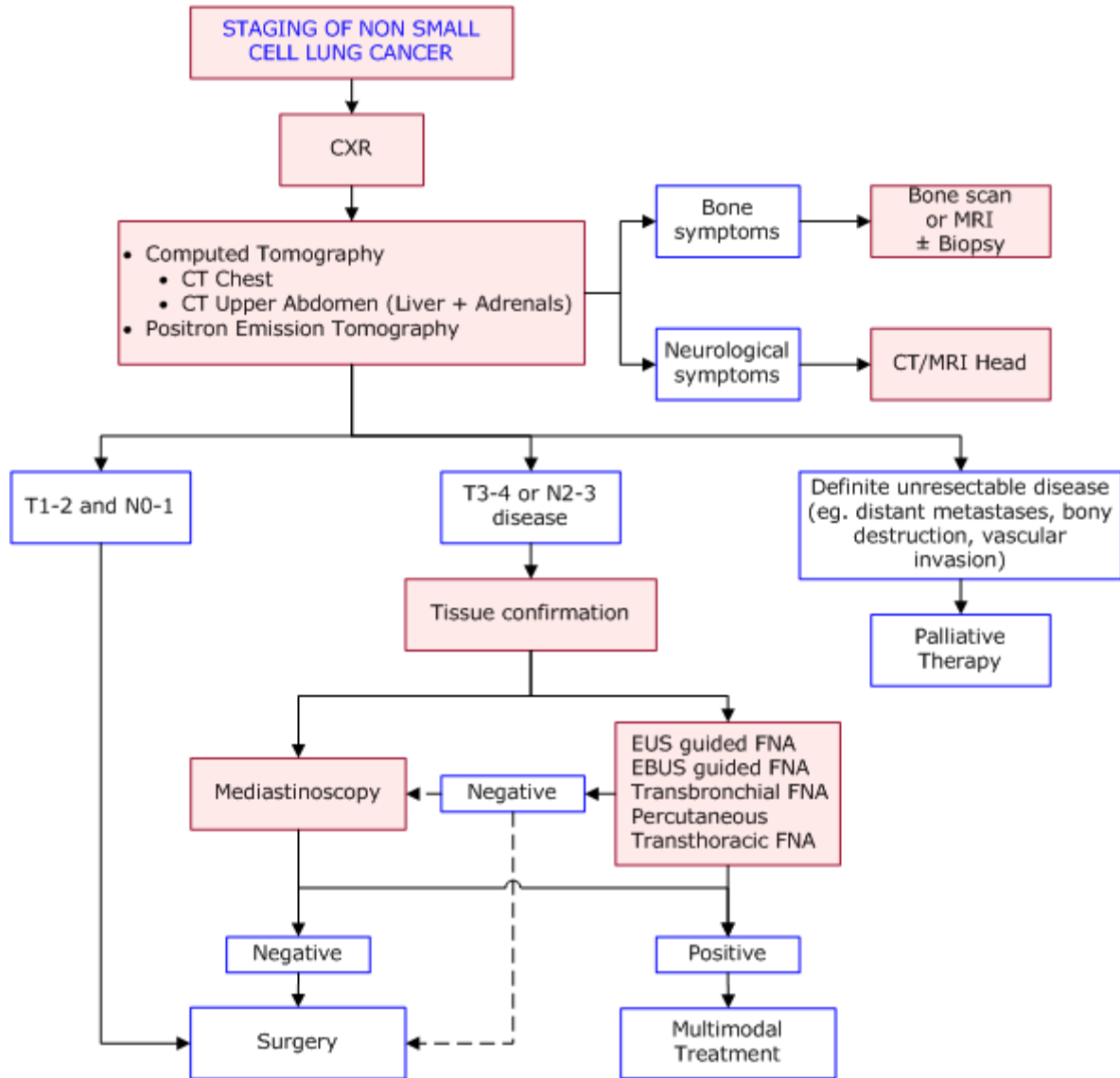




DIAGNOSTIC IMAGING PATHWAYS

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STAGING OF NON-SMALL CELL LUNG CANCER (NSCLC)



STAGING OF NON-SMALL CELL LUNG CANCER (NSCLC)

- Accurate staging is essential for therapeutic decision making and prognostic information. [1](#)
- TNM classification is the preferred system of staging. [1,2](#)
- Important to accurately differentiate stages I to IIIA (potentially resectable) from stage IIIB to IV (non-resectable) cancer. [2](#)

TNM STAGING OF NON-SMALL CELL LUNG CANCER [33](#)

Primary Tumour (T)	
Tx	Primary tumour cannot be assessed, tumour proven by the presence of malignant cells in sputum or bronchial but not visualised by imaging or bronchoscopy.
T0	No evidence of primary tumour.
Tis	Carcinoma in situ.
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura. No evidence of invasion proximal to the lobar bronchus.
T2	Tumour with any of the following features: <ul style="list-style-type: none"> • More than 3 cm in greatest dimension. • Involving the main bronchus, 2cm or more distal to the carina. • Invades the visceral pleura. • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T3	Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; or separate tumour nodules in the same lobe; or tumour with a malignant pleural effusion.
Regional Lymph Nodes (N)	
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumour.
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s).
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
Distant Metastasis (M)	
Mx	Distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis present (includes separate tumour nodule(s) in a different lobe - ipsilateral or contralateral).

STAGE GROUPING	T	N	M
O	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T1	N1	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T1-3	N2	M0
	T3	N2	M0
IIIB	T1-3	N3	M0
	T4	N0-3	M0
IV	T0-4	N0-3	M1

PLAIN CHEST RADIOGRAPHY

- Chest radiography is a readily available, inexpensive & low radiation dose modality that is useful for evaluating lung nodules or masses. It is routinely indicated in patients with lung cancer. [2](#)
- Limitations: lacks sensitivity in the detection of mediastinal lymph node metastases, and in chest wall and mediastinal invasion. [3](#)

COMPUTED TOMOGRAPHY

- CT is the initial investigation of choice in staging non-small cell lung cancer. [2](#)
- The usual CT protocol for NSCLC involves a CT chest with extension into the upper abdomen (adrenals). This allows for evaluation of the size and extent of the primary tumour as well as any metastatic spread to the mediastinum or upper abdomen (particularly liver, adrenal glands). [2](#) IV contrast may be administered to help distinguish vascular structures from centrally located tumours & lymph nodes. [55](#)
- Limitations:
 - Note that currently there is little evidence about the accuracy of modern MDCT for lung cancer staging, and the majority of evidence relates to single detector axial CT. [56](#)
 - CT has only moderate T staging accuracy. The sensitivity and specificity of CT for T3/T4 disease is 55% and 89% respectively. The positive predictive value (PPV) of CT for T3 or T4 disease is only 68% and as such, a positive result should be confirmed histologically before denying patients curative surgery (unless there is overt evidence of non-resectable disease such as bony destruction or vascular invasion). [34,35](#) Multiplanar reformats using MDCT can improve the accuracy, sensitivity & specificity for detecting local invasion.
 - CT has only moderate accuracy for mediastinal lymph node involvement with sensitivity of 51% and specificity of 86%. Despite this, CT provides good anatomic information and can guide the choice of lymph nodes for further invasive biopsy. [55](#)
 - CT has limited ability to evaluate superior sulcus tumours due to its axial format and streak artefacts from the shoulders. MRI may be of benefit in this circumstance. [11,12](#)
- More recently, CT has been integrated with PET (PET-CT) to provide combined functional & anatomical imaging in the same sitting. More information is found in the [section on PET](#).

POSITRON EMISSION TOMOGRAPHY

- PET utilises a radioactive glucose-analogue (18-FDG) to image tissues that preferentially uptake glucose. Non small cell lung cancer tumours have a very high affinity for glucose and readily take up 18-FDG.

- PET is able to accurately detect unsuspected distant metastases in 15% of surgical candidates and changes management in 25% of patients. [37, 42](#)
- PET is superior to other non-invasive modalities in differentiating resectable from non-resectable disease. [7, 35, 36](#)
- PET is indicated in all patients with non-small cell lung cancer unless CT scan unequivocally shows evidence of stage greater or equal to 3b disease. [37](#)
- Advantages:
 - Superior to CT for nodal staging of non-small cell lung cancer. [4,14,35,36 56](#)
 - Superior to CT and bone scan for detection of distant metastases, except for brain metastases. [4](#)
 - High negative predictive value (93%) for N2/3 disease allows thoracotomy to proceed without further invasive staging procedures, even in the presence of enlarged nodes on CT. [37,38,45](#)
 - Cost-effective in reducing the number of unnecessary thoracotomies. [4,18,19,37](#)
- Disadvantages: [4](#)
 - Relatively poor resolution to assess tumour size and determine invasion into adjacent tissues, such as chest wall, large vessels, or other features that define tumour status.
 - Low sensitivity for detection of brain metastases.
 - Moderate positive predictive value (79%) for diagnosis of mediastinal lymph node metastases, thus histological confirmation of PET positive nodes has been recommended [37, 38](#)
 - Limited availability and high expense.
- Some studies have shown that the negative predictive value of PET in nodal staging may be reduced in large (>15mm) nodes, in patients with central tumours and in patients with pure bronchoalveolar carcinomas. [39-41](#) These patients may require invasive lymph node staging following a negative PET scan to avoid unnecessary thoracotomy. [38](#)
- Integrated PET-CT systems are increasingly being used for cancer staging. The limited evidence so far indicates that PET-CT is as accurate or superior to PET alone. [43,44,56](#) PET-CT has a good sensitivity & specificity for nodal staging (84%, 89% respectively), and for staging distant metastases (93%, 96% respectively). Sensitivity for brain metastases is limited however (60%). [56](#)

CT ADRENAL GLANDS

- CT is the primary imaging modality for characterisation of adrenal masses. [20](#)
- While the majority of adrenal lesions are benign, the risk of malignancy increases with primary tumour stage & the size of the adrenal lesion. Lesions >5cm in size are likely to be malignant and these patients should be referred for surgery. [20-22](#)
- Unenhanced CT attenuation values are useful in distinguishing benign from malignant lesions: [23,24](#)

1. Lesions of <10 HU can be regarded, as benign (47% sensitivity and 100% specificity) and further work-up is not required. [22,25,26](#)
 2. Lesions with a density >20 HU are likely malignant and should be biopsied when the result influences management.
 3. CT indeterminate lesions (11-20 HU) can be further characterised by MRI, PET, PET-CT or by using CT washout criteria. Adrenal adenomas generally exhibit greater washout of contrast material than non-adenomas on contrast-enhanced CT. There is some debate about the "cutoff point" - one study used a value of 60% washout at 15 minutes, reporting a sensitivity and specificity of 88% and 96% respectively. [27](#)
- When the adrenal lesion is the sole potential site of metastatic disease, biopsy & histopathological confirmation should be sought. [56](#)

BONE SCAN

- Routine skeletal imaging is usually not indicated. [13](#)
- Some studies have indicated that bone scintigraphy following PET is of limited use as PET is more sensitive and specific in detecting bone metastases secondary to NSCLC. Some authors have recommended use of MRI when an abnormality on PET has been detected. [46-49](#)

CT/MRI HEAD

- Routine use of brain imaging in asymptomatic patients with NSCLC is not indicated. Clinical examination is useful for ruling out cerebral metastases with a negative predictive value of 94%. [8,35,37](#)
- Cerebral metastases are more commonly found in patients with adenocarcinoma or large cell tumours & patients with large primary tumours or N2 disease. In this group of patients, careful clinical examination is recommended. [37,55](#)
- CT may be the preferred initial investigation for cerebral metastases, but MRI has higher sensitivity. [56](#) Both CT and MRI are more effective than PET for assessing cerebral metastases due to high physiological glucose uptake in the brain. [46](#)

TISSUE CONFIRMATION OF CT/PET RESULTS

- Tissue confirmation is important to accurately diagnose & stage NSCLC. The histological subtype and other cellular characteristics can influence prognosis and affect the choice & aggressiveness of treatment. [56](#)

- Tissue sampling can be obtained surgically (e.g. mediastinoscopy) or non-surgically (e.g. using CT/US guidance, endoscopic ultrasound or endobronchial ultrasound). These procedures each have their own advantages & disadvantages, including the lymph node stations that they are able to sample. In general, the sampling target should be the lesion(s) that will establish the highest disease stage. Non-invasive imaging (e.g. CT, PET-CT) will help guide which lymph node stations should be sampled. [56](#)

ENDOSCOPIC ULTRASOUND GUIDED FINE NEEDLE ASPIRATE (EUS-FNA)

- EUS-FNA is a minimally invasive method of obtaining lymph node tissue for staging. It is performed under sedation and is less invasive compared to mediastinoscopy. [28](#)
- Accurate staging is important to identify patients who will benefit from surgical resection. Patients with N2 or N3 disease are not generally considered for curative surgery. Non-invasive investigations such as PET and CT are able to identify suspicious lymph nodes, but with moderate accuracy, and therefore further assessment is usually required. [29, 30](#)
- Pooled data from a recent meta-analysis of 18 studies, demonstrated that for lymph node staging of NSCLC, EUS-FNA had a sensitivity of 83%, specificity of 97%, positive predictive value of 98% and negative predictive value of 78%. [Micames 2007] The accuracy of EUS-FNA ranges from 85% to 97%. [28-32](#)
- The NPV of 78% means that a significant proportion of patients may be false negative. To avoid unnecessary thoracotomy, mediastinoscopy following a negative EUS-FNA has recommended by some. [38](#) More recently, endobronchial ultrasound guided transbronchial aspirate (EBUS-TBNA) has offered an alternative to mediastinoscopy, and when used together with EUS, almost all of the mediastinal lymph nodes can be sampled.
- EUS-FNA has been shown to be safe, with one meta-analysis showing only 10 minor complications in 1200 procedures. [Micames 2007] It is also cost effective in the work up of patients with NSCLC. [29](#)
- EUS-FNA is able to assess and biopsy lymph nodes in the lower mediastinum, which has traditionally been difficult to reach using mediastinoscopy. [29, 54](#)

ENDOBONCHIAL ULTRASOUND GUIDED TRANSBRONCHIAL NEEDLE ASPIRATE (EBUS-TBNA)

- EBUS-TBNA is a minimally invasive technique that allows lymph node tissue sampling and staging. It is performed under sedation and is less invasive than mediastinoscopy. [28](#)
- Accurate staging is important to identify patients who will benefit from surgical resection. Patients with N2 or N3 disease are not generally considered for curative surgery. Non-

invasive investigations such as PET and CT are able to identify suspicious lymph nodes, but with moderate accuracy, and therefore further assessment is usually required. [29,30](#)

- EBUS-TBNA is an alternative to mediastinoscopy, as both procedures can access the same mediastinal nodes. It is complimentary to EUS-FNA, and together almost all of the mediastinal lymph nodes can be sampled, with a reported sensitivity of 93%.
- A recent randomised controlled multicenter trial compared surgical (mediastinoscopy) staging alone to combined endosonographic (EUS & EBUS) and surgical staging. They found that the sensitivities of surgical staging alone, endosonographic staging alone and combined staging were 79%, 85% and 94% respectively. A combined approach also resulted in fewer unnecessary thoracotomies (surgical alone 21 vs combined 9). [Annema 2010]

MEDIASTINOSCOPY

- Mediastinoscopy is a surgical method of tissue sampling & is considered the gold standard procedure for staging the mediastinum. [56](#) It involves making an incision above the suprasternal notch to allow access to the mediastinum using an endoscope. It is more invasive than EUS and EBUS. [28](#)
- Accurate staging is important to identify patients who will benefit from surgical resection. Patients with N2 or N3 disease are not generally considered for curative surgery. Non-invasive investigations such as PET and CT are able to identify suspicious lymph nodes, but with moderate accuracy, and therefore further assessment is usually required. [29,30](#)
- Mediastinoscopy is generally associated with higher negative predictive values than EUS-FNA. To avoid unnecessary thoracotomy, mediastinoscopy following a negative EUS-FNA may be recommended. [38](#)
- Sampling of lymph nodes in the lower mediastinum may be more accurate with EUS-FNA. [29, 54](#)

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