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Guidelines for multimodality radiological staging of lung cancer

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Summary Lung cancer is among the most common type of cancers and is a leading cause of cancer-related deaths with smoking representing the leading risk factor.

It is classified into non-small cell lung cancer (NSCLC) representing 70—80% of cases and small cell lung cancer (SCLC) which has neuroendocrine properties with poor outcome.

Staging of NSCLC is based on the TNM classification system while SCLC was usually classified into limited and extensive disease, though the use of TNM staging system for SCLC is recommended.

Imaging studies are used to determine the pre-operative staging of lung cancer. Accurate radiological staging is essential to determine tumor resectability as well as to avoid futile surgeries and to assess patient's outcome. Moreover, radiological examinations are used for the evaluation of tumor response to treatment.

This manuscript will review the utilization of imaging studies in the management of lung cancer based on the most recent guidelines by the National Comprehensive Cancer Network (NCCN).

Radiological staging of lung cancer

The treatment and prognosis of patients with NSCLC depend on disease staging (the determination of anatomic extent of disease at initial presentation) [1,2].

Uniform criteria for reporting the findings of clinical and/or pathologic evaluation are essential in the initial management of patients with NSCLC. Imaging is directed toward detecting unresectable disease [1—3].

Most lung cancers are initially discovered on chest radiographs [4]. Lung cancer may present as a nodule, mass or unresolved consolidation. Nodules smaller than 2 cm or located in the hidden areas such as the hila or lung apices are frequently missed on chest radiographs. Therefore, chest radiographs are useful in the initial diagnosis of lung cancer

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[1] On behalf of the Lung Cancer Guidelines Committee. See Appendix A.

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and guiding more sophisticated imaging but not for tumor staging [5].

Computed tomography (CT) covering the chest and upper abdomen including the liver and adrenal glands is the main imaging modality for the diagnosis and staging of lung cancer [5]. CT scan can also help in guiding tissue sampling of the primary lung cancer, lymph node metastasis or distant metastasis.

PET-CT, MRI of the chest, brain CT or MRI and bone scan are additional imaging modalities that can be utilized according to CT findings, clinical data and histologic type of lung cancer.

Assessment of tumor extent (T descriptor)

T descriptor reflects the spread of primary lung cancer determined by tumor size, local invasion, relationship to the tracheobronchial tree and the presence of ipsilateral satellite nodules [6].

T1 and T2 tumors are confined to the lungs whereas T3 tumors are associated with chest wall or limited mediastinal invasion. T4 status reflects more aggressive invasion of vital mediastinal structures or ipsilateral satellite nodules.

The distinction between T3 and T4 status is crucial since T4 tumors are considered unresectable [5].

CT is the main modality for noninvasive evaluation of the local extent of lung cancer. The use of IV contrast material is not absolutely necessary [4]. However, the administration of IV contrast can help in the distinction between blood vessels and enlarged lymph nodes, in more accurate delineation of mediastinal invasion and in more precise characterization of upper abdominal deposits in the liver and the adrenal glands.

PET imaging has limited role in the T-staging of lung cancer and can both underestimates and overestimates the T-stage of many tumors. Some tumors may show no or little FDG uptake such as biologically weak tumors like previously known ''bronchoalveolar cell carcinoma'' and carcinoid tumors. Conversely, inflammatory or infectious conditions can demonstrate vivid FDG uptake mimicking malignant tumors [7].

Integrated FDG-PET/CT scanning has a major benefit of combining both anatomical and metabolic data of the studied structures. It was shown in recent studies to represent the best non-invasive imaging modality for the accurate determination of T stage as compared with CT alone or PET alone [7].

FDG-PET/CT can delineate central tumor from associated post-obstructive pneumonitis which shows mild to moderate uptake compared with the primary mass. This distinction may not affect surgical resectability but it has an impact on radiotherapy planning [5]. MRI with the added value of IV contrast administration can also be helpful in delineating atelectasis, which can be hyperintense, from central lung mass [8].

Pancoast tumor is a superior sulcus neoplasm which has a propensity to invade the adjacent vertebrae, subclavian vessels, the brachial plexus and the base of the neck.

Clinically, patients may present with Horner's syndrome secondary to sympathetic chain invasion.

Chest radiographs may detect an apical mass or opacity. CT with multiplanar reconstruction (MPR) can define the outline of the tumor and invasion of important adjacent structures such as the brachial plexus.

MRI imaging is reserved for equivocal cases and it is useful to detect extension into the brachial plexus, the vertebrae and the neural foramina [9]. The combined use of CT and MRI imaging in Pancoast tumors may be useful for the accurate preoperative prediction of tumor respectability [10].

Invasion of the subclavian, common carotid, and vertebral arteries, less than 50% vertebral body involvement, and extension into the neural foramina should be considered relative contraindications to surgery [10].

Assessment of regional lymph node extension (N descriptor)

The presence of mediastinal lymph node metastasis has a great impact on tumor resectability and therefore patient's survival. The likelihood of lymph node metastasis is linked to increased tumor size, central location and adenocarcinoma histology [5].

Nodal staging with CT scan is based on morphological characterization. The current consensus defines a lymph node with a short axis diameter more than 1 cm on an axial CT scan as a possible positive lymph node [7].

The pooled sensitivity and specificity of CT scan in the detection of malignant mediastinal lymph nodes were 51% and 86%, respectively. CT scan is therefore an imperfect modality to rule in or rule out lymph node involvement [4].

False positive CT results are caused by postobstructive pneumonitis or atelectasis and are more

common with central tumors and false negative CT results are especially associated with adenocarcinomas [11].

An additional role of CT scan is in guiding mediastinal lymph node biopsy by invasive techniques; therefore it continues to play an important role for lung cancer diagnosis [4].

Several studies demonstrated high accuracy of PDG—PET for the detection of malignant mediastinal lymph nodes. Meta-analyses confirmed a sensitivity of 74% and specificity of 85% in 2865 patients [4]. Many studies have shown a high negative predictive value estimated as $\geq$90% in lymph node staging [12].

False positive FDG-PET results can be related to inflammatory or infectious changes in the lymph nodes as well as residual brown fat. False negative results can occur when tumor load in metastatic mediastinal lymph nodes is low (Micormetastases) [7].

Lee et al. found that the risk of FDG-PET false negative results is increased in central tumors, increasing T-stage, adenocarcinoma histology, and higher primary tumor standard uptake value (>6) [13].

Integrated FDG-PET/CT imaging which has the benefit of combining metabolic and anatomic data demonstrated on initial studies to be superior to CT alone and FDG-PET alone with pooled average sensitivity of 73%, average specificity of 80%, accuracy of 87% and negative predicative value of 91% [7]. Therefore, FDG-PET can decrease the number of futile thoracotomies by 20% [14].

Due to false positive results, positive PET findings should be confirmed by targeted biopsy prior to surgical resection of the primary tumor.

Mediastinoscopy remains the standard for mediastinal staging, even when lymph nodes are not accessible by mediastinoscope and it should be done in all cases with positive FDG-PET mediastinal lymph nodes [15].

Omitting invasive procedures is recommended by European Society of Thoracic Surgeons in case of peripheral tumors and negative FDG-PET lymph node results. On the other hand, central tumors, PET-based hilar N1 disease, low FDG uptake of the primary tumor and lymph nodes larger than 15 mm on CT scan should be surgically staged [16].

Endobronchial ultrasound (EBUS) permits identification and localization of mediastinal lymph nodes during flexible bronchoscopy and allows a more reliable needle aspiration of small lymph nodes with great sensitivity. A sensitivity of 92% and a specificity of 100% are comparable to surgical staging of the paratracheal, subcarinal and hilar lymphadenopathy [17,18].

According to the most recent recommendations from the National Comprehensive Cancer Network (NCCN), FDG-PET positive mediastinal lymph nodes should be sampled with endobronchial ultrasound/trans-bronchial needle aspiration (EBUS-TBNA) whenever possible with pathologic confirmation by mediastinoscopy when EBUS result is negative.

Assessment of metastatic disease (M descriptor)

The new 7th edition of TNM staging system has subcategorized M descriptor into intrathoracic metastasis (M1a) that includes malignant pleural effusion, pleural dissemination, pericardial disease and pulmonary nodules in the contralateral lung, and extrathoracic metastasis (M1b) that commonly involves liver, adrenal glands, brain and bones.

Pleural effusion

Malignant pleural effusion is associated with poor outcome leading to its subclassification as M1a disease as compared with T4 disease previously. Pleural involvement by lung cancer can be secondary to direct invasion or metastatic deposits.

Pleural effusion can develop in any lung cancer histologic type, though it is more commonly seen with adenocarcinomas which can cause diffuse nodular pleural thickening mimicking malignant pleural mesothelioma [19].

Inflammatory and infectious conditions can be benign causes of pleural effusion which cannot be differentiated from malignant pleural effusion on CT or ultrasound unless pleural masses are identified. PET imaging has a high sensitivity for the detection of both primary lung cancer and pleural deposits [20].

Cytologic examination can detect approximately 65% of malignant effusions. If the first thoracentesis is negative, a second thoracentesis should be performed. If the second thoracentesis is negative, thoracoscopy for pleural metastasis is recommended [21—23].

In a study by Decker et al., large pleural effusion was always associated with poor prognosis even if cytologic analysis was negative for malignancy [24].

Distant metastases

About 40% of patients with NSCLC have distant metastases at the time of presentation [25]. The most common sites for metastases from lung

cancer are adrenal glands, the liver, the brain and the bones [5].

Adrenal metastases are present in up to 20% of NSCLC patients at presentation [5]. Incidental benign adrenal nodules are also common in both general population and lung cancer patient. A small adrenal nodule with a CT density measurement <10 HU on unenhanced CT assures the diagnosis of lipid-rich adenoma [26]. In most patients, the combination of CT criteria and FDG-PET findings will be sufficient to characterize adrenal nodules as benign or malignant [5].

MRI imaging with in-phase and out-of-phase sequence can be utilized in equivocal cases.

Adrenal CT, MRI and FDG-PET can potentially rule in a benign lesion, but their specificity is insufficient to rule in malignancy [27]. Therefore, adrenal biopsy is recommended, particularly if this is the only finding that can render the disease inoperable [5].

Liver metastases can be reliably detected by CT and FDG-PET reaching a sensitivity and specificity of approximately 100% [7]. Abdominal MRI and liver biopsy are required for discordant or indeterminate results [27].

Bone metastases are common in lung cancer. Bone scintigraphy can detect bone metastases with high sensitivity but with a false-positive rate reaching 40% limiting its diagnostic accuracy [28].

FDG-PET is superior to bone scintigraphy with similar sensitivity and improved specificity and negative predictive value [27]. Therefore, bone scintigraphy is no longer indicated if FDG-PET/CT is obtained [5].

Brain metastases are most frequently encountered in poorly differentiated tumors and adenocarcinomas [5]. Despite the fact that MRI is more sensitive than CT in detecting more and smaller brain lesions, this observation was not shown in several studies to alter patient's survival [4].

According to American College of Radiology (ACR) appropriateness criteria, cerebral imaging is used more effectively in symptomatic patients, those with advanced disease, and prior to treatment with a curative intent for T2 tumors and IIIA disease [27].

The role of FDG-PET/CT

PET-CT is considered the most accurate imaging modality for the overall evaluation for lung cancer metastases. The diagnostic capabilities of FDG-PET/CT for preoperative staging of lung cancer are superior to that of PET alone or CT alone [29].

Due to normal cerebral grey matter avidity to FDG, PET has a low sensitivity (approximately 60%) for the detection of brain metastases, so dedicated brain imaging with CT or MRI remains necessary [4,5].

In a randomized clinical trial, Pischer et al. demonstrated that the preoperative staging of lung cancer by the use of FDG-PET/CT can reduce the total number of thoracotomies and the frequency of futile thoracotomies without any effect on overall survival [14].

According to the most recent NCCN guidelines, the use of integrated PET/CT is recommended over the use of PET and CT side by side.

The use of whole body magnetic resonance imaging (MRI)

Whole body MRI examination with DW (diffusion weighted) images can replace PET scan with good reliability due to its high sensitivity and good resolution and whole body coverage.

Two major studies proved the accuracy of 3 T whole body MRI and its comparable results with FDG-PET/CT imaging for the evaluation of metastasis. MRI was even superior in evaluating liver, bone and brain metastasis. FDG-PET/CT was superior in the detection of lymph node and soft tissue deposits [30,31].

Considering these studies among other supporting studies, we recommended whole-body MRI for initial evaluation of metastasis if PET is unavailable. If whole-body MRI cannot be performed, the old recommendation of bone scan and brain MRI can be followed (institute preference).

Small cell lung cancer (SCLC)

SCLC represents 15% of overall lung cancers. It is distinct from other types of lung cancer by neuroendocrine cell origin and aggressive biological behavior [32].

The International Association for the Study of Lung Cancer (IASLC) encourages the use of new TNM staging for SCLC to replace the old staging system of limited and extensive disease.

Contrast-enhanced CT with contrast of the abdomen is recommended as a part of routine staging since distant metastases can involve abdominal organs in up to 60% of cases, most commonly affecting the liver and the adrenal glands [27].

Brain metastases can present in up to 10% of patients at the time of presentation, therefore brain imaging should be carried out in all patients [33].

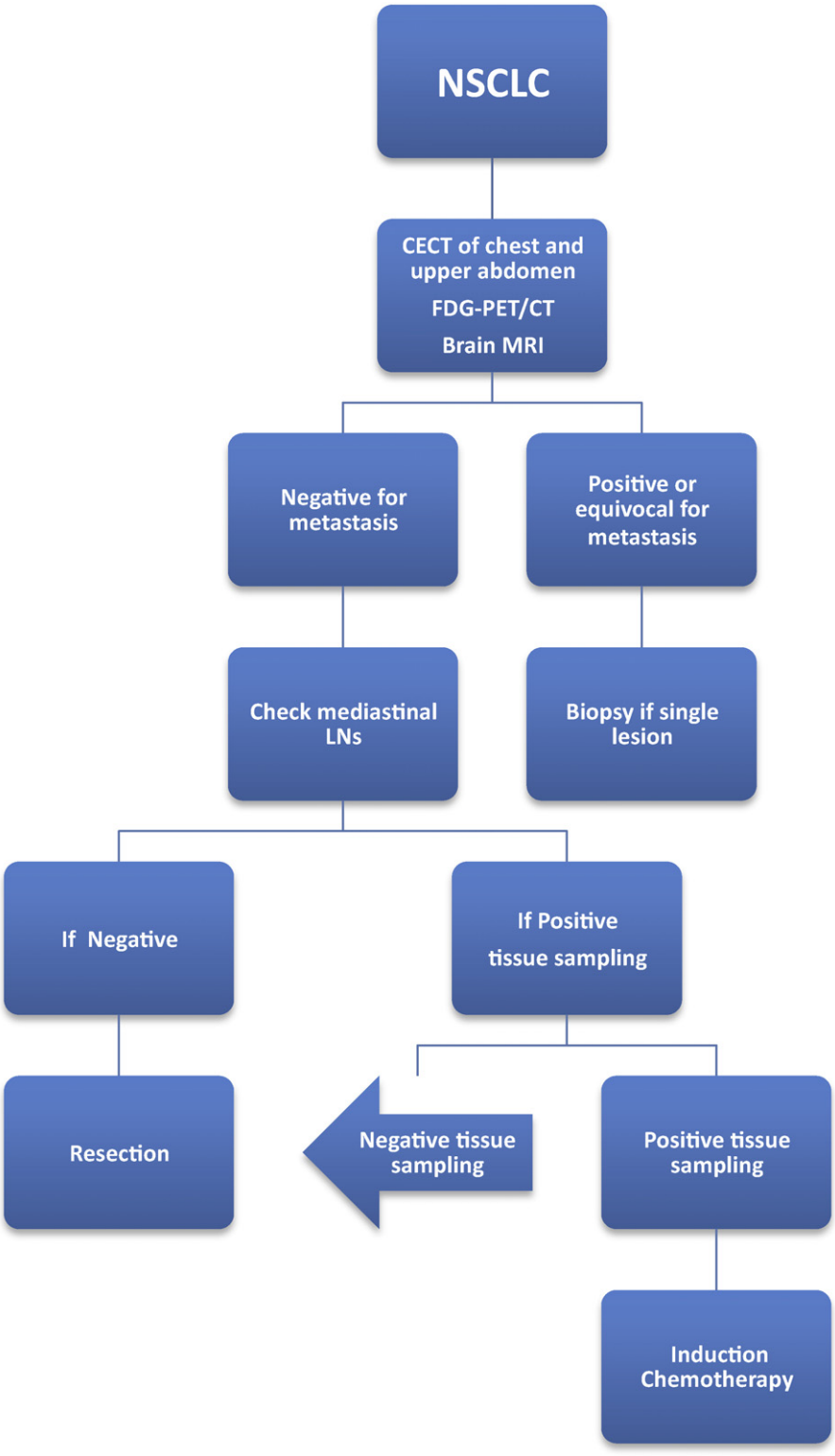

Figure 1 A proposed algorithm for staging of NSCLC.

Bone metastases are present in 30% of cases and bone scan is a part of the radiological work-up. Experience with FDG-PET in SCLC is limited though few studies demonstrated stage shift of up to 17% of cases [34]. Furthermore, new mediastinal lymph nodes detected by FDG-PET can modify radiotherapy planning in nearly 25% of patients [35].

According to recent NCCN recommendations, FDG-PET/CT can be used if limited stage is suspected.

Summary

Correct staging of lung cancer is essential for the selection of appropriate therapeutic plan and determination of patient's prognosis.

Contrast-enhanced CT (CECT) is the imaging modality of choice for the assessment of primary tumor and local extension with MRI reserved for the evaluation of superior sulcus tumors.

Mediastinal lymph nodes and distant metastases are best evaluated by FDG-PET/CT.

Despite advances in imaging techniques, preoperative sampling of lymph nodes or suspected distant metastases is frequently required in selected patients.

Modified NCCN guidelines for radiologic work-up of NSCLC (Fig. 1)

- All patients should receive CECT of the chest and upper abdomen covering the liver and the adrenal glands.
- FDG-PET/CT which can be replaced with whole-body MRI, if not available.
- MRI of the brain is recommended for stage IB (category 2B): The recommendation is based on lower level evidence and there is non-uniform NCCN consensus with no major disagreement.
- For stage IIIB: Thoracocentesis is recommended if pleural effusion is present, and if negative two times, thoracotomy should be performed to rule out malignant pleural effusion.
- Stage IV (solitary metastasis): FDG-PET/CT and brain MRI are recommended.
- Stage IV (disseminated disease): Work-up as clinically indicated.

Follow-up:

- CT scan of the chest every 4—6 months, then yearly CT scan of the chest.

Modified NCCN guidelines for radiologic work-up of SCLC

- CECT of the chest and abdomen covering the liver and the adrenal glands.
- MRI of the brain or alternatively CT if MRI is unavailable.
- FDG-PET/CT for limited stage disease.
- If FDG-PET/CT is unavailable, bone scan can be performed.

Follow-up:

- Chest imaging during each follow-up oncology visit: every 2—3 months during the first year, every 3—4 months at 2—3 years, every 4—6 months at 4—5 years, and then annually.

Conflict of interest

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Appendix A. Lung Cancer Guidelines Committee Members

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