Restaging patients with N2 non-small cell lung cancer after neoadjuvant chemotherapy: TCMS accuracy using a multi-criteria approach

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Purpose

An appropriate staging of lung cancer is critical, because stage dictates treatment and treatment regimens vary considerably according to the stage [1]. The involvement of mediastinal lymph nodes has long been recognized as the most important prognostic factor in non-metastatic non-small cell lung cancer (NSCLC) [2,3]. It is very important to correctly identify preoperative patients with N2 disease (stage IIIA), because for these patients surgery should be avoided offering instead a multimodality approach [4]. Computed tomography (CT) is the method of choice in the preoperative staging of patients with NSCLC. In the CT assessment of mediastinal lymph nodes the majority of the studies use the size of the node as the only criterion suggestive of malignancy, thus limiting the usefulness of such method in comparison with PET [5].

Considering our previous study on this topic [6], the aim of this work has been to evaluate the accuracy of MDCT in restaging patients with N2 NSCLC, after neoadjuvant chemotherapy using a multi-criteria approach.
Methods and Materials

Two separate radiologists, both with previous experience in oncologic imaging, retrospectively reviewed 40 contrast-enhanced MDCT of the chest, performed before and after neoadjuvant chemotherapy in 20 patients with histopathologically proven NSCLC (stage IIIa), after ethical approval.

Technical information.

MDCT of the chest was obtained using a 64-detector row configuration (LightSpeed Plus, General Electric Healthcare, Milwaukee, USA) for 8 patients, a 16-detector row configuration (Light-Speed 16 Pro, General Electric Healthcare, Milwaukee, USA) for 10 patients and a 4-detector row configuration for the other 2 patients. In all patients CT of the chest was performed with a spiral technique in caudo-cranial direction (from the bases of the lungs to a plane cutting through the upper thoracic outlet, with the patient lying supine). Enhanced CT scans were obtained after a bolus intravenous injection of a 370 mgI/mL (lopamiro 370, Bracco, Industria Chimica Milano) contrast material at 4 mL/s followed by 20-30 mL of saline solution from a volume of 2 mL/kg up to a maximum volume of 160 mL, through an 18-gauge needle inserted in the antecubital vein and using a power injector (SIAS 757, Italy), with a scan delay of 65-80 seconds c.a., in consideration of the functional cardiovascular parameters of each patient.

The following technical parameters were used by 4 rows CT effective: slice thickness 3.75 mm, beam pitch 0.75, reconstruction interval 1.5 mm, 120-140 kVp, 200-320 mA; by 16 rows CT: effective slice thickness 2.5 mm, beam pitch 1.375/0.937, reconstruction interval 0.8 mm, 120-140 kVp and 250-500 mA; and by 64 rows CT: effective slice thickness 2.5 mm, beam pitch 0.984, reconstruction interval 0.8 mm, 120-140 kVp, 200-600 mA. Standard reconstruction algorithm was used.

Surgical Information.

All patients underwent surgical lymph nodes resection within 30 days from the CT examination. The systematic nodal dissection was performed for all patients during major resective surgery by thoracotomy. On the right side a total of 7 nodal groups (hilar, interlobar and mediastinal lymph node levels 2R, 4R, 7, 8R and 9R), and on the left side a total of 9 nodal groups (hilar, interlobar and mediastinal lymph node levels 2L, 4L, 5, 6, 7, 8L and 9L) were removed [7]. All lymph nodes, mapped by both the surgeon and the pathologist using the IASLC lymph node map, were examined histologically (Fig. 1) [8].

The IASLC lymph node map was also used for the radiological localization of lymph nodal stations. The lymph nodal stage is reported as follows:
- N0/N1: no presence of pathological lymph nodes/presence of primary tumour in the peribronchial and/or the ipsilateral hilar nodes, with direct extension to the intrapulmonary lymph nodes.

- N2: presence of metastatic mediastinal lymph nodes, in line with the IASLC lymph node map [8].

In Figures 2-9, the CT anatomic position and boundaries according to the IASLC lymph node map were showed.

**Imaging analysis.**

Each CT scan was analyzed on a reconstruction and image interpretation console (Advantage Workstation 4.4, GE Healthcare), adjusting each time the image's level, window and enlargement values, and using a 2D multiplanar reconstruction technique when necessary. The criteria used for lymph node evaluation were the following:

1. **Lymph node metastasis according to location of primary tumor:** based on the usual lymphatic pathways of tumour spread into the mediastinum compared to the location of primary tumours. High risk nodal stations were considered as follows: for neoplasms of the right upper lobe (RUL) and the middle lobe (ML), stations 10R, 4R and 2R; for neoplasms of the right lower lobe (RLL), stations 8R and 7; for neoplasms of the left upper lobe (LUL), stations 10L, 5, 4L, 2L and 6; and for neoplasms of the left lower lobe (LLL), stations 8L and 7 (Figures 10-12) [9].

2. **Size:** to assess the dimensional parameters, the short axis of the lymph node was measured; normal limits used were the ones proposed by Glazer et al. [10], modified by the radiologist with the most experience (L.V.) for stations 4R/L, 5 and 7, for which normal limits were shifted from 10 to 9 mm, from 9 to 8 mm, and from 11 to 12 mm respectively (Table 1). Generally, a lymph node located in a high risk station with respect to the site of the tumour and bigger than the cut-off established for the corresponding station was considered as pathologic. However, this statement becomes untrue if the lymph node, even though bigger than the identified cut-off, presents lipomatosis or central calcifications. A lymph node with short axis superior to the cut off identified for its station was considered non-pathologic if located in a low risk nodal station in relation to the site of the T and if the draining stations preceding the one being analysed are negative (i.e. a lymph node > the cut-off identified for station 4R in the presence of a T localized in the LLL and presenting negative lymph nodes in station 7, the only connecting station).

3. **Structure:** was assessed by taking into consideration the following characteristics: (1) central hypodensity, measured with a Region of Interest (ROI) analysis: negative Hounsfield unit (HU) values, typical of adipose tissue, were considered as indicators of benignity, even in enlarged lymph nodes, whilst higher values, coupled with the presence of necrosis, were considered as indicative of malignancy of the lymph node; (2) calcifications: presence of calcifications localized in the centre of a lymph node, also if
enlarged compared to the cut-off size, was considered an indicator of benignity, whilst the finding of eccentric calcifications was considered as evidence of metastatic involvement of the lymph node;

4. **Enhancement patterns (visual assessment):** a homogeneous pattern was considered indicative of benignity; enhancement with a ring-pattern, diffusely inhomogeneous, or a pattern similar to that seen in the primary lesion, was considered as evidence of lymph node infiltration, regardless of the lymph node’s actual size.

The CT results were compared, station by station, with the results obtained during the post-surgical pathological staging for all 20 patients.

To validate our approach a comparison with the most common method used in the literature (metastatic lymph node if with short axis #10 mm) was also investigated.

**Statistical analysis.**

Inter-observer agreement was measured using a kappa unit regarding the N2 status. The kappa unit varied from 0 (chance agreement) to 1 (total agreement). K-values were interpreted as follows: K < 0.20, poor agreement; K = 0.21-0.40, fair; K = 0.41-0.60, moderate; K = 0.61-0.80, good; K = 0.81-1.00, very good. The sensitivity, specificity, positive and negative predictive values and accuracy were calculated for each modality (MDCT multi-criteria approach and MDCT staging using the size of the node as the only criterion suggestive of malignancy).
**Fig. 1:** The new IASLC lymph node map, which reconciles differences between earlier nodal maps including the Naruke and MD-ATS (Mountain-Dresler-American Thoracic Society) maps.

Fig. 2: The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node station number 1.

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Fig. 3: The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node station number 2.

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Fig. 4: The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node station number 2.

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**Fig. 5:** The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node stations number 2 and 4(R).

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**Fig. 6:** The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node station number 4.

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Fig. 7: The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node stations number 5 and 6.

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**Fig. 8:** The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node station number 3.

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Fig. 9: The CT anatomic position and boundaries, according to the IASLC lymph node map, for lymph node stations number 7 and 8.

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Fig. 10: Lymph node metastasis according to the location of primary tumor: high risk nodal stations for neoplasms of the right upper lobe (RUL) and middle lobe (ML).

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Fig. 11: Lymph node metastasis according to the location of primary tumor: high risk nodal stations for neoplasms of the right lower lobe (RLL) and left lower lobe (LLL).

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Fig. 12: Lymph node metastasis according to the location of primary tumor: high risk nodal stations for neoplasms of the left upper lobe (LUL).

Table 1: Threshold sizes for nodal enlargement [6].

Results

Among 20 lesions the histopathological exam revealed 12 adenocarcinomas, 6 squamous cell carcinomas and 2 large cell carcinomas. At histopathologic examination, with respect to the N descriptor, 11 on 20 (55%) patients were staged as N0/N1 and 9 on 20 (45%) as N2.

Nine out of 20 (45%) patients staged as N2 at histologic examination after the completion of neoadjuvant chemotherapy were correctly staged with MDCT using a multi-criteria approach; 9/11 (81%) of malignant mediastinal nodal groups detected at pathology were correctly identified.

The K-values regarding the N2 status between the two reviewers were very good (K = 0.962).

Sensitivity, specificity, positive and negative predictive values, and accuracy of our method resulted in 100%, 82%, 82%, 100% and 90% respectively.

Instead, using for the same population only the dimensional criterion defined in the literature (#1 cm) for the pre-surgical staging of the N parameter, we obtained values of sensitivity, specificity, positive and negative predictive values, and accuracy of 23%, 64%, 33%, 50% and 45% respectively.

Figures 13 and 14 showed two case examples of our case population.
Fig. 13: CT examination of a patient with an ADK of the RLL with enlarged lymph nodes, in station 10R, 7 and 4R, before the chemoterapic treatment, (a and b); after the completion of neoadjuvant chemotherapy, the patient was correctly staged at CT examination as N0/ N1 because the dimensional reduction of the lymph node and the presence of central lypomatosis in the lymph node of station number 4R.

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Fig. 14: CT examination of a patient with an ADK of the RLL with enlarged lymph nodes, in station 10R, 4R and 7, before the chemoterapic treatment, (a-c); after the completion of neoadjuvant chemotherapy, the patient was correctly staged at CT examination as N2 because the enhancement of the lymph node in station number 7, diffusely inhomogeneous, that was considered as evidence of lymph node infiltration, regardless of the lymph node's actual size.

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Conclusion

Our preliminary findings suggest that when other criteria are associated with size the diagnostic accuracy of MDCT in restaging patients N2 with NSCLC after neoadjuvant chemotherapy is improved.
References


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