Diagnosis, staging and treatment of patients with non-small cell lung cancer for the surgeon

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Abstract This article covers the risk factors, diagnostic tools, staging methods/modalities and treatment for patients with non-small cell lung cancer (NSCLC). Also presented is the new 7th edition American Joint Cancer Committee (AJCC) TNM classification for staging of NSCLC and a recommended treatment algorithm.

Keywords Lung cancer · Surgery · Treatment for NSCLC

Introduction

Lung cancer is currently the leading cause of cancer death worldwide, accounting for 1.2 million new cases annually. Surgical resection remains the main potentially curative therapy for patients with localised non-small cell lung cancer NSCLC. Lung cancer is divided into several histologic types. The most important distinction is between NSCLC which affects 80% and small cell lung cancer (SCLC) which affects the remaining 20% of patients. Sometimes patients are asymptomatic and a lung mass is discovered incidentally on a chest X-ray (CXR) being performed for reasons unrelated to pulmonary disease. However, other patients present with symptoms indicative of lung cancer. The clinical manifestations of lung cancer can be due to intrathoracic effects of the tumour (e.g. cough, haemoptysis, pleural disease), extrathoracic metastases (most commonly liver, bone, brain), or paraneoplastic phenomena (e.g. hypercalcemia, Cushing's syndrome, hypercoagulability disorders, various neurologic syndromes). In this review, we will address the aetiology, diagnosis, staging and treatment of NSCLC only.

Several risk factors have been associated with NSCLC. The primary risk factor for development is tobacco/cigarette smoking. Smoking has been attributed to 90% of all lung cancer cases [1]. A direct link between tobacco smoking and NSCLC was demonstrated based upon the finding that a specific metabolite of benzo(a)pyrene, a chemical constituent of tobacco smoke, damages three specific loci on the p53 tumour-suppressor gene that are known to be abnormal in approximately 60% of cases of primary NSCLC [2]. Other risk factors include environmental exposures such as second-hand smoke, asbestosis, radon, certain metals (nickel, arsenic, chromium), ionizing radiation, hard metal dust, vinyl chloride and polycyclic aromatic hydrocarbons.

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Pre-existing health conditions such as pulmonary fibrosis have also been associated with NSCLC [3]. There is also an increased incidence of NSCLC in patients with HIV and in patients with tuberculosis [4–7]. Genetic factors can also affect both the risk and prognosis of NSCLC. Although the genetic basis of lung cancer (including genetic markers) are still being elucidated, there is a clearly established familial risk. Many of these risk factors act synergistically with tobacco smoke to produce lung cancer, and are also independent risk factors in non-smokers as well.

Diagnostic tools

Chest X-ray is one of the most available and commonly used diagnostic tools. The standard CXR is useful in detecting some primary tumours especially if it is either a large peripheral tumour or a central obstructing lesion, however it is not sensitive. CXR will often miss small peripheral cancers and is considered a poorly sensitive test for cancer surveillance. CXR may show a pleural effusion, evidence of rib or vertebral body destruction or involvement of the phrenic nerve with elevation of the haemidiaphragm. CXR is inferior to CT in evaluating mediastinal nodal disease. When an abnormality is seen on a CXR and there is a high index of suspicion for cancer, the patient should be evaluated for cancer by additional tests such as computed tomography (CT) scan or an integrated positron emission tomography and computed tomography (PET/CT) scan. Although these tests do not provide histologic evidence of cancer they

often provide enough data that makes biopsy of the primary lesions unnecessary since excision biopsy will be required if there are no areas of suspicious metastatic disease. Biopsy can also be used but it is often falsely negative and thus a benign biopsy often is not helpful. It should not be assumed that a patient who has a new or enlarging lung nodule has tuberculosis, even with a positive skin test. In tuberculosis endemic countries, it is common for as many as 70% of patients to be treated as tuberculosis before being seen by the thoracic surgeon [8].

Other diagnostic tools to obtain tissue include bronchoscopy, transbronchial bronchoscopy, navigational bronchoscopy and diagnostic thoracoscopy (also referred to as video assisted thoracoscopic surgery). Electromagnetic (EM) guidance systems (navigational bronchoscopy) is a promising new technology that is superior to bronchoscopic or transthoracic needle biopsy. Based on earlier publications, biopsy yields could be improved to 75% with the EM technology even for abnormalities as small as 9 or 10 mm [9]. Fig. 1 shows a commonly used clinical staging algorithm. Fig. 2a shows the location of the mediastinal and hilar lymph nodes and Fig. 2b lists the common modalities used to sample the lymph nodes.

Clinical staging

The treatment of NSCLC is based on the stage of disease at the time of patient presentation and is based on staging tests (clinical staging). Staging of NSCLC (Table 1) utilises

Fig. 1 Staging/treatment algorithm
PFT = Pulmonary function tests, EKG = Electrocardiogram

the tumour, node and metastasis (TNM) system [10]. Fig. 2 shows a commonly used clinical staging algorithm. The most common non-invasive modalities for staging lung cancer is chest CT scan.

PET takes advantage of the high glucose metabolism of tumour cells. The sensitivity for the detection of NSCLC has been reported to be 95% range [11]. Some benign processes, including several types of infectious lesions can simulate cancer with this test. For this reason, biopsy is required to confirm the diagnosis. PET scanning can also be used to find spread of disease outside the chest (M1 disease). The technique of “fusing” or “integrating” CT with PET images has greatly enhanced the ability of doctors to detect and characterise the extent of disease. It is important to note that FDG-PET does not replace the need for tissue biopsies for N1 or N2 lymph nodes or for metastatic lesions. There are false positives and negatives in all lymph node stations. However, FDG-PET does result in better patient selection before pulmonary resection. In addition to the qualitative information gained from PET, also it provides quantitative information in the form of standardised uptake value (SUV) [12]. Several studies, including a meta-analysis, based upon 13 retrospective studies that included 1,474 patients with NSCLC, found that a high SUV was associated with a poor prognosis [13–15]. PET may also be useful in predicting response to chemotherapy as well as for detection of occult distant metastases (M1 disease). PET has been shown to be more efficacious for detection of NSCLC metastases to the liver and bone; however it is

not well suited to the detection of brain metastases due to high glucose uptake of normal surrounding brain tissue. A prospective study of 109 patients with NSCLC found that whole-body FDG-PET changed the metastatic (M) stage determined by conventional imaging in 14% of patients [16]. In other studies, a change in patient management was reported in 25–52% of patients who underwent PET, with upstaging being more frequent than down-staging due to the detection of M1 disease [17, 18]. Integrated PET/CT may be better than PET or CT alone in detecting M1 disease. In a retrospective study of 217 patients with lung cancer who underwent integrated PET/CT, 41 presumed malignant extrathoracic lesions were identified [19]. The sensitivity, specificity, positive predictive value, and negative predictive value of integrated PET/CT for detecting presumed malignant extrathoracic lesions was 98, 92, 89 and 98%, respectively. These values were better than those obtained by PET alone (98, 22, 75, and 89, respectively) and CT alone (98, 18, 71 and 89, respectively) [20].

In general, PET and CT provide targets for biopsy. If either test suggests that N2 nodes are involved with metastatic disease they should be biopsied via several different methods such as mediastinoscopy, VATS, endoscopic ultrasound with fine needle aspiration (EUS-FNA), or endoscopic bronchial ultrasound (EBUS). The techniques chosen depend on the availability for the different tests and the location of the suspicious N2 lymph node (Fig. 2b). Invasive staging allows the physician to obtain tissue and subsequently confirmation of disease; additionally it may now permit selection of chemotherapeutic agents to which the tumour is most responsive by way of drug resistance assays.

Magnetic resonance imaging (MRI) may also be used in patients who have had previous adverse reactions to iodine contrast media and in patients with significant renal impairment. MRI is superior to CT in assessing the invasion of the pericardium, heart and great vessels. Coronal images are useful in demonstrating the extent of tumour in the subcarinal region, aortopulmonary window, and superior vena cava. However, it is limited by poorer spatial resolution, as compared with that of CT, and by cardiac and respiratory

Fig. 2a Location of the lymph nodes – Hilar (N1) nodes are #10–14 and mediastinal (N2) nodes are #2, 4, 5, 6, 7, 8, 9 as shown in this picture. Location of nodes by station number: 1 – Highest mediastinal; 2R, 2L – upper paratracheal; 4R, 4L – lower paratracheal; 5, 6 – aortopulmonary window; 7 – subcarinal; 8 – paraesophageal; 9 – pulmonary ligament; 10 – Hilar; 11 – Interlobar, 12 – Lobar; 13 – Segmental; 14 – Subsegmental lymph nodes.

Procedure (LN sampled)	Lymph node stations that can be sampled
Mediastinoscopy	2R/2L, 4R/4L, 7 (superior portion)
EUS-FNA	5, 6, 7, 8
EBUS	2, 4, 5, 7, 10–13
VATS, left sided	5, 6
Thoracotomy	All

Fig. 2b Location of target lymph node station determines the best modality to sample the lymph nodes

motion artifacts. In addition to evaluation of a pulmonary nodule and of mediastinal lymph nodes, MRI is invaluable for the assessment of bone metastases, invasion of the great vessels and of the brachial plexus for patients with Pancoast tumours.

The detection of distant metastases (M1 disease) contraindicates curative surgical resection in most patients. In patients with clinical or biochemical evidence of disease elsewhere, targeted imaging of those sites is performed. These sites include the brain, which can be examined with MRI, and the skeleton, which can be examined with bone scans and MRI. Brain MRI is superior to brain CT. Usually, these tests are not ordered in asymptomatic patients with NSCLC. Technetium-99m (^{99m}Tc) radionuclide bone scanning is indicated in patients with bone pain or local tenderness. The test has a 95% sensitivity for the detection of metastases but a high false positive rate because of degenerative disease and trauma [21].

Assessing risk of resection

While a patient with lung cancer may be “resectable” by virtue of having a surgically removable lesion and no evidence of N2 or M1 disease, he may not be an operative candidate due to poor pulmonary function or comorbidities. Suggested tests to evaluate suitability for resection include measurement of preoperative pulmonary function and calculation of predicted postoperative (postresectional or commonly called “ppo”) pulmonary function. The most important tests are the forced expiratory volume in 1 second percent predicted value ($\text{FEV}_1\%$) and the diffusing capacity of the lung for carbon monoxide percent predicted value ($\text{DLCO}\%$). The FEV_1 and DLCO are commonly used values for preoperative assessment. Studies have reported that when postoperative predicted (ppo) $\text{FEV}_1\%$ and the ppo $\text{DLCO}\%$ are $<40\%$ the patient is at significantly increased risk of morbidity [22].

Guidelines from the American College of Chest Physicians consider a patient to be at increased risk for lung resection with ppo values for either $\text{FEV}_1\%$ or DLCO $<40\%$ predicted [23]. Preoperative exercise testing is recommended for patients with either of these criteria to assess their surgical risk. Patients with a predicted postoperative $\text{FEV}_1\%$ <30 predicted or a value $<1,650$ for the product of predicted pop FEV_1 and predicted pop DLCO (each expressed as percent predicted) are particularly singled out for their risk of perioperative death and cardiopulmonary complications; they should be counseled about non-standard surgical options and non-operative treatment modalities in preference to standard lung resection.

Treatment

Comments for treatment are reserved only for patients who have early stage lung cancer and who do not benefit

from preoperative chemotherapy or chemoradiotherapy. Although surgical resection is the preferred approach for patients with early stage NSCLC, stereotactic body radiotherapy (SBRT), external beam radiotherapy (EBRT) and radiofrequency ablation (RFA) are used in patients who are not candidates for surgery. Previous experience with conventional EBRT showed that control of the primary lesion is directly related to the dose of radiation, suggesting that higher doses might offer better local control. SBRT has been extensively evaluated in patients with early stage primary NSCLC. SBRT dosing is influenced by a number of parameters, including the size of the tumour and the number of fractions. The potential role of SBRT in early stage lung cancer has been illustrated by two large series of medically inoperable patients with stage I NSCLC [24, 25] RFA involves placement of an electrode into a specific location to cause focal tissue destruction with thermal energy. Tissue heating is achieved through the generation of heat by an alternating electric current in the frequency of radio waves (460–500 kHz). In a study by Lee et al. in 2004, in 30 patients treated for palliation of symptoms, RFA alleviated mild haemoptysis in 80%, but was effective in treating chest pain, dyspnoea, or cough in only about one-third of cases [26].

Surgery

Surgical resection remains the optimal management of patients with NSCLC. The goals of surgery are to remove the entire tumour, remove all of the N2 lymph nodes and ensure there are no other nodules in the parts of the lung that are not removed. Lobectomy remains the standard of care in medically fit patients; however segmentectomy can be utilised in patients with poor pulmonary function or in isolated carefully selected patients with small tumours <2.0 cm. Although pneumonectomy is a viable options for patients with lung cancer it should only be performed when a sleeve resection of the bronchus and/or of the pulmonary artery is not able to achieve complete resection. Furthermore, pneumonectomy should only be performed in patients with acceptable pop $\text{FEV}_1\%$ and $\text{DLCO}\%$ and should always be the last type of pulmonary resection offered.

New ways to open and close the chest have been developed that blur some of the perceived advantage of VATS lobectomy. This techniques involved a rib and nerve sparing thoracotomy. [27–29] In addition, new post-operative techniques that avoid the surgical intensive care unit (SICU) entirely for most of patients and that apply water seal instead of suction of chest tubes allow patients to leave the hospital after 3–4 day hospital stay after surgery. It has been shown that chest tubes can be removed when the drainage is 450 cc/day or less and the more traditional numbers of 150 or 200 cc are not needed and unnecessarily delay discharge [30].

Table 1 Seventh edition TNM staging of NSCLC [9]

Tumour (T) - Stage					
T1 - Tumour ≤ 3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus					
T1a - Tumour ≤ 2 cm in diameter					
T1b - Tumour > 2 cm but ≤ 3 cm in diameter					
T2 - Tumour > 3 cm but ≤ 7 cm, or tumour with any of the following features:					
Involves main bronchus, ≥ 2 cm distal to carina					
Invades visceral pleura					
Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung					
T2a- Tumour > 3 cm but ≤ 5 cm					
T2b- Tumour > 5 cm but ≤ 7 cm					
T3- Tumour > 7 cm or any of the following:					
invades: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus < 2 cm from carina (without involvement of carina)					
Atelectasis or obstructive pneumonitis of the entire lung					
Separate tumour nodules in the same lobe					
T4- Tumour of any size that invades the media stinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodules in a different ipsilateral lobe					
Regional lymph nodes (N)					
N0- No regional lymph node metastases					
N1- Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension					
N2- Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)					
N3 - Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).					
Distant metastasis (M)					
M0- No distant metastasis					
M1a- Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion					
M1b- Distant metastasis					

Table 2 Authors stage groupings and recommended treatment

Stage	T	N	M		
IA	T1a-T1b	N0	M0	R0 resection	No adjuvant treatment
IB	T2a	N0	M0	R0 resection	If T ≥ 4 cm or if N1 disease adjuvant chemotherapy
	T1a	N1			
IIA	T2b	N0	M0	R0 resection	Adjuvant treatment (chemotherapy)
	T2a	N1			
IIB	T2b	N1	M0	R0 resection	Adjuvant therapy (chemotherapy)
IIIA	T3,	N1,	M0	Surgery for T3N1	Adjuvant therapy (chemoradiation)
	T1-3,	N2,		Neoadjuvant chemotherapy and surgery for T1-3 N2	
	T4	N0, N1		Chemoradiation for T4 N0, N1 (surgery in rare situations)	
IIIB	T4,	N2,	M0	No resection, refer to oncologist	Adjuvant therapy (chemoradiation)
	T1a, T4	N3			
IV	Any T	Any N	M1a or M1b	No resection usually, refer to oncologist	Palliative chemotherapy Palliative radiation for bone/brain metastases

Adjuvant treatment

Patients with stage IB tumours, T status >4 cm, those with stage II disease, from N1 nodes or those with unsuspected N2 disease (stage IIIA) NSCLC are at substantial risk for recurrence and death even after complete surgical resection. As many as half of patients with stage IB, 70% of stage II and a greater percentage of those with stage IIIA NSCLC eventually recur and die of their disease despite potentially curative surgery. The development of active platinum-based combinations and the completion of large clinical trials assessing the activity of adjuvant chemotherapy for resected NSCLC has led to a recognition of the role of adjuvant therapy in improving the disease-free and overall survival outcome in patients with completely resected NSCLC.

The improved survival with adjuvant chemotherapy using modern drug regimens was confirmed in a meta-analysis that combined individual patient data from the four largest trials, all of which used cisplatin-based chemotherapy: JBR10 [31], IALT [32], European Big Lung Trial [33] and the Adjuvant Lung Project Italy (ALPI) [34–36]. Some adjuvant treatments are based on molecular marker status. Molecular markers may provide additional information about the likelihood of relapse beyond that obtained from pathologic staging. Approaches and specific markers under study include gene expression profiling, ERCC 1 gene (protein-coding) expression, abnormalities in the k-ras oncogene and p53 tumour suppressor gene, and DNA methylation markers. Additional studies will be required to determine whether these markers are useful in selecting patients for adjuvant platinum-based chemotherapy. An international randomised clinical trial (RADIANT) evaluating the effect of Tarceva on the recurrence and overall survival in patients with resected NSCLC and who are epidermal growth factor receptor (EGFR) positive (by either fluorescence *in situ* hybridisation or immunohistochemistry) is currently underway. A summary of treatment recommendations for various stages of NSCLC is given in (Table 2).

Follow-up and recurrence

Patients who undergo a complete (R0) resection for NSCLC are at risk for recurrent NSCLC and/or metastatic disease. Therefore we recommend follow up clinic appointments with the surgeon or oncologist that includes a physical examination and chest CT scan every 6 months for the first 2 years after resection and then yearly thereafter. Additionally, prior to discharge patients should be educated on signs of recurrence such as weight loss, haemoptysis, increased dyspnoea, return of their initial symptoms, as well as counseled for smoking cessation.

Multiple factors influence survival following disease recurrence. A few of these factors include tumour

histology, degree of differentiation, presence or absence of lymphovascular invasion, receptor status. In a series of 1,073 patients who underwent a complete resection, recurrent NSCLC was identified in 445 patients (41%) [37]. The median time for recurrence following surgery was 11.5 months, and the median survival following recurrence was 8.1 months. Multivariate analysis identified poor performance status, disease-free interval of 1 year or less, prior use of neoadjuvant chemotherapy or adjuvant radiation therapy, and distant metastases (as opposed to intrathoracic recurrence alone) as predictors of a shorter disease-free survival.

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