically helpful. Radiotherapy caused considerable non-specific IMT uptake, which also limits applicability in evaluating the results of treatment.

### 9.2 INTRODUCTION

Metabolic imaging of non-small cell lung cancer is gaining clinical interest. In contrast with anatomical imaging methods like computer tomography (CT), imaging methods such as SPECT and PET visualize metabolic activity within tumor lesions. This metabolic information can be used for characterization of tumor lesions, primary staging and evaluation of treatment. The most prominent example of these methods is PET using \(^{2-}[^{18}F]\)-fluoro-2-deoxy-D-glucose (FDG) (1-4). However, PET has several disadvantages as its availability is still limited, costs are high, and the tracer FDG is also taken up in inflammatory lesions (5).

Radiolabeled amino acids may be an interesting alternative in the metabolic imaging of lung cancer. Since amino acid uptake in inflammatory lesions is less prominent than FDG uptake, these tracers may be more tumor specific (6,7). This tumor specificity might especially be helpful in evaluation of residual tumor activity after treatment or in the detection of recurrence.

The radiolabeled amino acid \(L-3-[^{123}I]\)odo-alpha-methyl-tyrosine (IMT) has been introduced for brain tumor imaging, but is also taken up in many other tumors (8,9). Uptake is based on the increased transport of amino acids, present in nearly all cancer cells (10-12). Uptake appears to be related to tumor proliferation, as demonstrated in vivo in brain and soft-tissue tumors and in vitro in tumor cell lines (13,14). Application of IMT in lung cancer patients has not been studied. The iodine-123 radiolabel makes the tracer suitable for SPECT. In comparison with PET, this an advantage because of better availability and lower costs, but a disadvantage with respect to image resolution. The aim of this study was to investigate the feasibility of IMT SPECT in detection, primary staging and evaluation of radiotherapeutic treatment in patients with non-small cell lung cancer.
9.3 PATIENTS AND METHODS

Patients

Patients with histologically proven non-small cell lung cancer were included between September 1997 and October 1998. We selected consecutive inoperable or irresectable patients with stage IIIA or IIIB who were scheduled for radiotherapy. Patients were imaged three times: prior to radiotherapy, 1-2 weeks after the termination of radiotherapy and 3 months after the second study. Written informed consent was obtained from all patients prior to inclusion. The study was approved by the Medical Ethics Committee of the Groningen University Hospital.

Mediastinal lymph node staging was based on histology or cytology, obtained during endobronchial carinal puncture, cervical mediastinoscopy or explorative thoracotomy. When direct mediastinal tumor involvement (T4 tumor) was observed, patients were not further staged using invasive procedures. In all other cases the mediastinal status was based on histological or cytological information.

Assessment of tumor size before and after treatment was based on CT (Philips Tomoscan SR7000, 5-10 mm slice thickness, Omnipaque (Nycomed) contrast). Size measurements were performed by measuring the two largest perpendicular dimensions on a representative transverse slice through the tumor. The criterion for malignancy in mediastinal lymph nodes was a diameter > 1 cm. Patients were all treated with radiotherapy (60 Gy, in 30 daily fractions) on the primary tumor and mediastinal metastases. Assessment of response was based on measurement of remaining tumor size on CT images obtained within 2 weeks after the termination of radiotherapy and on repeat bronchoscopy with biopsy when possible.

Patients were followed until June 2000. The duration of survival and the cause of death were recorded.

IMT SPECT.

Synthesis of IMT was carried out as previously described (9). After at least a 5 hr fast, SPECT imaging of the chest was performed 15 min after the intravenous injection of 250-300 MBq IMT using a large-field-of-view double headed gamma camera (MULTISPECT 2, Siemens Inc, Hoffman Estates, Illinois) with a medium energy all purpose collimator (64 views, 30 seconds/view). Additional planar spot views were acquired for 10 min. Transaxial tomograms were reconstructed using filtered back-projection with a Butterworth filter (6th order, cutoff 0.275 Nyquist). System resolution was 12 mm FWHM at 10 cm distance.

All images were interpreted from a computer monitor by an experienced nuclear medicine physician, blinded for other imaging information. Planar images were qualitatively analyzed using a simple scoring system: + = uptake
### Table 1. Patients, primary tumors and IMT uptake.

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*) RUL=right upper lobe, RML=right middle lobe, RLL=right lower lobe, LUL=left upper lobe, LLL=left lower lobe

§) – = not visible, + = uptake just above background, ++ = uptake higher than background, +++ = uptake much higher than background.

Just above background, ++ = uptake higher than background, +++ = uptake much higher than background uptake. Areas of abnormal IMT uptake were defined as areas with clearly increased SPECT uptake compared to normal background uptake (9).

Semi-quantitative measurements of IMT uptake were carried out by defining regions-of-interest (ROI) around the lesion under study. These regions were drawn on transverse SPECT slices with maximum tumor visibility, and were drawn in a standardized fashion at 80% of the maximum pixel value in the lesion. A background ROI was drawn in contralateral normal lung tissue, and from the uptake intensity (counts per pixel) in both ROI’s the tumor-to-background ratio (TB ratio) was calculated. TB ratios were calculated before and after radiotherapy on corresponding transverse SPECT slices. After radiotherapy, ROIs were identically drawn at 80% of the maximum pixel value of the remaining tumor, that usually had shrunk through the irradiation. Radiotherapy induced volume changes were not taken into account in this
way, and TB ratios after radiotherapy thus represent tracer uptake density in the remaining tumor volume.

To study the effect of radiotherapy on normal lung tissue, an additional ROI was drawn in normal lung tissue that had been included in the radiotherapy field. In this way a radiated-to-non-irradiated ratio (RNR ratio) was calculated.

**Statistics.**

Paired Student’s t-tests were used to compare TB ratios and RNR ratios at various time points, as differences did not deviate from normal distribution, as evidenced by Kolmogorov-Smirnoff tests. One sample t-tests were used to compare RNR ratios with the expected value 1. Mann Whitney U tests were used to compare IMT uptake data in patients with positive versus negative biopsy or mediastinal status. Spearman’s rank correlation was used to compare tumor area reduction with IMT TB ratio reduction. Two tailed P values < 0.05 were considered significant.

**9.4 RESULTS**

**Patients**

Seventeen patients underwent an IMT SPECT study before radiotherapy (Table 1). In patient 13, the primary tumor had been removed for diagnostic purposes, leaving 16 primary tumors evaluable. The maximal tumor diameter was between 1.5 and 7 cm with a mean of 4.5 cm. In 4 patients an explorative thoracotomy had been performed 20, 32, 44 and 50 days before the IMT study. Five patients had also undergone FDG PET scanning.

The mediastinum was positive for lymph node metastases in 14 of the 17 (84%) patients using the staging method described above. Six patients had direct tumor involvement of the mediastinum (T4). In 11 patients CT of the chest revealed one or more mediastinal lymph nodes > 1 cm diameter, in the other 6 patients mediastinal lymph nodes were either absent or smaller than 1 cm diameter. The patient-based sensitivity of CT for the detection of mediastinal metastases therefore amounts to 79% (11/14). The 14 patients with mediastinal metastases had a total of 20 metastatic locations, 8 of which contained metastases between 2 and 4 cm in diameter. Twelve locations contained metastases < 2 cm diameter of which six were < 1 cm.

**First IMT SPECT: tumor detection and mediastinal staging.**

IMT SPECT clearly depicted 15 of the 16 evaluable primary tumors (94%). Examples are presented in Figure 1 and 2. The only tumor that was not detected was the smallest in this study and was 1.5 cm in diameter (patient 16 in table 1). Tumors were usually already visible on planar images, but SPECT
**Figure 1.** Transverse (A) and coronal (B) SPECT slice through a squamous cell lung carcinoma in the right middle lobe (patient nr 2), showing intense IMT uptake.

**Figure 2.** (A) IMT planar image of the chest showing uptake in a primary squamous cell carcinoma in the left upper lobe and uptake in the mediastinum (small arrows). Minor, presumably bone marrow, uptake in the sternum overlies the mediastinal lesion (B) Transverse SPECT slice from the same patient, showing better delineation of the primary tumor in the left upper lobe and a clear mediastinal metastasis (arrows).
greatly increased visibility and improved localization. IMT tumor uptake was high with a mean TB ratio of $3.0 \pm 1.0$ (sd) with a range of 1.7 - 6.1 (Table 1).

In 12 of the 14 patients with mediastinal metastases IMT SPECT detected abnormal uptake in the mediastinum, yielding a (patient-based) sensitivity of 86% (Figure 2B). One patient had multiple small mediastinal metastases (1 - 2 cm in diameter) that were not visible on the IMT images (patient 4). In the other patient a 2 cm hilar/paratracheal lesion was not detected, presumably due to low uptake (patient 11). There were no false positive findings.

Analyzing individual mediastinal lesions, IMT SPECT detected 13 of the 20 metastatic locations (overall lesion-based sensitivity 65%). All eight locations containing metastases over 2 cm in diameter were detected. However, only five of the twelve locations containing metastases < 2 cm were detected (small lesion sensitivity 42%). Due to limited resolution, it was not always possible to clearly separate metastatic locations. For example, patient 12 had a metastasis of 2 cm diameter located in the transition zone between the hilar and paratracheal region and an additional carinal metastasis. Although increased uptake was found in the entire perihilar region, the two histologically confirmed metastases could not be visualized separately on the IMT SPECT images.

In one patient IMT SPECT showed clearly increased uptake in an unexpected supraclavicular lesion. This was originally considered to be false positive, since the lesion had not been found during staging, but 3 months later (after radiotherapy, not including the supraclavicular area) a palpable metastatic node was found on this location. Apart from this case, no other unexpected abnormalities were found, in particular no distant metastases.

In 5 patients FDG PET had also been performed and the results were compared with IMT SPECT. All primary tumors were also visualized using PET. In one patient IMT did not detect a 2 cm mediastinal lymph node, which was positive on PET (patient 11). However, PET showed 2 false positive mediastinal locations (1.5 cm) that were correctly negative on IMT SPECT. In two other patients PET detected small distant metastases (one in bone, one intrapulmonary). As expected, PET image quality, anatomic resolution and lesion to background activity were superior to IMT images (Figure 3).

**Second IMT SPECT: after radiotherapy**

The second IMT SPECT, shortly after the end of radiotherapy, was performed in 14 patients. In 3 patients post treatment scan were not performed as radiotherapy had been canceled, due to disease progression shortly after the start of treatment in one patient, and two patients had died. Patient 13, whose primary tumor had been removed for a diagnostic purpose, had been irradiated on a 3 cm mediastinal metastasis. This lesion was used in the response analysis. In all 14 patients post-treatment tumor size was determined using CT. Additionally, in 10 patients adequate histological or cytological material was obtained through repeat bronchoscopy.
In all patients the TB ratio had decreased after radiotherapy. An example is shown in Figure 4. The mean TB ratio decreased from $2.95 \pm 0.78$ to $1.84 \pm 0.29$ ($p<0.001$). Considering a posttreatment TB ratio = 1 as a complete disappearance of tumor activity, the average reduction of IMT TB ratios was $52\% \pm 18\%$. Data are shown in Figure 5.

Tumor dimensions after radiotherapy, as measured with CT, also diminished significantly in all but one patient. The mean tumor area decreased from $21 \pm 14 \text{ cm}^2$ to $7 \pm 9 \text{ cm}^2$ ($p<0.01$), an average reduction of $60 \pm 37\%$. No correlation was found between IMT TB ratio reduction and tumor size.

![Figure 3](image)

**Figure 3.** IMT SPECT (left) and FDG PET (right) images of patient 1. (A) IMT SPECT coronal slice through a 1.5 cm squamous cell lung carcinoma located in the apex of the right upper lobe (arrow). Non-specific uptake in the lower right chest wall is caused by a thoracotomy 20 days earlier. (B) Corresponding FDG-PET coronal image, obtained before thoracotomy demonstrating intense FDG uptake in the primary tumor and in a hilar metastasis. (C) IMT SPECT coronal slice through the hilar region also shows intense uptake in this hilar metastasis (arrow). (D) Corresponding FDG-PET coronal image through the middle of the hilar metastasis with higher contrast. Furthermore, an additional lesion in the right middle field (thick arrow) is found on PET that is missed on the IMT SPECT image.
reduction.

Considerable uptake was observed in irradiated normal lung tissue (Figure 6), with a mean RNR (radiated-to-non-radiated) ratio of 1.79 ± 0.53 (range 1.05 - 2.27) being significantly different from 1 (p<0.001). The mean uptake ratio between tumors and the adjacent irradiated lung tissue was 1.27 ± 0.34.

Biopsies from the tumor area after radiotherapy still contained vital tumor cells in 4 (out of 10) patients. The reduction in IMT uptake of these 4 patients was not different from those with a negative biopsy after radiotherapy, neither was the absolute pre- or post-treatment uptake (Figure 5), although the number of studied patients is low. Also in patients with and without mediastinal metastases, IMT TB ratios before and after radiotherapy were not different.

Figure 4. Corresponding transverse IMT SPECT (lower row) and CT (upper row) slices through a squamous cell carcinoma (thin white arrows) in the right upper lobe, before radiotherapy (left) and shortly after (right). CT images demonstrate significant tumor regression, but IMT SPECT shows reduced, but lightly persisting uptake (arrows). Vital tumor cells were found after bronchoscopic biopsy. Also note increased uptake in the irradiated field (arrowheads).
Third IMT SPECT: follow-up.

Three months after the second IMT scan 13 patients underwent a third IMT SPECT. One patient had died between the second and third study. The mean TB ratio had decreased slightly from 1.84 ± 0.29 to 1.61 ± 0.41, but this change between second and third scan was not significant. Only in one of the four patients with a positive biopsy, but also in 2 patients with a negative biopsy after radiotherapy, TB ratios had now risen again.

At the end of the follow-up period 6 patients were still alive, all others had died from their lung cancer. Median survival was 20 months. Using Cox regression analysis no significant relation was observed between survival and IMT TB ratio before or after radiotherapy (Relative Risk 0.9, with a wide 95% Confidence Interval 0.45 - 1.8), but more observations are required for this purpose.

Average RNR had decreased from 1.79 ± 0.53 to 1.50 ± 0.50, a significant difference (p<0.05) but still much higher than 1 (p<0.001). The tumor-to-irradiated lung tissue ratio was 1.21 ± 0.31, not different from the ratio after the second study.
IMT SPECT IN NON-SMALL-CELL LUNG CANCER

Figure 6. Planar IMT image obtained 1 week after 60 Gy radiotherapy on the right middle lobe tumor of patient 2 (see figure 1). Increased uptake is present in the entire irradiated field (arrow). The diaphragm is located at the very bottom of the image

9.5 DISCUSSION

This study shows that non-small cell lung cancer lesions can be visualized using IMT SPECT. Apparently, this simple and potentially widely available SPECT method is able to visualize the increased amino acid metabolism in these tumors, which has not been demonstrated before. However, there were serious drawbacks that will limit its clinical applicability. Firstly, while all primary tumors over 1.5 cm were detected, a smaller primary tumor was missed. Secondly, lesion-based sensitivity for mediastinal metastases was low (65%) and for small lesions (< 2 cm) even as low as 42%. Because of this detection limit of 1.5 - 2 cm, IMT SPECT does not appear helpful in mediastinal staging, and will not reduce the need for invasive staging procedures.

Shortly after radiotherapy we found a considerable decrease in IMT uptake intensity in the remaining tumor, which indicates decreased amino acid metabolism induced by radiotherapy although the reduction in size in itself may also contribute to the decreased uptake. We did not observe a relation between the presence of residual viable tumor tissue and IMT uptake or changes in uptake, but more study is required for this purpose and a certain degree of sampling error might have influenced this finding. However, we also did not find a correlation between survival, another outcome parameter, and IMT uptake. Furthermore, considerable uptake was found in normal lung tissue.
that had been included in the irradiated field. This phenomenon was present in nearly all patients shortly after radiotherapy and had hardly diminished 3 months later. It was not related to the occurrence of radiation pneumonitis or other radiotherapeutic lung damage. Apparently, tissue changes after radiotherapy (inflammation, fibrosis, apoptosis) are associated with increased amino acid demand. This limits the specificity of IMT for evaluation of the results of radiotherapy. Therefore, it seems unlikely that even in larger groups, IMT SPECT will have predictive value in response evaluation for individual patients.

Radiolabeled amino acids have hardly been applied in lung cancer imaging. Since amino acids play a minor role in the metabolism of inflammatory cells, the theoretically better specificity may be advantageous in comparison with FDG (5-7, 15). A high specificity of 91% was indeed reported in a recent study by Yasukawa who retrospectively analyzed $^{11}$C-methionine PET for mediastinal staging (n=41). PET correctly diagnosed 10/14 enlarged lymph nodes as tumor-negative, but intense methionine uptake was also present in many histologically negative lymph nodes, independent of size (16). Nettelbladt found both FDG and carbon-11-methionine PET positive in 4 patients with mediastinal metastases, but also found methionine (and FDG) to be taken up in post-obstructive pneumonia and in mucous membranes of the carina and proximal main bronchi (17). Kubota could separate a group of patients with early tumor recurrence from a group with late recurrence using L-[methyl-$^{11}$C]-methionine uptake in a similar study as the current, but found CT to be better in the prediction of ultimate local recurrence (18). Increased amino acid uptake in irradiated lung tissue, as observed in our study, however, has not been described before.

IMT, as a relatively new metabolic tracer and the only amino acid tracer suitable for SPECT, compares well to other single photon tracers applied in lung cancer. Using Thallium-201, Tc99m-MIBI or Gallium-67, sensitivities between 50 and 90% are reported for primary tumor detection with TB ratios between 2.4 and 3.8 (19-24). Few studies have addressed mediastinal staging but in nearly all of these sensitivity for small lesions (<1.5 cm) was too low to be clinically helpful, and frequently uptake in benign processes decreased specificity (23-25). In addition, most authors report only patient-based sensitivities, whereas lesion or lymph node station based sensitivities are usually lower. Although as sensitive as these other SPECT agents, the sensitivity of IMT SPECT is too low to be clinically acceptable. Apparently, amino acid uptake is not high enough to compensate for the limited resolution of SPECT. Therefore, a negative scan does not rule out the presence of (especially small) metastases, which still necessitates invasive staging with mediastinoscopy or surgery. However, one should realize that CT alone does not perform better than single photon studies (26), as is suggested also in this study using IMT SPECT.
9.6 CONCLUSION.

SPECT using the radiolabeled amino acid IMT is able to visualize non-small cell lung cancer lesions with a high sensitivity for the primary tumor. However, IMT SPECT appears to have a detection limit of approximately 1.5 cm. For mediastinal staging this results in a sensitivity that is too low to be clinically helpful. Although tumor uptake significantly decreased after radiotherapy, relatively high and persistent uptake was observed in irradiated normal lung tissue. The specificity of IMT is therefore lower than expected, which will also limits application in treatment evaluation.

9.7 REFERENCES