Review Article



# Hilar tumours—how to predict the need for an extended resection from preoperative investigations

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**Abstract:** The aim of this article is to review the evidence and clinical implications of preoperative investigations in assessing hilar tumours. All current available paraclinical investigations, invasive and non-invasive, were analysed in order to establish the predictability of a more extended resection. We concluded the following: it is difficult to exclude the possibility of an extended resection from the current investigations without exploratory thoracotomy.

**Keywords:** Hilar tumours; lung cancer; extended resections; exploratory thoracotomy

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## Introduction

Lung cancer is the leading cause of cancer worldwide, with more than 1.8 million new cases diagnosed each year (1,2). Overall survival for clinical stage IIIB non-small cell lung cancer remains, disappointingly, at 26% in 5 years (3). Correct clinical staging, although challenging, defines the extent of the disease, determines treatment and impacts survival. Thus, it is essential to distinguish between operable and non-operable patients.

Surgical resection offers the best chance for curative treatment for early-stage and selected cases of locally advanced lung cancer (4,5).

Unfortunately, the majority of patients are diagnosed with an advanced disease at presentation. Surgical management can still be offered in selected cases of locally advanced disease.

Hilar or centrally located lung tumours display as a heterogeneous group, which includes T2, T3 and T4 status (*Figures 1* and *2*). According to the 8$^{th}$ edition of UICC TNM classification for lung cancer (6), in T2 there is involvement of the main bronchus without carinal involvement, regardless of the distance from the carina. In T3, the pericardium or phrenic nerve are involved and in T4 mediastinum structures like superior vena cava (SVC), recurrent laryngeal nerve, carina, trachea or spine are involved. The stage of the disease can be anywhere between IB and IIIB.

In this review article, the majority of the references use the 7$^{th}$ edition of UICC TNM classification for lung cancer.

When surgical management results in the total removal of a tumour with microscopically clear margins and N0–N1 disease, the prognosis is favourable.

It is of utmost importance therefore, to accurately stage hilar tumours to avoid understaging or overstaging, and to ensure a successful outcome.

## Extended resections

Extended resection of hilar lung cancer includes carinal, bronchial and vascular sleeve resections, resection and reconstruction of the SVC and in rare cases resection of the atrial wall and aortic wall (7,8). Mediastinal nodal metastasis (N2) should be excluded (9) but extended resections can be considered after induction chemoradiotherapy (10).

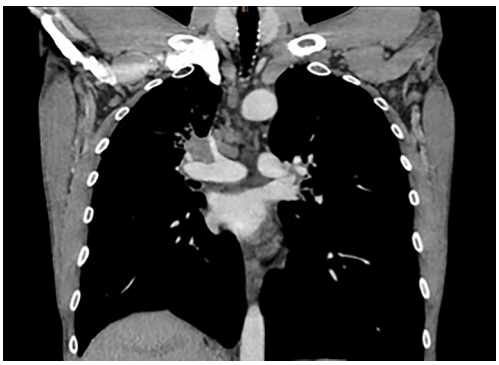

**Figure 1** Centrally located tumour, coronal view.

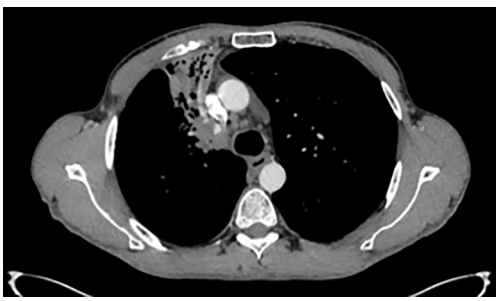

**Figure 2** Centrally located tumour, axial view.

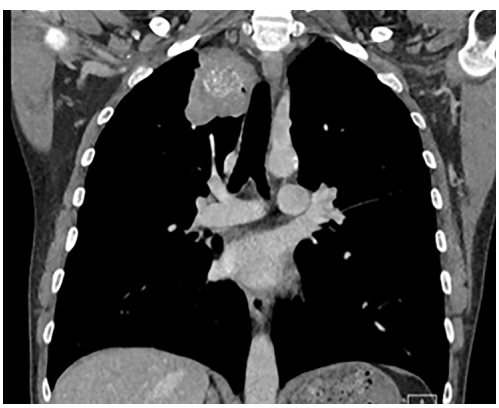

**Figure 3** Tumour close to the SVC, coronal view. SVC, superior vena cava.

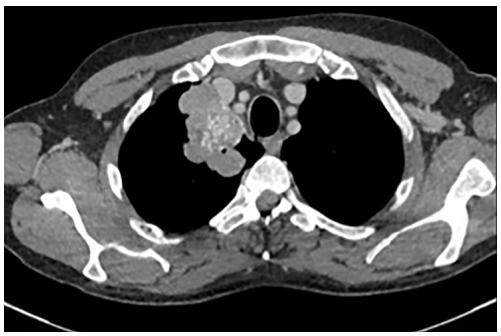

**Figure 4** Tumour close to the SVC, axial view. SVC, superior vena cava.

## Investigations

Surgical resection continues to provide the highest chance for cure for non-small cell lung cancer (11) but many diagnosed with clinical stage T4 may be regarded as non-surgical candidates and thus not offered surgery. Staging to define resectability is challenging, as well as crucial in patients presenting with centrally located disease. Muehling *et al.* (12) retrospectively studied patients who underwent lung resection for stage IIIA, either clinically or pathologically. The staging for T, N and UICC stage was confirmed to be correct in 38.7%, 40.8% and 36.7% of the cases respectively. Sensitivity was 28.5%, specificity was 80.9%, positive predictive value (PPV) was 20%, and negative predictive value (NPV) was 87.1%. The accuracy of clinical staging in T4 tumours can be lower or clinically overstaged to as high as 40%.

Preoperative investigations include the following techniques: computed tomography (CT), integrated positron emission tomography-CT (PET-CT), bronchoscopy with fine-needle aspiration (FNA), endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and invasive mediastinal staging.

## Radiological investigations

### *CT*

CT of the chest, neck and upper abdomen with intravenous contrast is best for defining invasion of main bronchus, artery, SVC or aorta (*Figures 3* and *4*). It can help determine whether a sleeve resection might be needed (13). When the chest CT is combined with angiography and venography, the vessels can be more precisely delineated, as it has been shown when investigating suspected pulmonary embolism (14). Contrast-enhanced multidetector row computed tomography (CE-MDCT) has been investigated extensively in evaluating tumour invasion of pulmonary vasculature and depicting anomalies of pulmonary arteries and veins with high sensitivity and specificity (15,16).

However, there is limited ability to assess tumour

invasion to adjacent structures. According to Herman *et al.* (17), there are three criteria for diagnosing vascular invasion on CT: the disappearance of the fat layer, the angle of tumour contact >90, and stenosis and deformation of the vascular lumen. Munden *et al.* (18) advocated that the diagnosis of vascular and mediastinal tumour invasion based on the CT was of limited use. They reported the sensitivity, specificity, and accuracy of CT imaging for confirming invasion into the mediastinum to be 40–84%, 57–94%, and 56–89%, respectively. Accurate preoperative assessment of the T status may not always be satisfactory as shown in the papers below. Cangemi *et al.* (19) showed a sensitivity, specificity and accuracy of 84.6%, 68.4%, 79.3% for T2; of 66.6%, 95.9%, 91.3% for T3 and of 50.0%, 94.4%, 91.3% for T4 status with CT scan. Gdeedo *et al.* (20) suggested that mediastinal structures involvement (T4) could not be reliably detected by CT scan in about 50% of the patients. Cetinkaya *et al.* (21) found that centrally located tumours were correctly staged in 62% of the cases. More recently, Oka *et al.* (22), on investigating patients in whom pulmonary artery, pulmonary vein or left atrium (LA) invasion was suspected on preoperative CT findings, discovered that the PPV of the CT for tumour invasion to thoracic vessels was ranging from 20% to 36%. They advocate that surgery should still be offered to patients whose tumours are located near the major thoracic vessels on preoperative CT. According to other studies (18,23), sensitivity and specificity vary from 40% to 84% and from 57% to 94%, respectively. Spaggieri *et al.* (24) considered that if more than 50% of the diameter of the aorta is involved on the CT scan, then it is completely infiltrated by the tumour, whereas if it is less than 50%, the tumour is attached, but not involving the aorta.

### *PET-CT*

PET-CT (25,26) which is included in the guidelines for lung cancer staging (27), does not offer much information in delineating mediastinal organ invasion (T4 status) due to its poor spatial and anatomical resolution. Uptake in the primary tumour will merge with that in the adjacent hilar and mediastinal nodes. Nevertheless, it is very useful in the assessment of lymph nodes and in detecting mediastinal nodal involvement, as well as identifying metastatic disease (23). It can also provide an indication of the tumour's metabolic activity.

### *Magnetic resonance imaging (MRI)*

MRI (28), which has the advantage of no radiation, may be useful to assess great vessel and vertebral body involvement. However, it has a low specificity and accuracy (29), at 33% and 46% respectively. Magnetic resonance angiography (MRA) has been reported to adequately delineate thoracic vessels invasion by tumour (30) and can be comparable to CT. Unenhanced MRA has the benefit of not using contrast media. Cine MRI (31) has been reported to be accurate in determining aortic invasion using a gap between cardiac motion and respiratory movements. Respiratory dynamic (RD) MRI (32) can give additional information when CT scan or conventional MRI is equivocal in determining aortic invasion by cancer, this applies especially to descending thoracic aorta. Cardiac MRI (24,33,34) can provide information regarding tumour borders and can be useful in assessing LA invasion by a tumour.

## Pulmonology investigations

### *Bronchoscopy*

Fiberoptic bronchoscopy is a standard investigation to assess central bronchial invasion. Apart from being the recommended investigation to obtain a pathological sample in centrally located tumours (2) (ESMO guidelines class III, A), it can determine the proximal and distal extent of a tumour and whether complete resection with airway reconstruction is feasible, thus predicting the need for a sleeve or carinal resection. It can also assess the extent of pulmonary resection. The sensitivity for analysing the primary tumour is about 88% (28). The combined use of narrow-band imaging bronchoscopy (35) or autofluorescence (36) bronchoscopy and conventional white-light examination has been found to have greater sensitivity and specificity for assessing tumour margins, which are really important when assessing central lung tumours and a therapeutic strategy. This technique also significantly improves the assessment of central lung cancer infiltration and influences the therapeutic strategy.

### *Endoluminal ultrasound (EBUS)*

EBUS (37) and EUS with fine needle aspiration have mostly been investigated in the assessment of mediastinal lymph nodes (27,38). There are only a few studies investigating their role in diagnosing and assessing intrapulmonary lung

 

lesions (38,39).

EBUS can localize lesions close to the airway and may be useful in assessing extra-bronchial invasion. Surrounding structures and vessels can also be identified safely. It has been shown to be effective in diagnosing centrally located lung lesions close to the major airways (40) with a sensitivity and NPV for centrally located lung lesions not visible at bronchoscopy at 82% and 23% (41) respectively.

EUS provides excellent access to the posterior mediastinum through the oesophageal wall (42). It may be useful to assess suspected oesophageal invasion by a lung tumour, especially when the lesion cannot be accessed by standard flexible bronchoscopy (39,43,44). When a lung lesion is adjacent to or abutting the oesophagus, invasion of the mediastinum by a tumour is shown as loss of interface between the tumour and the mediastinum with an irregular border. The relationship of the tumour to centrally located vessels can also be demonstrated. Vascular invasion can be defined as interruption of the intimal layer of a great vessel or evidence of tumour encroachment into the vessel or LA (45). When investigating mediastinal invasion by lung cancer, EUS was found to have a sensitivity of 87.5%, a specificity of 98%, a PPV of 70%, and an NPV of 99% (46).

But predicting mediastinal invasion by irregular loss of interface between the mediastinum and the tumour can be highly inaccurate, thus resulting in overstaging. In the paper by Vazquez-Sequieros *et al.* (47), when the lung mass was visualised, the sensitivity of EUS was 96.7%, but it dropped to 80% when the non-visualized masses were included. In the study by Annema *et al.* (48), EUS-FNA established the diagnosis of lung cancer in 97% of the patients with a tumour near or adjacent to the oesophagus. Furthermore, it demonstrated tumour invasion in 39% of the patients. However, this was not verified during surgery. The combination of EUS and CT had high specificity, PPV and NPV. Kuijvenhoven *et al.* (45) found that the specificity and PPV of EUS for diagnosing mediastinal and great vessel invasion were 95% and 73% respectively, compared to 61% and 41% on chest CT findings.

EUS-FNA and EBUS-TBNA appear to be complementary investigations. A combined approach with both EUS-FNA and EBUS-TBNA may be able to replace more invasive methods for evaluating unclear hilar or mediastinal lesions (49) with serious and minor adverse events in the area of only 0.14–0.2% and 0.22%, respectively (50).

Direct invasion to the oesophagus is much less common than metastasis via subcarinal and para-oesophageal lymph nodes. When oesophageal resection is suspected, preoperative fiberoptic endoscopy with mucosal assessment is required. When there is limited muscular wall involvement, enucleation might be considered. However, experience with this type of tumours is limited and prognosis is considered to be poor mainly due to extensive disease which makes R0 resection a particular challenge (33).

### *Echocardiography*

Either transthoracic or trans-oesophageal (TOE), it can be used to assess atrial tumour invasion (51,52), thrombus formation, SVC and midline great vessels. TOE (53) can be useful when invasion of the thoracic aorta is equivocal on the CT scan with a diagnostic accuracy of 90%.

## Surgical investigations

### *Rigid bronchoscopy*

It is useful when rigid bronchoscopy is performed by the operating surgeon, close to the time of the planned resection, to accurately plan the extent of the resection (28). The planned proximal and distal resection margins can be confirmed and an impression of the mobility of the airway can give an indication of the likely resectability.

### *Mediastinoscopy*

Whilst widely used for mediastinal lymph node staging, mediastinoscopy can also assess extrabronchial invasion around the carina and the tracheobronchial angle (54). It allows for a direct examination of the proximal extent of the tumour, as well as for ruling out N2 disease. It can therefore determine resectability and also mobilize the tissue planes around the area and facilitate airway reconstruction. Ideally, it should be performed close to or on the same day with the definitive operation to prevent postoperative paratracheal scarring that may render bronchoplastic or tracheoplastic procedures more challenging. However, one must be aware of the danger of a potential false-positive finding when a biopsy of a centrally-located tumour may be falsely thought to be N2 nodal disease (28).

### *Video assisted thoracoscopy surgery (VATS)*

VATS (11), despite its widespread use, is not easy to directly assess central vascular invasion. It may have some use

 

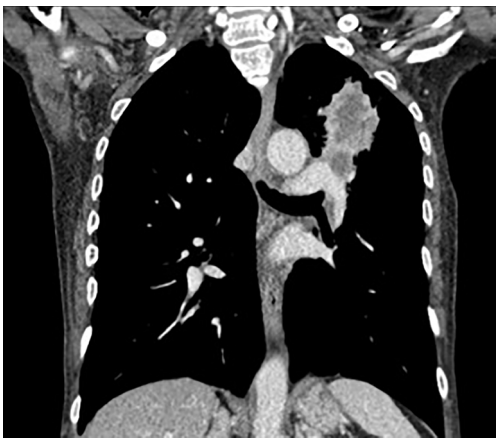

**Figure 5** Tumour close to the aortic arch and the pulmonary artery, coronal view.

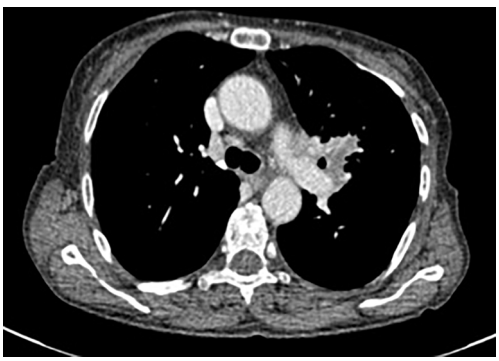

**Figure 6** Tumour close to the aortic arch and the pulmonary artery, axial view.

for left-sided lung tumours to assess the aortopulmonary window and the aortic wall. It may also diagnose lymphangiosis carcinomatosa in the mediastinum. It is more useful in assessing pleural effusion and lymph node involvement. It can assess mediastinal pleural invasion and resectability (44).

Flexible videopericardioscopy (FVP) (55) has been described to assess intrapericardial, cardiac and proximal vascular invasion; superior and inferior pulmonary veins and main pulmonary arteries can be assessed bilaterally. This may help to determine resectability of a centrally located lung tumour.

### *Thoracotomy*

A limited anterior thoracotomy or mediastinotomy can be performed through the 2nd right intercostal space or the 3rd left intercostal space (Chamberlain procedure) (11) where it is useful to assess invasion of the aorto-pulmonary window. A combination of direct visual inspection and digital palpation can directly assess whether the mass is separable from mediastinal structures. This gives extra information to VATS and is preferable for assessment of SVC invasion.

Exploratory thoracotomy (33) is the ultimate and final assessment. Although the role of exploratory thoracotomy in locally advanced non-small cell lung cancer is still a matter of debate, many surgeons believe that definitive surgical decision can be oriented only by direct palpation and accurate dissection. Trial dissection with proximal vascular control first must be performed in cases of doubt. Sometimes, pulmonary vascular sleeve resection may be required when the pulmonary artery is invaded by the tumour and can often only be assessed after trial dissection intraoperatively (13). For hilar tumours which are centrally located in the main bronchus close to the carina, bronchial sleeve may not become apparent until division of lobar vein and arteries is performed, especially if needed for hilar nodal invasion of the bronchus. When pericardium is involved, en bloc resection of the pericardium with the tumour is usually feasible. However, it is necessary to send a sample of the pericardial fluid for cytology and if is it proven to be malignant, then resection must be abandoned (4). Atrial resection requires opening of the pericardium (5) and intraoperative intrapericardial assessment to determine resectability (33) by trial clamping the LA and observing the cardiovascular consequences of the reduced atrial volume (5), prior to the en bloc removal of the tumour. Aortic invasion by lung tumours has more often been encountered on the left side, mostly with upper lobe tumours involving the descending aorta (8). The decision to operate can be based on preoperative investigations, but the ability to perform aortic resection requires intraoperative dissection of the aortic adventitia before withdrawing from lung resection (*Figures 5* and *6*). Sixty percent of the tumours that have been resected involved the aortic adventitia. Full-thickness aortic invasion or intrapleural spreading are contraindications for resection. If only the adventitia is involved and a dissection plane within the aortic wall can be developed, subadventitial dissection and direct closure can be performed.

Exploratory thoracotomy rates have decreased over the years (56) as a result of improved imaging but may still reach 25% of the patients who were deemed candidates for

 

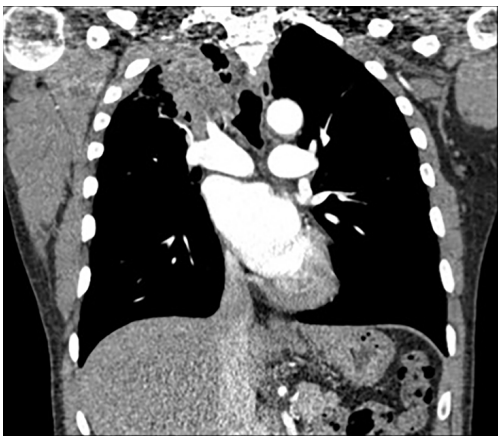

**Figure 7** Oesophageal invasion found in exploratory thoracotomy, coronal view.

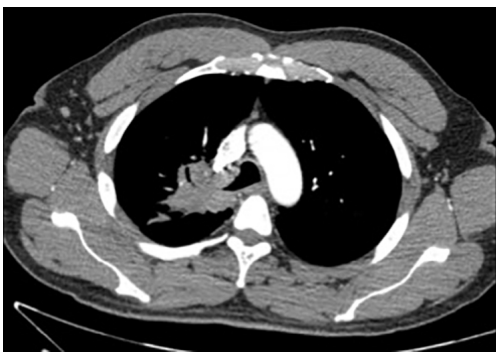

**Figure 8** Oesophageal invasion found in exploratory thoracotomy, axial view.

extended resection (24) (*Figures* 7 and *8*).

### *Intraoperative frozen section analysis*

Intraoperative frozen section analysis of the resection margin may be the final investigation used to determine whether an extended resection is necessary.

In a minority, the need for bronchial sleeve resection may not become apparent until intraoperative frozen section analysis of resection margin is performed. Sleeve resection allows more proximal division of the main bronchus, thus providing a better proximal margin. Tracheal reconstruction, similarly, may not be indicated until the intraoperative frozen section analysis of the proximal bronchial resection margin has been found to be positive. If this is the case, sleeve pneumonectomy or tracheo-carinal resection without lung resection may be required (57).

## Conclusions

The objective of extended resection of a hilar tumour is a complete R0 resection in the absence of N2 disease. Unfortunately, the accuracy of clinical staging in central and locally advanced disease, despite the use of various preoperative invasive and non-invasive methods, has been found to be suboptimal. It is difficult to exclude the possibility of an extended resection without exploratory thoracotomy which is generally a safe procedure (58,59). Whilst it is suggested that the frequency of ET should be 1% or less (56), an open-and-close rate closer to 1 in 30 may be more realistic to maximize the overall resection rate. A "zero exploratory thoracotomy rate" relying entirely on preoperative imaging or non-invasive procedures will mean that patients with otherwise resectable tumours will forego the opportunity.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



 

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