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The role of imaging in screening, diagnosis and staging of Non-Small Cell Lung Cancer (NSCLC)

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Abstract

Imaging plays a vital role in the management of NSCLC including diagnosis, staging and follow up. Computerised tomography (CT) is of value not only in the diagnosis of lung cancer, but also for screening and guiding intervention. CT and magnetic resonance imaging (MRI) are used in staging and provide anatomical information but have well known limitations in differentiating reactive from malignant nodes, fibrosis from active disease and in defining the extent of invasion. MRI, with its superior soft tissue contrast provides optimal information on brachial plexus and central nervous system involvement. Functional imaging using 2-18 fluoro-deoxyglucose positron emission tomography (FDG-PET) is increasingly being used to provide unique information and when combined with anatomic imaging will provide better staging information for both local disease and the extent of metastases. FDG-PET or ^{99m}Tc-depreotide may help in deciding which lesions need further investigation and the most appropriate lesion to biopsy. Multidetector CT is being used to detect lung cancer at an early stage when it is potentially curable by surgery although many problems exist, particularly the high false positive rates requiring further investigation, which will have implications on cost effectiveness for lung cancer screening programs.

Keywords: Non-Small Cell Lung Cancer; Computerised Tomography; Magnetic Resonance Imaging; Positron Emission Tomography; ^{99m}Tc-depreotide (NeoSpect); Mass screening; Lung neoplasm; Somatostatin receptors

1. Introduction

Lung cancer is one of the most prevalent malignancies representing 22% of cancers in men and 10% in women, with 191 000 new cases diagnosed each year in the EU. The incidence of adenocarcinoma is rapidly increasing in the USA, Japan and some other countries and now represents 30–40% of all cases, whereas the incidence of squamous cell cancer is falling representing 25–30% and large cell tumours make up 10–15% of cases. However in many other countries, although adenocarcinoma is commoner in women than in men and is increasing in incidence in both sexes, squamous cell carcinoma is still the predominant cell type [1–3].

The diagnosis of lung cancer is usually suggested by the chest radiograph and confirmed by bronchoscopy and biopsy, although lesions that are not directly adjacent to the major airways may be missed giving sensitivity for bronchoscopic biopsy of 65% [4]. CT may be used to guide percutaneous lung or mediastinal biopsy for diagnosis. At the present time CT and mediastinoscopy are the main staging investigations, with MRI used in a limited number of cases, but both CT and MRI have a low sensitivity for the detection of involved nodes and mediastinal and chest wall invasion thus inappropriate treatment may be undertaken in up to 40% of patients [5]. Mediastinoscopy and biopsy of suspicious nodes may be required prior to lung resection but mediastinoscopy provides limited mediastinal access and may not be the most appropriate surgical procedure. Functional imaging with FDG-PET can be used not only to identify involved nodes and distant metastases but can also be used to guide the surgical approach to the mediastinum.

2. Staging lung cancer

2.1. Diagnosis

Most patients present with advanced disease and the diagnosis is easily made on chest radiographs with CT

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identifying the majority of tumours including those that are occult on chest radiographs. Although the radiographic appearances are not diagnostic of a specific cell type, squamous cell cancers tend to be slow growing tumours that arise centrally and cause obstructive atelectasis, the tumours cavitate in 10–30% and extrathoracic metastases occur late. Adenocarcinomas arise more peripherally, have spiculated margins and may be associated with lymphangitic carcinomatosis with thickening of the interlobular septae and nodal metastases occur in 18–40% of cases. Large cell tumours are large peripheral poorly defined masses that rarely cavitate. Approximately 30% of new cancers present as solitary pulmonary nodules (<3 cm) and differentiating benign from malignant lesions may be difficult. The features suggesting malignancy include:

1. Size—the larger the nodule the more likely it is to be malignant, however 42% of cancers are less than 2 cm at presentation.
2. Margins—tend to be irregular and spiculated. However 20% of cancers may have a smooth margin and appear benign
3. Internal morphology—this cannot be used to differentiate benign from malignant lesions, unless the mass contains fat (attenuation value—120HU), which is diagnostic of a benign hamartoma. Calcification is seen in 6–14% of cancers on CT and is amorphous, rather than the punctate or popcorn calcification seen in benign disease. Cavitation which may occur in both benign and malignant lesions, is usually seen in the larger cancers and may be eccentric.
4. Growth—lung cancers double in volume (an increase in diameter of 26%) in 30–400 days (average 240 days). Growth in small tumours is best detected by serial volume measurements and this is part of the basis of screening using multidetector CT.
5. Blood supply—tumours exhibit increased vascularity and following intravenous contrast medium malignant nodules enhance by more than 20HU whereas benign nodules enhance by <15HU. Tumours may also be differentiated from distal atelectasis, as tumours will enhance less than the adjacent consolidated lung.
6. Metabolism—neoplastic tissue demonstrates increased glucose metabolism compared to normal tissues. This alteration in metabolic activity can be imaged with positron emission tomography (PET) using radio-labelled glucose analogues. Positron emission tomography is an imaging technique that can map functional and metabolic activity before structural changes have taken place. The most commonly used agent is 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG), which is a D-glucose analogue labelled with positron emitting F-18. FDG is preferentially taken up by lung neoplasms relative to normal lung and will identify the primary tumour, deposits in lymph nodes and as FDG-PET is a total body imaging system distant metastases. The uptake of FDG can be quantified as a standard uptake value (SUV) and FDG-PET may be helpful in assessing the response to induction chemo-radiotherapy prior to surgery as changes in uptake may precede any alteration in tumour size on CT. The disadvantages of FDG-PET is that any actively metabolising tissue, for example infection, may demonstrate increased uptake so differentiation between malignant and non malignant processes is not always possible, it is also expensive with limited availability world wide.

   A new metabolic agent being developed is Technetium labelled depreotide. Somatostatin is a tetradecapeptide secreted by the hypothalamus, which inhibits the release of neuroendocrine hormones including gastrin, insulin, glucagons and growth hormone. Somatostatin receptors (SSTR) are expressed by normal tissues but are over expressed by many malignant lesions including small cell and non-small cell lung cancer. These receptors can be imaged using ^{99m}Technetium labelled depreotide (NeoSpect, Nycomed Amersham), which is a synthetic peptide that contains an SSTR-binding domain, and this may be of value in the non-invasive assessment of pulmonary nodules.

   Both of these functional imaging techniques have limited spatial resolution and anatomical definition and should be read in conjunction with CT. The advent of combined PET-CT machines with improved image registration may help in this regard.

Treatment and prognosis in non-small cell lung cancer (NSCLC) depends of the anatomic extent of the disease at presentation. The International Staging System is used for lung cancer staging [6] and defines it in terms of primary tumour (T), nodal involvement (N) and metastases (M).

3. Primary tumour (T status)

The primary tumour is usually easy to define on CT, but 20–30% of patients present with a solitary pulmonary nodule (T1) and differentiation from benign disease may be difficult. Functional imaging may be helpful in these cases and FDG-PET will identify 95% of T1 lesions. If a SUV of greater than 2.5 is used to indicate

malignancy the sensitivity, specificity and accuracy of FDG-PET for differentiating between benign and malignant nodules is 94%, 71% and 86% with PPV of 90% and NPV of 85% [7]. Increased uptake will also be seen in tuberculosis, aspergillomas, rheumatoid nodules and amyloid, these false positives decrease the specificity. False negatives occur in small tumours, bronchoalveolar cell carcinoma and carcinoid, all of which are associated with a better prognosis [8]. Nodules in the basal segments are more likely to be missed because of respiratory motion and normal uptake in the adjacent liver.

Early results with ^{99m}Tc depreotide (NeoSpect) in the assessment of malignancy in solitary pulmonary nodules reported sensitivities of 97%, with a specificity 73% with a PPV of 91% and a NPV of 97% [9]. No relationship between histology or differentiation and the degree of uptake has been demonstrated and false positives occurred in granulomas and hamartomas. Further studies confirmed that NeoSpect had better specificity and negative predictive value than CT (NPV 100%, CT 67%) in the assessment of solitary pulmonary nodules and it could be used, where FDG-PET is not available, prior to biopsy particularly in those patients in whom the risk of biopsy would be high, perhaps allowing a wait and see policy if the NeoSpect study was negative [10,11]. There have been no large series comparing NeoSpect and FDG-PET so its role where both are available is not known.

T3 tumours include tumours of any size with direct extension into the chest wall, diaphragm, mediastinal pleura or pericardium. T4 tumours invade the mediastinum, great vessels, trachea, oesophagus and vertebral bodies. The exact anatomical extent of tumours is difficult to assess using CT for both chest wall and mediastinal invasion and also for differentiating tumour from adjacent consolidated lung. Even if there is chest wall invasion this is not a contraindication to surgery but it does adversely affect prognosis and alters the surgical approach, with en bloc resection of the tumour and chest wall associated with an operative mortality of 8–15%. CT will identify gross chest wall invasion with rib destruction and a mass in the chest wall but is inaccurate in differentiating contiguity from subtle invasion [12] Findings suggesting subtle invasion include tumour-pleura contact over more than 3 cm, an obtuse angle at the tumour–pleural interface and thickening of the pleura or increased attenuation of the extrapleural fat adjacent to the tumour. Webb and colleagues [13] found CT only 62% sensitive in differentiating between T3 and T4 tumours and Glazer and colleagues [14] found the sensitivity and specificity for chest wall invasion was 87% and 59% respectively. MRI has superior soft tissue contrast to CT and is better at identifying chest wall invasion with a reported sensitivity of 90% and specificity 86% [15], and it is much better than CT for superior sulcus (Pancoast) tumours with an accuracy of 94% compared to that of 63% for CT [16]. MRI is very good for identification of involvement of the inferior branches of the brachial plexus (C7, T1), vascular infiltration and invasion of the spinal canal or vertebral body and thus predicting non resectability. Some authors [17] also suggest that all patients with Pancoast tumors should have ultrasonography of the ipsilateral scalene area with percutaneous biopsy of nodes >1 cm in their transverse diameter. Scalene node biopsy is also indicated when the nodes are palpable or in patients who have proven N2 disease, prior to undergoing resection, with unsuspected microscopic involvement in 15% of patients with N2 disease at mediastinoscopy, and in 68% of patients with N3 disease [18].

CT and MRI can identify gross invasion of the mediastinum with vascular invasion but is poor at identifying subtle changes. Signs that suggest subtle invasion include tumour-mediastinal contact over more than 3 cm, obliteration of the fat plane between tumour and mediastinum and tumour contact of >90 degrees with aorta. The sensitivity for mediastinal invasion is reported to be as low as 40–44% by CT [19].

Glazer and colleagues [20] reviewed 80 patients who had indeterminate mediastinal invasion on CT scan and found 60% of the masses were resectable without true invasion of the mediastinum, in 22%, although there was focal invasion of the mediastinum, the lesions were still technically resectable and in only 14 (18%) was the tumour unresectable. MRI is more accurate than CT for mediastinal invasion [13] and overall both CT/MRI are reasonably accurate at assessing resectability, but not for non-resectability and thoracoscopy may be required.

Tumours associated with malignant pleural effusions or pleural metastases are T4. Positive cytology is obtained in only 66% of patients with malignant effusions at presentation and although pleural metastases are quite frequent they may be difficult to assess on CT, however FDG-PET may be helpful in these cases. FDG-PET is also useful for differentiating tumour from adjacent lung collapse and may be helpful in planning radiotherapy portals particularly if combined with CT data, although this has not as yet been validated.

4. Nodal status (N)

The presence of regional node metastases significantly alters prognosis. When the disease has progressed outside the ipsilateral hemithorax the outcome is poor with less than 3% of patients with N3 disease surviving five years. In those patients with N2 disease, the number and nodal levels involved influence survival and up to 20–30% 5-year survival can be achieved following surgery for N2 disease, provided complete tumour removal is possible. Nodal staging requires accurate

definitions of nodal groups and levels and follows the new international lymph node classification adopted by the American Joint group on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC). CT and MRI are both good at providing anatomic definition but FDG-PET is not as good and may be helped by co-registration with CT or MRI.

Using CT and MRI size is the only criteria used to assess malignant infiltration and nodes that have a short axis diameter greater than 1 cm are considered abnormal. Therefore enlarged reactive nodes will be over-called and metastases in normal size nodes will be missed and the patient either over or understaged. The frequency of metastatic normal-sized nodes is commoner with central adenocarcinomas than with central squamous cell cancers. The accuracy for the detection of N1 disease is similar for CT (62–88%) and MRI (68–74%). This poor accuracy is not necessarily very significant as N1 disease does not preclude surgery, although it is important in radiotherapy planning, however the results for mediastinal nodes (N2 and N3) are also poor [21,22]. In a meta-analysis of CT accuracy for assessment of mediastinal lymph nodes, Dales et al [23] reported a sensitivity, specificity, and overall accuracy of 79%, 78%, and 80% respectively with similar results for MRI [24,25] For these reasons, there is general agreement that enlarged lymph nodes require histologic confirmation if this finding alone would preclude surgery.

The use of intravenous contrast medium in CT has not helped define which nodes are involved, although there are reports that gadolinium enhanced MRI may be useful [26]. The use of ultra small superparamagnetic iron oxide particles (USPIO) as a MRI lymph node contrast agent has been developed and does offer potential for improvement. The small iron oxide particles are injected intravenously and are taken up by the reticuloendothelial system in normal or inflamed lymph nodes. These nodes show signal drop off on T2* weighted sequences whereas metastatic nodes do not show this effect. Early studies have suggested that the use of USPIO will increase the sensitivity for MRI to 92% with a specificity of 80% [27].

FDG-PET is more accurate than CT for staging mediastinal nodes as it is dependent not on size but on metabolic activity and will identify disease in nodes less than 1 cm in size, and although the sensitivity for small nodes is slightly less than that of nodes of 1–3 cm, the overall accuracy is the same [28]. The reported sensitivity for FDG-PET in N2 or N3 disease compared to CT is 89–92%, (CT 25–57%), specificity 93–99% (CT 94–98%) with a NPV for PET of 97% (CT 87%). Overall the correct stage is assessed by FDG-PET in 85–96% (CT 58-59%) [29,30]. Combining FDG-PET and CT is better than CT alone [31,32] with a very high NPV for staging N2 and N3 disease (95% overall and 99% for individual nodes) and therefore some authors would suggest a negative CT and negative FDG-PET would obviate the need for mediastinoscopy prior to surgery in patients with resectable tumours [33]. Mediastinoscopy should still be performed in those patients with a positive mediastinal FDG-PET as false positives occur in tuberculosis, histoplasmosis, sarcoidosis, and anthracosis and in these cases the combination of FDG-PET and CT will help to direct the most appropriate route for mediastinal biopsy.

However many authors [34–36] feel that all patients with a potentially resectable tumour should undergo pre-operative mediastinoscopy. De Leyn [35] performed mediastinoscopy on patients who were node negative on CT and found that 20% had N2 disease, and as these patients may benefit from induction chemotherapy [36], these authors state that mediastinoscopy should be performed on every patient with potentially operable NSCLC to exclude N2 disease. A recent study by Kernsteine [37] comparing FDG-PET, CT, and MRI with USPIO for nodal disease in NSCLC found a sensitivity, specificity, and accuracy of 70%, 86%, 84% (PET); 65%, 79%, 76% (CT); and 86%, 82%, 83% (MRI) respectively. These authors concluded that although PET and MRI were statistically more accurate than CT, the differences were small and no technique was either sensitive or specific enough to obviate the necessity for mediastinoscopy. Not all surgeons would agree with this policy and in those patients with early stage disease and a negative CT (and/or FDG-PET), where the likelihood of finding involved nodes is 3–16% [38,39], will undertake a thorocotomy with nodal sampling or lymphadenectomy at the time of surgical resection.

FDG-PET is used to assess tumour response to chemo/radiotherapy in many other tumour types but there are some problems with lung cancer. Although the response of the primary tumour and the metastases to induction therapy appears accurate, Akhurst and colleagues [40] found it was inaccurate for the response in the mediastinal nodes with 33% overstaged and 15% understaged. Thus if resection is to be undertaken following down staging mediastinal node biopsy should probably be performed prior to definitive surgery, irrespective of nodal size and FDG uptake.

5. Metastatic disease (M status)

In patients with more advanced disease metastases are not uncommon (upto 20% at presentation) with the commonest sites for metastatic disease in NSCLC being brain, bone, liver and adrenals (in decreasing order) [41]. A complete history will often reveal metastatic disease, with bone and brain metastases usually symptomatic whereas liver and adrenal metastases are often asymptomatic. Normal clinical examination and routine

laboratory tests have a negative predictive value of 95% and radiologic evaluation for occult metastases may not be required. In fact in patients with early stage T1, N0 or T2, N0 disease and no clinical evidence of metastases, the low incidence of metastases suggests only the chest needs to be imaged, however the liver and adrenals are often included as laboratory finding are limited in abdominal disease.

The sensitivity of CT for detecting adrenal metastases is low (41%) but the specificity is high (91%) [42]. However small, <3 cm, non functioning adrenal adenomas are a common finding in the normal population and need to be differentiated from metastases. Adenomas are more likely than an adrenal metastasis if there is no evidence of other extrathoracic metastases. Both CT and MRI can be helpful in evaluating adrenal masses. The features suggesting a malignant adrenal mass are a lesion greater than 3 cm with poorly defined margins and an irregular enhancing rim or invasion of adjacent structures and high signal on T2W sequences. If the lesion has a CT number of <10HU on an unenhanced CT scan it is benign (specificity 100%) [43] Using chemical shift, MR imaging will also differentiate benign from malignant lesions in about 85–90% of cases, benign lesions showing signal drop off on out of phase imaging (specificity 100%) [44]. Adrenal masses that do not exhibit these features may still be benign but the use of CT and MRI will decrease the number of indeterminate masses that will still require biopsy. A recent study by Kocijancic and colleagues [45] suggested that an isolated ipsilateral adrenal metastasis in a patient with resectable NSCLC should be treated as localised disease rather than a sign of systemic spread.

Metastases to the central nervous system are common and detected in 18% of patients with M1 disease at presentation, and up to 10% of these patients may be asymptomatic, particularly if secondary to large cell or adenocarcinoma, and some institutions would routinely image the CNS. However as most patients with CNS involvement have neurological signs it is not considered cost effective to image the CNS in all patients with NSCLC. FDG-PET may not be very useful in this respect as the brain normally shows increased metabolic activity and other isotopes such as C11-methionine may be more sensitive, but are not used routinely.

Skeletal metastases are usually symptomatic and therefore bone scintigraphy, which is sensitive but non-specific and MRI should only be used to evaluate local bone pain and not as a screening investigation.

FDG-PET is a whole body imaging system that will identify unsuspected metastases [46] and is being used to increase the accuracy of staging. FDG-PET can differentiate incidental adrenal adenomas, which have low uptake from adrenal metastases that exhibit increased uptake and FDG-PET has higher sensitivity and specificity than CT for the detection of liver, bone and extra-thoracic lymph node deposits. Clinician surveys have suggested that FDG-PET influences or changes management in 39–67% of patients [47,48] with the detection of extra-thoracic metastases in 11–14% of patients selected for curative surgery [49].

6. Staging classification

The TNM subsets are divided into stages, allowing the rational grouping of patients with similar disease states for prognostic and treatment options, and survival is related to the stage at diagnosis [6].

Patients with stage I disease are the most suitable candidates for surgery with survival rates of 57–85%, and if proper pre-treatment staging is accomplished, the rate of exploratory thoracotomy or incomplete resection should not exceed 8 to 10%. Prognosis decreases with larger tumours and more extensive nodal disease with the survival of stage 11B patients being 22–24%. Stage IIIA patients are still potentially resectable although involvement of high para-tracheal nodes is a contraindication to surgery and Stage IIIB disease is treated with chemoradiotherapy with a 5-year survival of 3–8%. Patients with stage IV disease have distant metastases and a very poor prognosis.

There are still controversies over whether early stage T1 tumours should be staged at all. Several studies have suggested the prevalence of nodal disease is low (5–15%) and because of this and the limited sensitivity of CT, staging may be unnecessary. However Seeley and colleagues [50] found a prevalence of nodal disease of 21% in T1 tumours with CT identifying 77% of cases and CT of the chest is undertaken in most institutions.

It is also controversial whether the abdomen should be included in routine staging. In early-stage asymptomatic tumours, the yield of routine organ screening is in the range of 1–4% [51–53] and screening the abdomen would therefore not be recommended. However in one study of potentially operable patients [54] CT of the abdomen and brain detected occult metastasis in 13% of patients, and in another study [49] using FDG-PET found unsuspected metastases in 9% of N0/N1 tumours and 28% of N2 tumours. It has been suggested that asymptomatic patients with mediastinal nodal disease or non-squamous histology, are more likely to have extra thoracic metastases and screening of the abdomen may be recommended [52,55–57], although Jung and colleagues [58] identified extra thoracic metastases in 13% of patients with T1 tumours at presentation, with no difference between squamous or adenocarcinoma and also irrespective of nodal status and many institutions would therefore include both the liver and adrenals with the chest CT.

7. Screening for lung cancer

It is estimated there will be 164 100 new cases of lung cancer in 2000 in the USA. Screening has not normally been recommended, but the number of deaths from lung cancer will exceed the next three commonest tumours of breast, colon and prostate combined [59] and screening is offered for these cancers with a reported decrease in mortality of 10–15%.

Screening for lung cancer using chest radiographs and sputum cytology has not been recommended since the completion of three randomised trials sponsored by the National Cancer Institute. This decision was based on the lack of a reduction in disease-specific mortality of the screened group when compared to the control group. Review of the evidence from the original Mayo Clinic study, suggests that the Mayo project pointed to no direct evidence for screening rather than evidence against screening.

It is suggested that the survival rate in small tumours is much better than for larger tumours and screening will allow lung cancer to be detected at an earlier stage. However there is no confirmation for this with lung cancer as there is no evidence that a 5 mm lung tumour (10^8 cells) has a significantly better prognosis than a 10 mm tumour (10^9 cells). All these lesions are found late in the course of the disease, since at the time of death patients typically have a tumour burden of 10^{12} and in a recent study of T1, N0, M0 disease there was no correlation between tumour size and survival [60]. For screening to be effective certain criteria should be met. These include a significant prevalence of the disease in the population to be screened, a significant health risk for those afflicted with an advantage to early detection. The screening technique must be relatively safe, sensitive without an excessive false positive rate and the cost must be acceptable to society [61].

The advent of helical CT has allowed screening with CT. Initial data is now available showing that low dose CT is better at detecting small nodules than chest radiographs (CXR) with a radiation dose for CT of 0.65 mSv compared to 0.1mSV for chest radiographs, although the dose for CT excludes follow up scans that may be required for indeterminate lesions. A study from Japan of 1369 subjects identified 15 cancers, only 4 being demonstrated on concomitant chest radiographs. The tumours detected on CT had an average size of 16 mm, compared to 30 mm on a previous screening program using CXR. A more recent study of 7956 subjects in Japan, which including non-smokers as well as those with a significant smoking history, identified 37 tumours (prevalence 0.44%, with only 14 of the 36 patients being smokers) and the majority of tumours were adenocarcinoma with 9 of the 13 bronchoalveolar carcinomas occurring in non smokers. The detection rate for the repeat annual screen was only 0.07% and all these subjects were smokers [62].

A study in New York of 1000 asymptomatic smokers identified 233 screen positive lesions of which 27 were lung cancers and 23 were stage I [61]. All the lesions required further investigation, but only one benign lesion underwent biopsy. The Mayo Clinic trial involving over 1500 subjects found 23 cancers, two-thirds being stage I [63] (Table 1). The final mortality data is not yet available in these trials and there is no evidence that the very small cancers that are being identified will present in the patients lifetime.

The important question is whether this prevalence data represents a true 'stage shift' enabling detection at an earlier stage or whether they represent detection of slow growing tumours that may not affect overall disease-specific mortality (lead-time bias—tumours detected earlier but same mortality and length time bias—more indolent tumours detected at screening, aggressive tumours present rapidly with symptoms) and this question should be answered with randomised trials. Unfortunately this has not occurred and several institutions are already offering lung cancer screening [64]. Recent data from the USA discloses an 80% false-positive rate in the nodule detection, with the morbidity associated with biopsy, and the potential medico-legal implications for false negative screens [65]. Screening is most successful for peripheral lesions and may not be suitable in countries where central squamous cell cancers are the most common presentation. The frequency of screening also has not been defined, all of which will have considerable financial implications and population screening should not be undertaken until some of these results become available [66] and the role of CT in lung cancer screening has been defined, unfortunately a study that would have answered some of these questions in the United Kingdom has been rejected but large studies are

Table 1
Data from Lung cancer screening studies using low dose CT

Study site. Year of publication	Population screened	Patient numbers	Abnormal results No. (%)	Malignancy detected No. (%)
USA Cornell 2000 [61]	Smokers, former smokers >10 pack year	1000	233 (23)	27 (2.7)
Japan 1998 [68]	Smokers and non smokers	3967	223 (5.6)	19 (0.48)
Japan 2002 [63]	Smokers and non smokers	7956	2099 (26)	36 (0.44)
USA Mayo 2002 [63]	Smokers >20 pack year	1520	1000 (66)	23 (1.5)

underway in the United states that will provide useful data [67].

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