Lung cancer: defining the target for radiotherapy

H Jane Dobbs

Department of Clinical Oncology, Guy’s & St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH, UK

Corresponding address: H Jane Dobbs, Department of Clinical Oncology, Guy’s & St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH, UK. E-mail: sjnd@ukonline.co.uk

Abstract

Accurate delineation of the radiotherapy target volume for lung cancer requires close collaboration between radiologists and radiation oncologists. A detailed knowledge of radiological anatomy is needed to avoid pitfalls in interpretation of CT images which are used to define the exact size and limits of the gross tumour volume for treatment planning. PET scanning can distinguish atelectasis from primary lung tumour and has been shown to outline the tumour more accurately, thereby reducing inter-observer variation in target definition.

Movement of the target volume can be reduced using newly developed methods such as respiratory gating, active breathing control devices or deep inspiration breath hold. Reduction in motion is necessary to create smaller target volumes for dose escalation to improve local control.

The key to improved cure rates for non-small cell lung cancer lies in accurate target volume definition without which sophisticated conformal radiotherapy will be delivered as a geographical miss.

Keywords: Radiotherapy; non-small cell lung cancer; CT; target volume.

Introduction

Conformal radiation therapy (CFRT) is the delivery of high precision radiotherapy using beams shaped to an individual tumour in its entire 3D configuration. This facility to treat a 3D volume containing macroscopic tumour with a surrounding margin instead of a cube or rectangular box has reduced the volume of tissue irradiated by 30–50% compared with standard radiotherapy techniques. Preliminary experience with 3D CFRT for locally advanced non-small cell lung cancer (NSCLC) suggests that this technique may improve the therapeutic ratio, with the potential for higher doses of radiation delivered with sparing of normal tissues, giving the possibility of improved cure rates\(^1,2\). However, the full potential of dose escalation is entirely dependent on accurately including the entire gross tumour in a high dose volume every day during a course of many fractions of irradiation.

ICRU Reports 50 and 62\(^3,4\) have provided definitions for target volumes which are used internationally as a template to design target volumes for all tumour sites enabling a comparison of results of treatment between different centres. The gross tumour volume (GTV) is the gross demonstrable extent and location of the tumour and represents the macroscopic disease where the tumour cell density is greatest. The clinical target volume (CTV) contains the GTV and/or subclinical disease. The margin for the CTV may be very difficult to quantify as data are often lacking on histopathological spread patterns. The CTV contains a lower tumour cell density at its periphery and needs to be treated in its entirety to the prescribed radiation dose in order to elicit a cure. The planning target volume (PTV) is a geometric concept designed to ensure that the prescription dose is actually delivered to the CTV on a daily course of radiotherapy.
which may be given over 6 or 7 weeks (Fig. 1). Variations in size, shape or position of the CTV due to physiological movements in the chest such as respiration, swallowing or cardiac pulsation affect the CTV both during radiotherapy delivery and between daily treatments. Uncertainties in the position of the patient in relation to the beam and other geometric variations in the set-up of the treatment can be measured using verification systems such as electronic portal imaging and minimised with accurate patient immobilisation techniques [5].

**GTV for lung cancer**

The delineation of the GTV for lung cancer is critical, as the volume needs to be as small as possible to enable dose escalation with the possibility of improved local control. However, it must also include all known macroscopic disease because if tumour is missed then even with sophisticated CFRT the hope of cure is lost. The oncologist is hence entirely dependent on the expertise of the radiologist to advise on the best imaging modality to depict the primary lung tumour and to interpret the images accurately in 3D.

The oncologist needs to know the exact site of the tumour according to fixed reproducible co-ordinates, taking account of conditions such as respiration during the 1 or 2 minutes of radiotherapy delivery. Three-dimensional measurements of the tumour are required as well as details of the edge of the tumour where it forms a boundary with adjacent tissue. Atelectasis and mediastinal vessels provide particular pitfalls for the oncologist in interpreting computed tomography (CT) images of the chest and education in radiological anatomy is needed from a specialist cancer radiologist. Many studies have shown that the variability in delineating tumour and target volumes between different clinicians for lung cancer can be very high [6,7]. Giraud et al [6] showed that radiologists delineated the radiological limits of the tumour on CT scan more tightly than oncologists with smaller more accurate volumes particularly in ‘difficult’ cases. These authors recommend delineation of the GTV under the joint supervision of an experienced radiation oncologist and radiologist.

**Margins around the GTV**

Attempts are made to minimise the margin added to the GTV to produce a PTV which must be as small as clinical constraints allow if it is to permit dose escalation within the limits of normal tissue tolerance. Firstly a margin is added to account for microscopic disease to create the CTV. Giraud et al [8] examined 70 surgical lung resection specimens of NSCLC for microscopic extensions. They concluded that a margin of 6 mm for squamous cell tumours and 8 mm for adenocarcinomas was required to treat 95% of microscopic extensions. Systematic errors of set-up are reported with standard deviation in the order of 3.3, 4.4 and 2.2 mm in the x, y and z directions, respectively, using high-resolution portal imaging devices on the linear accelerators to measure deviations. Erridge et al [9] also reported tumour shrinkage of at least 20% in 40% of 97 patient studies. This new finding offers the possibility of dose escalation to a remaining smaller tumour volume. More studies are needed to determine whether clonogenic cells remain in the peripheral tissues around the shrunk tumour. An alternative approach to creation of the PTV is postulated by McGibney et al [10], focusing on the GTV which has the high tumour cell density to which a safety margin must be added for geometric uncertainties. This results in a small GTV to PTV margin which means that subclinical disease may move outside the PTV during the course of treatment into a ‘rind’ volume which receives a lower dose. However, their study showed that dose to some of this ‘rind’ volume
was unacceptably low and below 50 Gy required for microscopic disease, so was not suitable for clinical use.

**The role of positron emission tomography (PET) scanning in defining the target volume**

The use of fluorine-18-labelled fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG-PET) for improved staging of lung cancer$^{[11,12]}$ has refined the selection of patients for radical radiotherapy treatment. The ability of PET to detect disease in lymph nodes with increased accuracy compared with CT has had an impact on the choice of target volume. The value of elective lymph node irradiation in lung cancer is not proven and its use may enlarge the volume too much and so prevent dose escalation of the primary tumour to levels which might achieve gross tumour eradication. Hence, better lymph node staging enables higher doses of radiation to be focused on the primary tumour alone.

PET scanning has been shown to distinguish atelectasis from tumour at the primary lung tumour enabling the volume to be reduced accurately, a helpful prerequisite for dose escalation$^{[13]}$. Co-registration of $^{18}$F-FDG-PET and CT images has been shown to reduce inter-observer variation significantly and improve consistency in the definition of the GTV$^{[14–16]}$. Furthermore, PET images are acquired slowly over minutes and thus involve several cardiac and respiratory cycles, a state more comparable to that during irradiation. Combined PET-CT scanners may provide an advantage in delineating the GTV, using CT scans to give an accurate anatomical map and PET data on both function and motion of the tumour in 3D to reduce the margin of the PTV.

**CT data acquisition of the GTV**

CT scans are used directly to produce 3D dose calculations for treatment planning of CFRT for lung cancer. Hence the acquisition of data for delineation of the GTV for CFRT must be under identical conditions to those subsequently used for treatment. Patients are immobilised supine using an Alpha cradle or alternative device with the arms placed above the head. This allows selection of oblique lateral and postero-lateral treatment beams without obstruction from the arms. Usually spiral CT scans are taken with 3 mm slice thickness for good resolution of digitally reconstructed radiographs (DRR).

Pre-set CT lung window settings should be standardised and adhered to as these have been suggested as the most representative of the macroscopic tumour size$^{[17]}$. More correlation studies of tumour size using optimum CT lung settings and subsequent histological examination of pneumonectomy specimens would be helpful in defining the GTV for radiotherapy treatment planning.

**Respiratory motion of the GTV**

Respiration can have a significant influence on the position of the GTV and may lead to a ‘geographical miss’ during irradiation. It has been postulated that geometrical errors arising due to tumour mobility, especially for those located in the lower lobe, may be an important cause of local failure of radiotherapy treatment. The size of the movement varies from patient to patient and can be dependent on factors such as the site of tumour in the lung (lower lobe greater than upper), fixation to adjacent structures, lung capacity, general condition and mental state of the patient and patient immobilisation. Fluoroscopy can be used to measure this respiratory movement as shown by Ekberg et al$^{[18]}$. They found in a group of 20 patients with lung cancer that on average the craniocaudal movement was 3.9 mm (range 0–12 mm) with 2.4 mm in the mediolateral and dorsoventral directions.

Several techniques have been tried to control the impact of organ movement in lung cancer irradiation including the deep inspiration breath hold$^{[19]}$ and automatic breathing control device$^{[20]}$ and gating the treatment to a part of the respiratory cycle$^{[21]}$. These have the advantage of potentially reducing the margin around the GTV required for movement uncertainty, thereby creating a smaller PTV, a prerequisite for dose escalation.

When rapid CT scans are used for treatment planning, tumour may be imaged in a ‘snapshot’ that is unrepresentative of the whole respiratory cycle which is played out during treatment delivery during several minutes. Recent studies have shown that incorporation of data from a single co-registered slow CT scan into a conventional rapid planning CT scan improves the definition of target volumes for peripheral lung tumours$^{[22–24]}$. In addition Caldwell et al$^{[25]}$ have shown recently using a phantom study model that PET imaging can give a more accurate representation of the 3D extent of tumour motion.

These issues are particularly important when considering intensity-modulated radiotherapy (IMRT) where the dose distribution and intensity are planned with such high level precision that organ motion becomes a prohibitory factor for accurate delivery.

**Target volumes for palliative lung radiotherapy**

The use of CT virtual simulation has been shown to improve tumour coverage compared with conventional simulation in locating the target volume for palliative lung radiotherapy$^{[26]}$. An alternative method of virtual simulation based on the use of multiplanar reconstructions of the CT data set has been shown to be simpler and achieve the same advantage without the need to define the 3D tumour volume on each CT slice$^{[27]}$, which is a time-consuming process (Fig. 2). The advantage of CT
localisation has also been shown by these authors to be greatest when the tumour approaches midline where CT gives improved visualisation compared with conventional simulation.

**Summary**

Detailed knowledge of the radiological anatomy of the mediastinum and chest is essential for the accurate definition of the GTV\(^{[28]}\). This requires close collaboration between radiologists and radiation oncologists to avoid pitfalls in the interpretation of CT images. Techniques to reduce movement of the GTV and thereby limit the margin and size of the final PTV are important if dose escalation is to be feasible without unacceptable pneumonitis from large volumes. Increased sophistication of radiotherapy delivery using CFRT and IMRT is entirely dependent on hitting the tumour in its entirety and hence accurate delineation of the target volume is the key to successful treatment outcome.

**Key points**

- Accurate GTV delineation is the key to improved cure rates for NSCLC and a prerequisite of sophisticated radiotherapy delivery using CFRT and IMRT.
- GTV delineation requires combined skills of both radiologist and oncologist working in collaboration.
- PET-CT fused images have been shown to improve staging of NSCLC and more accurately define the GTV, thereby reducing inter-observer variation in GTV definition.
- Active research into improved definition of the ‘mobile’ target volume using methods such as slow CT/spiral CT scan fusion or reduction in motion using respiratory gating, active breathing control devices or deep inspiration breath hold is on-going.
- Reduction in motion of the GTV is needed to create smaller target volumes for higher radiation doses with the same normal tissue morbidity in order to provide improved cure rates.

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Lung cancer: CT staging†

Leslie Eisenbud Quint

Department of Radiology, Box 0030, University of Michigan Health System, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0030, USA

Corresponding address: Leslie E Quint, Department of Radiology, Box 0030, University of Michigan Health System, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0030, USA. E-mail: lequint@umich.edu

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Abstract

Patients with non-small cell lung cancer routinely undergo computed tomography (CT) scanning for tumor staging prior to therapy. CT is useful in suggesting local invasion and spread to mediastinal lymph nodes and distant sites. However, a patient should not be denied potentially curative surgery based on unproven CT findings, due to the frequent occurrence of false-positive findings. CT findings should be used to direct the appropriate method of biopsy, in order to confirm the tumor stage.

Keywords: Lung cancer; computed tomography; cancer staging.

Introduction

Preoperative tumor staging in patients with non-small cell lung cancer (NSCLC) is important in order to identify those patients with localized disease who are likely to benefit from surgical resection. The TNM staging system, revised in 1997, is the most widely accepted and used classification system for lung cancer staging (Table 1) [2,3].

Evaluation of the primary tumor

Pleural invasion

A pleural effusion in a patient with lung cancer may be malignant, caused by pleural metastases, or it may be benign, particularly in a patient with postobstructive pneumonia. The hallmark for a malignant effusion is soft-tissue nodularity along the pleural surfaces, accompanying the effusion, although this finding is not always present (Fig. 1). Pleural nodularity and/or fissural thickening are suggestive of pleural metastases, even in the absence of pleural effusion. Pleural tumor dissemination is classified as T4 disease and is generally considered unresectable.

Chest wall invasion

Computed tomography (CT) has shown somewhat disparate results in assessing for chest wall invasion by tumor, with sensitivity ranging from 38% to 87% and specificity from 40% to 90% [4–6]. Signs of invasion may include pleural thickening, loss of the extrapleural fat plane, obtuse angle between mass and chest wall, and greater than 3 cm of contact between mass and chest wall. However, the only reliable criterion for diagnosing chest wall invasion with routine CT is definite bone destruction, with or without tumor mass extending into the chest wall (Fig. 2). Some investigators have employed induced pneumothorax and inspiratory/expiratory imaging in order to increase the accuracy of CT in diagnosing chest wall and mediastinal pleural invasion. It should be noted that chest wall invasion (primary stage T3) does not preclude surgical resection, because the surgeon may perform en bloc resection and chest wall reconstruction. However, this procedure is associated with increased operative morbidity and mortality.
Table 1  TNM classification for staging of NSCLC (adapted from reference [2])

| T: Primary tumor |  |
|------------------|---|
| T1               | Tumor <3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus) |
| T2               | Tumor with any of the following features of size or extent: >3 cm in greatest dimension |
|                  | Involves main bronchus, ≥ 2 cm distal to the carina |
|                  | Invades visceral pleura |
|                  | Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| T3               | Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung |
| T4               | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with malignant pleural or pericardial effusion or with satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung |

| N: Regional lymph nodes |  |
|-------------------------|---|
| N0                      | No regional lymph node metastasis |
| N1                      | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor |
| 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) |

| M: Distant metastasis |  |
|-----------------------|---|
| M0                    | No distant metastasis |
| M1                    | Distant metastasis present (includes separate metastatic tumor nodule(s) in the ipsilateral non-primary tumor lobe(s) of the lung) |

Stage grouping

| Stage | T   | N   | M   |
|-------|-----|-----|-----|
| Stage IA | T1  | N0  | M0  |
| Stage IB  | T2  | N0  | M0  |
| Stage IIA | T1  | N1  | M0  |
| Stage IIB | T2  | N1  | M0  |
|           | T3  | N0  | M0  |
| Stage IIIA | T3  | N1  | M0  |
|           | T1–3 | N2  | M0  |
| Stage IIIB | T4  | Any N | M0  |
|           | T1–3 | N3  | M0  |
| Stage IV   | Any T | Any N | M1  |

Mediastinal invasion

Although invasion of the mediastinum falls into the T4 category in the TNM staging classification, minimal invasion of fat only (without invasion of vascular or other structures) is generally considered resectable by many surgeons. Therefore it is not usually necessary to preoperatively diagnose minimal mediastinal fat invasion. On the other hand, a reliable diagnosis of invasion of mediastinal vessels (Figs 3–5), trachea, esophagus (Fig. 6), and/or vertebral body (Fig. 7) would preclude surgical resection. CT diagnosis of minimal mediastinal fat or mediastinal structure invasion is generally unreliable[4,6,7] (Figs 3 and 4), and a patient should not be denied surgery based on unproven CT findings. Gross mediastinal fat invasion (Fig. 8) may be proved via mediastinoscopy or transtracheal Wang needle biopsy, if the location is accessible using these techniques. Findings suggestive of central tracheobronchial invasion at CT are usually further evaluated using bronchoscopy.

Evaluation of mediastinal lymph nodes

Tumors with metastatic disease to ipsilateral mediastinal nodes (N2 disease) are potentially resectable, generally after neoadjuvant chemotherapy and/or radiation therapy, as long as the nodes are not numerous and/or bulky. Contralateral mediastinal, contralateral hilar, or any scalene or supraclavicular nodal metastases are classified as N3 disease; such patients are not surgical candidates. CT criteria for lymph node metastases theoretically include morphological features such as nodal attenuation and margination. In practice, however, these features are usually unhelpful, and nodal enlargement (> 1 cm in short axis diameter) is the only currently useful diagnostic criterion (Fig. 9).

Disparate results have been reported regarding the accuracy of CT in diagnosing mediastinal lymph node metastases. Recent studies have shown low accuracy, resulting from both poor sensitivity (48–65%) and...
poor specificity (53–79%)\textsuperscript{[4,7–11]}. Low sensitivity in some studies was attributed to the high frequency of microscopic metastases within normal-sized nodes. Low specificity arose from the frequent occurrence of enlarged, hyperplastic nodes, particularly in patients with postobstructive pneumonitis\textsuperscript{[8]}.

**Figure 3** Indeterminate CT for mediastinal and superior vena caval invasion. Soft tissue mass is contiguous with superior vena cava; at surgery the mediastinum was not invaded (T2 disease).

It is generally agreed that all patients with enlarged mediastinal lymph nodes at CT need lymph node biopsy for confirmation; therapy should not be planned based upon unproven, positive CT findings. If enlarged mediastinal lymph nodes are detected, CT may be used to direct preoperative lymph node sampling via transbronchoscopic Wang needle biopsy, mediastinoscopy, or mediastinotomy, according to the location of the lymph nodes.

**Figure 5** Gross invasion of main pulmonary artery at CT (T4 disease).

**Figure 6** Esophageal invasion (T4 disease). Tumor mass abuts and narrows the esophagus (arrow), suggesting invasion (a). Narrowing is confirmed on a barium esophagram (b).

Unlike patients with bulky mediastinal lymph node metastases, those with microscopic metastases in normal sized lymph nodes may benefit from surgical resection\textsuperscript{[12]}. Therefore, many surgeons believe that a negative CT obviates the need for mediastinoscopy, and these
patients should go directly to thoracotomy. The exception occurs in patients with adenocarcinomas or T3 tumors, including Pancoast tumors; mediastinoscopy may be indicated in such patients because the concomitant presence of mediastinal nodal metastases portends a poor prognosis, and therefore such patients are not usually felt to be surgical candidates. On the other hand, some investigators still advocate surgical mediastinal lymph node staging in all patients, because they believe that CT is neither sensitive nor specific enough to obviate this technique.\textsuperscript{[10]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Gross invasion of spine at CT (T4 disease) (arrow).}
\end{figure}

\section*{Evaluation of distant metastases}

Approximately 18–36\% of patients with a new diagnosis of NSCLC have distant metastatic disease. Patients with adenocarcinoma appear to be at significantly greater risk for metastases outside the thorax than those with squamous cell cancer. Brain, bone, liver, and adrenal glands are the most common sites of disease, in decreasing order. Brain metastases often occur as an isolated finding. Some investigators suggest obtaining brain CTs for all patients with adenocarcinoma and large cell carcinoma, as well as for patients with squamous cell cancer and neurologic symptoms. Unlike brain metastases, isolated liver metastases are uncommon, and therefore the incremental yield of abdominal CT over chest CT is quite small.\textsuperscript{[13]}

Despite the high prevalence of adrenal metastases from bronchogenic carcinoma, approximately two-thirds of adrenal masses in patients with NSCLC actually represent adenomas, rather than metastases. Unfortunately, there is significant overlap in the appearance of adrenal metastases and benign adenomas on routine, contrast-enhanced CT. Therefore detection of an adrenal mass in such a study requires further work-up. Considerable work has recently been done using non-contrast CT, delayed enhanced CT, and magnetic resonance in evaluating adrenal masses.\textsuperscript{[14]} and there are some data suggesting that positron emission tomography scanning may be useful in this setting.\textsuperscript{[15]} Using these techniques, it is usually possible to definitively diagnose benign adrenal cortical adenomas without biopsy. If these imaging studies suggest the presence of a metastasis, biopsy proof is generally required before altering therapy.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Gross mediastinal invasion (T4 disease). CT shows bulky, abnormal soft tissue within mediastinal fat (arrow). This particular location is not accessible for biopsy proof via mediastinoscopy or transtracheal needle biopsy.}
\end{figure}

\section*{Conclusion}

CT offers useful information in the work-up of patients with NSCLC. However, CT staging accuracy is imperfect, and it is important to know the capabilities and limitations of the technique in order to appropriately triage patients for therapy or further diagnostic testing.

\section*{Key points}

- CT staging accuracy is imperfect.
- A patient should not be denied potentially curative surgery based on unproven CT findings.
Figure 9 Mediastinal lymph node metastases (N2 disease). CT shows a central left upper lobe mass (white arrow), postobstructive atelectasis, and enlarged lymph nodes (yellow arrow) in the aortopulmonary window.

CT findings should be used to direct the appropriate method of biopsy, in order to confirm the tumor stage.

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[18F]FDG-PET in lung cancer: current status

K A Miles

Division of Clinical and Laboratory Investigation, Brighton & Sussex Medical School, University of Sussex, Falmer, Brighton, BN1 9PX, UK

Corresponding address: K A Miles, Division of Clinical and Laboratory Investigation, Brighton & Sussex Medical School, University of Sussex, Falmer, Brighton, BN1 9PX, UK. E-mail: k.a.miles@bsms.ac.uk
Abstract
Increasingly, evidence of safety, effectiveness and cost-effectiveness is required to support funding of new diagnostic technologies. However, diagnostic imaging is a rapidly changing speciality with new data constantly being added to the evidence base. This article aims to review the evidence base for the application of fluorodeoxyglucose positron emission tomography ($^{18}$FFDG-PET) in lung cancer and to identify areas in which the evidence base is evolving. Currently, there is strong evidence for $^{18}$FFDG-PET in characterisation of pulmonary nodules when there is a relative contra-indication for needle biopsy or when biopsy results are indeterminate, and for staging patients with non-small cell lung cancer without enlarged mediastinal lymph nodes on computed tomography (CT). Evidence is emerging for a role in patients undergoing radiotherapy but the impact on outcomes and cost-effectiveness is unknown. For patients with small cell lung cancer, $^{18}$FFDG-PET can change clinical management but cost-effectiveness is yet to be evaluated is this patient group. PET/CT is more accurate than PET alone but it is unclear how this technology can be most effectively and cost-effectively incorporated into management pathways. The potential impact of quantitative contrast-enhanced CT on the cost-effectiveness of $^{18}$FFDG-PET in characterisation of pulmonary nodules illustrates the need for continual re-evaluation of the evidence base as new techniques emerge.

Keywords: Positron emission tomography; fluorodeoxyglucose; lung neoplasms; effectiveness; cost-effectiveness.

Introduction

The emergence of positron emission tomography (PET) in clinical oncology has coincided with the increasing application of evidence-based medicine (EBM) to diagnostic imaging technologies. In many countries, funding of PET has been predicated on sufficient evidence of safety, effectiveness and cost-effectiveness. The need to meet the requirements of EBM has meant that the amount of evidence supporting clinical applications for PET exceeds that of most other imaging modalities. However, diagnostic imaging is a rapidly changing speciality with new data constantly being added to the evidence base. These new studies may not only strengthen the existing evidence base, for instance by allowing meta-analyses, but also refine the existing indications or extend them to new groups of patients. In addition, technological advances may further improve the performance of new modalities such as PET. Conversely, the evidence base may also need to be reviewed in the light of developments in rival technologies. This article aims to review the existing evidence base for the application of fluorodeoxyglucose ($^{18}$F)FDG PET in lung cancer and to identify those areas in which the evidence base is evolving.

Current evidence base

Safety

The safety of $^{18}$FFDG-PET has been confirmed by clinical trials and by the scarcity of adverse reactions despite wide-spread clinical use. The short half-life of fluorine-18 results in a radiation dose to patients that is comparable to body computed tomography (CT).

Solitary pulmonary nodules

The effectiveness of $^{18}$FFDG-PET in characterising solitary pulmonary nodules is confirmed by several studies demonstrating high diagnostic accuracy. Reported sensitivities range between 89 and 100% and specificities between 58 and 100% [1]. Granulomatous diseases, such as histoplasmosis, may produce false-positive results and thus specificity values for $^{18}$FFDG-PET are lower in populations with a high incidence of such diseases. Although false-negative studies can occur with alveolar cell carcinoma and carcinoid tumours, such instances are rare and a negative $^{18}$FFDG-PET scan often means that the cost and morbidity of needle biopsy or excision can be avoided. Thus, the diagnostic accuracy for $^{18}$FFDG-PET translates to improved cost-effectiveness, as has been shown for a range of countries with differing health care cost structures and prevalence of malignancy within nodules [2]. The level of evidence is such that, in many countries, clinical practice guidelines advocate the use of $^{18}$FFDG-PET for characterising pulmonary nodules when there is a relative contra-indication for needle biopsy or when biopsy results are indeterminate.

Pre-operative staging of non-small cell lung cancer

There is high-level evidence for superior effectiveness of $^{18}$FFDG-PET over CT in mediastinal staging of non-small cell lung cancer (NSCLC). A recent meta-analysis of 39 studies reported median sensitivity and specificity of 61% (inter-quartile range 50–71%) and 79% (inter-quartile range 66–89%) respectively for CT compared to 85% (inter-quartile range 67–91%) and 90% (inter-quartile range 82–96%) for PET [3]. Distant metastases, especially in bone or adrenal glands, are also accurately depicted by $^{18}$FFDG-PET. The
Care should be taken when using $^{18}$F-FDG-PET to stage patients with lung cancer complicated by interstitial lung disease (left: high resolution CT) which can be associated with increased pulmonary $^{18}$F-FDG uptake (right) and falsely positive mediastinal lymph nodes.

Superior sensitivity of $^{18}$F-FDG-PET can impact upon clinical outcomes by identifying unsuspected tumour sites outside of the proposed operative field. Surgery would become inappropriate for such patients and the associated morbidity, mortality and costs would be avoided. Indeed, significant changes in management occur in 32–51% of patients examined. However, the diagnostic performance of $^{18}$F-FDG-PET varies depending upon the appearance of mediastinal nodes on CT, with reduced specificity for PET (median 78%) when mediastinal lymph nodes are enlarged[3]. False-positive lymph nodes on $^{18}$F-FDG-PET may be particularly likely in patients with other pulmonary complications such as interstitial pneumonitis, previous tuberculosis and silicosis (Fig. 1)[4]. Hence, there remains some uncertainty as to how $^{18}$F-FDG-PET is best incorporated into clinical management pathways. Should $^{18}$F-FDG-PET be performed in all patients or reserved for those without nodal enlargement on CT? Should patients with positive mediastinal nodes on PET undergo mediastinoscopy and biopsy? These questions combined with variations in costs of PET relative to surgery have produced variable results from studies evaluating the cost-effectiveness of PET in staging NSCLC[2]. The evidence for effectiveness and cost-effectiveness of $^{18}$F-FDG-PET is strongest for patients without nodal enlargement on CT and clinical guidelines increasingly advocate the use of $^{18}$F-FDG-PET for pre-operative staging in this sub-group of patients with NSCLC.

New patient groups

Patients undergoing radiotherapy

Evidence is emerging to indicate an effective role for $^{18}$F-FDG-PET for patients with NSCLC undergoing radiotherapy. By revealing tumour sites that would be unsuspected on CT, $^{18}$F-FDG-PET can make radiotherapy inappropriate, alter the treatment intent from curative to palliative or result in extension of the treatment volume. The treatment volume can also be reduced by excluding atelectasis which is more easily distinguished from tumour on $^{18}$F-FDG-PET images than on CT. Changes in treatment volume have been observed in 30–60% of patients for whom definitive therapy is planned[5]. There is evidence from a single non-randomised study that these changes in management impact on survival as patients selected for radiotherapy after PET experience lower early cancer mortality[6]. However, more studies are required to assess the impact of changes in treatment volume upon survival, particularly if treatment volumes are reduced from those selected using conventional planning techniques. $^{18}$F-FDG-PET may also be more effective than CT in assessing response to radiotherapy or chemoradiotherapy. A study of 73 patients showed marked differences in apparent response between the two modalities but only the PET response significantly correlated with survival on multi-factorial analysis[7]. The cost-effectiveness of PET for patients undergoing radiotherapy is yet to be evaluated.

Patients with small cell lung cancer

Small cell lung cancers (SCLC) also demonstrate significant $^{18}$F-FDG uptake. Accurate staging of patients with SCLC is important as patients with localised disease may benefit from chemoradiation whereas chemotherapy alone is more appropriate for those with extensive disease. As for NSCLC, $^{18}$F-FDG-PET often reveals sites of SCLC that are not apparent on conventional imaging resulting in changes in management for many patients[8,9]. Either radiotherapy is withheld or the
treatment volume is extended to include additional tumour foci. Verifying that these management changes are appropriate has been constrained by the fact that few patients with SCLC undergo surgery. However, when confirmation has been possible, \[^{18}\text{F}]\text{FDG-PET}\) has proved highly accurate. \[^{18}\text{F}]\text{FDG-PET}\) may also have a role in assessing the therapeutic response for patients with SCLC. As yet, no cost-effectiveness studies are available for PET in this group of patients.

**Technological advances**

**PET/CT**

New imaging systems that combine PET and CT within a single integrated imaging device are set to have a major impact upon cancer imaging. Although a significant aim in the development of this technology was faster image acquisition through use of CT for attenuation correction, the co-registration of PET and CT data sets has proved advantageous by allowing better anatomical assignment of PET findings. Early indications of the application of this technology in lung cancer are that PET/CT confers statistically significant improvements in accuracy over PET and CT alone\[^{10,11}\]. There is also a small benefit over visual correlation of PET and CT images\[^{10}\]. In one study, the improved diagnostic accuracy of PET/CT resulted in changes in the treatment plan in 15% of cases when compared to PET and in 19% when compared to CT\[^{11}\]. However, there are unresolved questions as to how PET/CT can be most effectively and cost-effectively incorporated into management pathways for patients with lung cancer. Should PET/CT replace CT or, as can be argued for conventional PET, be reserved for patients without enlarged mediastinal nodes on CT? If PET/CT were to replace CT altogether, a number of patients would undergo the additional PET component when the CT data alone would have contra-indicated surgery. Furthermore, if replacing CT, should PET/CT be performed with intravenous contrast media and the higher tube current used for conventional diagnostic CT or is the low-dose unenhanced technique as required for attenuation correction sufficient? On the other hand, there are as yet insufficient data to indicate the effectiveness of PET/CT specifically in the sub-group of patients without nodal enlargement on CT. The cost-effectiveness of PET/CT for either strategy remains to be determined.

**Quantitative contrast-enhanced CT**

Current guidelines recommending \[^{18}\text{F}]\text{FDG-PET}\) for the characterisation of pulmonary nodules were made on the basis of evidence acquired before the development of quantitative contrast-enhanced CT (QECT) as a means to improve the diagnostic accuracy of CT for such patients. Following a previous multi-centre study, the technique has attracted some interest, for example in the evaluation of pulmonary nodules detected during CT screening for lung cancer\[^{12,13}\]. Low enhancement values imply a benign lesion, thereby reducing the need for further investigation by fine needle aspiration and/or \[^{18}\text{F}]\text{FDG-PET}\). Thus, by improving the effectiveness of CT, QECT has the potential to alter the apparent gains in cost-effectiveness hitherto afforded by PET strategies. Indeed, a previous modelling study has shown that QECT alone is potentially more cost-effective than \[^{18}\text{F}]\text{FDG-PET}\) strategies when there is a higher likelihood of malignancy within a nodule and when the cost of \[^{18}\text{F}]\text{FDG-PET}\) is high relative to the cost of surgery\[^{14}\].

**Summary**

To date, \[^{18}\text{F}]\text{FDG-PET}\) has met the requirements of EBM such that PET imaging is increasingly advocated in clinical practice guidelines for the management of selected patients with lung cancer. However, the evidence base will need to be continually re-evaluated not only as data emerge to support the use of PET in new groups of patients but also as advances accrue in PET technology. It is also necessary to be mindful of advances in alternative imaging modalities, as these developments may impact on the relative effectiveness and cost-effectiveness of \[^{18}\text{F}]\text{FDG-PET}\) in lung cancer.

**Key points**

- There is strong evidence to support the use of \[^{18}\text{F}]\text{FDG-PET}\) in characterising pulmonary nodules and for staging patients with NSCLC in selected cases.
- Evidence is emerging to indicate an effective role for \[^{18}\text{F}]\text{FDG-PET}\) for patients with NSCLC undergoing radiotherapy but the impact on outcomes and cost-effectiveness is unknown.
- \[^{18}\text{F}]\text{FDG-PET}\) can change clinical management for patients with SCLC but cost-effectiveness is yet to be evaluated in this patient group.
- PET/CT is more accurate than PET or CT alone but it is unclear how this technology can be most effectively and cost-effectively incorporated into management pathways.
- The evidence base for \[^{18}\text{F}]\text{FDG-PET}\) will need to be re-evaluated as new techniques emerge.

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