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REVIEW

Volume definition in radiotherapy planning for lung cancer: how the radiologist can help

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Abstract

Effective treatment for carcinoma of the lung remains one of the biggest challenges in oncology. Radical radiotherapy may be a curative option for patients who are unsuitable for radical surgery either because of disease stage or because of co-morbidity. Long-term disease control with radical radiotherapy is disappointing with only about 6% of patients treated being alive at 5 years[1]. Technological advances involved in the planning and delivery of radiotherapy may improve this. The advent of conformal radiotherapy, utilizing computed tomography and three-dimensional planning systems, allows much more accurate shaping of the radiation fields. This greater accuracy of target volume definition facilitates a reduction in the radiation dose to normal tissues, allowing for dose escalation to the tumour. Delineation of the target volume can be problematic. Conventional CT has limitations in term of distinguishing between benign and malignant tissues, e.g. the size criteria for involved lymph nodes. The oncologist uses a combination of radiological and clinical information when defining the target volume but their radiological interpretation of imaging is inferior to that of a radiologist.

The Royal College of Radiologists (RCR) issued guidance in 2004 on the optimal imaging strategies for common cancers. These guidelines address issues regarding the localisation and staging of cancers and treatment planning, and also reporting and training. They recommend the development of closer links between radiologists and oncologists to optimise the interpretation of imaging and target volume definition.

This article aims to briefly explain the planning process involved in irradiating lung cancers, highlight problematic areas and suggest ways in which co-operation with radiologists may improve the delivery of radiotherapy and therefore the treatment outcomes for this group of patients.

Keywords: Lung cancer; radical radiotherapy; target volume definition; conformal planning; imaging.

Introduction

Carcinoma of the lung is one of the most common cancers worldwide and has the poorest survival rates. In the UK, over 38,000 patients are diagnosed with lung cancer annually. It accounts for 25% of male and 18% of female cancer deaths and the overall 5 year survival rate is just 6%[2]. This is due in part to late stage at presentation, but even those who are considered fit for radical treatment have low survival rates, approximately 20% 5 year survival after radical surgery and just 6% after radical radiotherapy[1]. The survival difference between the two treatment modalities is partly attributable to selection bias. Patients with more advanced stage, irresectable disease, or co-morbidities that preclude surgery, may still be offered radical radiotherapy. Five year survival after radical radiotherapy has been as high as 40% in selected series.

The number of patients treated radically for carcinoma of the lung varies greatly between centres but improvements in diagnostic pathways, with increased use of neoadjuvant chemotherapy, means that in the future more patients will be considered suitable for radical treatments.

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Radiotherapy is becoming increasingly sophisticated both in terms of its planning and in the delivery. The goal of any radical radiotherapy treatment is to deliver a tumouricidal dose to macroscopic and microscopic disease while minimising the dose to sensitive normal tissue. Recent improvements in radiation technology have enabled greater conformity of the treated volume to the target volume. It is becoming accepted practice to geometrically shape the treatment volume and to deliver a 3D high dose volume to the tumour while avoiding neighbouring organs at risk (OAR) (Figs 1 and 2). This is termed conformal radiotherapy. A further development on this theme is intensity-modulated radiotherapy (IMRT), which both allows conformity of beam shape and modulates the fluence of the beam. This means that not only can the radiation field be shaped to fit the tumour but also the dose across the volume can be modified with the potential of improving dose distribution.

The planning process involves a complex chain of events and successful treatment is dependent on optimisation of each step. Each part of the process (tumour definition, simulation, treatment planning, treatment delivery) can be strengthened and enhanced by improvements in imaging and technologies.

Fundamental to this process is the accurate definition of the target volume. The close proximity of lung cancers to critical organs such as the spinal cord or oesophagus often limits the dose that can be given to the tumour. Accurate assessment of tumour versus benign tissue is vital if doses are to be increased without increasing toxicity. Dose escalation is an area of considerable research in lung cancer as several studies have shown promising results in terms of local control[3].

Studies comparing the delineation of lung cancers both between oncologists and between oncologists and radiologists show a large degree of variation between clinicians as to what is considered to be ‘normal tissue’ and what is tumour. Radiologists have less inter-clinician variation, especially with more difficult cases, and produce smaller volumes[4,5]. In the UK there is little formal training of oncologists in cross-sectional imaging and it is not common practice for radiologists to become intimately involved in the planning process.

### The planning process

#### Patient selection

Both non-small cell lung cancers (NSCLC) and small cell lung cancers (SCLC) can be treated with radical intent utilising radiotherapy. For patients to be considered for radical radiotherapy the disease volume must receive a tumouricidal homogeneous dose while the dose to the OAR is maintained at an acceptable level of predicted late toxicity. This may include patients with Stage I, II or IIIa NSCLC (or limited stage for SCLC) who are unsuitable candidates for surgery, usually due to co-morbidity. Stage IIIb tumours will also be considered depending on the size of tumour, and where neoadjuvant chemotherapy has been successful in reducing tumours to a volume where radical treatment is feasible. Lung function is an important consideration. The tolerance of lung to radiotherapy is dependent both on the dose received and on the volume of lung treated. The pneumonitis and long-term fibrosis caused by radiotherapy causes permanent reduction in lung function therefore the pre-treatment pulmonary function criteria are similar to those required for radical surgery. There may be certain circumstances where tumours are in poorly ventilated or perfused areas where the loss in functional capacity is less than predicted for the volume irradiated. There is a high incidence of smoking-related lung disease in this group and there must be sufficient respiratory reserve for patients to continue with normal activities subsequent to therapy. Performance status (PS) is an important predictor of how a patient will tolerate treatment and their overall survival. Patients should normally be expected to have a PS of 0 (asymptomatic) or 1 (symptomatic, fully ambulatory) (ECOG criteria) to be considered for radical treatment.

#### Planning preparation

Once a patient has been selected for radical radiotherapy a planning computed tomography (CT) scan is acquired with the patient immobilised in the position in which they will be treated; 3–5 mm sections would be considered standard. The data from this scan are then transferred to planning systems. The clinician defines the target volume and dose limiting normal tissues and subsequently the planning process is continued by a physicist or a planning radiographer.

#### Volume definitions

The volumes used for 3D conformal radiotherapy for NSCLC are defined by the International Commission on Radiation Units (ICRU) report 50 and the supplement ICRU 62[6]. The gross tumour volume (GTV) is the gross palpable, visible or demonstrable extent of malignant disease. To ensure adequate coverage of subclinical or microscopic disease a 3D margin may be added to the GTV known as the clinical target volume (CTV). In turn a further margin is required to account for technique-dependent variations such as positional inaccuracy for the individual, internal organ movement (e.g. breathing), and parameters of the treatment machine that may result in inadequate dose coverage of the CTV. The addition of this margin produces the planning target volume (PTV). In lung cancer planning, a margin of 1–2 cm is added to the disease visible on CT scan to produce the PTV (Fig. 3).

Opinions as to what should be included in the CTV in NSCLC vary between departments. In general the primary tumour and involved nodes only are included in the GTV. An 8 mm margin is estimated to cover 95%
of microscopic extension in adenocarcinoma and a 6 mm margin will cover 95% in squamous carcinoma\cite{7}, and this is added to form the CTV. There is currently no evidence that elective nodal irradiation of uninvolved nodes improves outcome\cite{8} but this is an area of ongoing research. What is less clear is whether pre-chemotherapy volumes should be used or residual disease post-chemotherapy. The borders of the GTV are assessed using all the imaging modalities available to the oncologist. This may be only the diagnostic and planning CT but increasingly positron emission tomography (PET) and PET-CT are being used.

In thoracic radiation the critical normal structures (organs at risk) that are likely to receive a significant radiation dose are: spinal cord; lungs; heart and pericardium; oesophagus.

It is important to know the dose delivered to these structures, as this must be kept within normal tissue ‘tolerance’. The tolerance doses are defined according to a late toxicity incidence of 5% at 5 years (TD 5/5)\cite{9}. In practice a late toxicity rate of 5% may be considered unacceptably high, e.g. for spinal cord damage, potentially leading to paraplegia, so lower doses are considered acceptable. The tolerance of an organ depends not only on the dose it receives but also the volume of the organ irradiated. For example, the entire lung volume can only tolerate a dose of 24 Gy before 50% of patients treated develop pneumonitis\cite{9}. However, small volumes of lung can be taken to much higher doses, as the functional loss of a small fraction of lung tissue will have little clinical significance in otherwise healthy lungs. For lungs a value, $V_{20}$, is calculated. This is the percentage volume of both lungs minus the PTV receiving 20 Gy or more and is used to predict for the risk of high-grade radiation pneumonitis. All of the above structures are outlined so their volumes can be calculated.

Target definition for lung cancer is beset by a number of problems:

1. Window settings. The extent of the parenchymal disease is defined on the lung window settings. The exact setting chosen will seem to increase or decrease the size of the abnormal area. One study has found that $W = 1600$ and $L = -600$ gives the best correlation between measured and actual volumes for parenchymal
disease, and $W = 400$ and $L = 20$ for mediastinal disease\cite{10}. The planning software will not necessarily pre-set these levels so the oncologist should be aware of the significance of these parameters and select them accordingly (Fig. 4).

The ability to differentiate between consolidation and tumour is therefore very important. It may be easily recognisable on CT as patchy consolidation, or homogenous opacification with air bronchograms. Where this is not clear, dynamic contrast-enhanced CT may be helpful as collapsed lung enhances more than central tumour\cite{11} (Fig. 5). T2-weighted or gadolinium enhanced T1-weighted magnetic resonance imaging (MRI) can also be useful as the tumour has lower signal than the mucus-filled distal bronchi. Isointense signal should be interpreted with caution as organising pneumonia and atelectasis will give a signal identical to tumour. PET imaging has not been shown to be helpful in this situation.

3. Identification of lymph nodes. The differentiation of lymph nodes from other structures can be quite a challenge for the oncologist. A good knowledge of the position of the intrathoracic vasculature, the thymus and the pericardium, and the ability to track them over several sections, is essential to avoid confusion between lymph nodes and normal structures. Aberrant vessels or normal vessels with delayed enhancement are likely to cause some confusion (Fig. 6). The Royal College of Radiologists’ guidelines recommend the use of intravenous contrast and this will assist the clinician to differentiate lymph node from vessel\cite{12}, but some lymph nodes enhance with contrast and may be mistaken for vessels (Fig. 7). The pericardiac recesses can easily be mistaken for enlarged lymph nodes by the uneducated eye and only experience will allow an oncologist to correctly identify this structure (Fig. 8).

4. Lymph node enlargement. Elective nodal irradiation is not standard practice in radical radiotherapy for lung cancer, but involved lymph nodes are included in the GTV. The detection of involved lymph nodes is notoriously difficult in the mediastinum. There can be discrepancy between CT and surgical staging in 60% of cases\cite{13}. The routine use of intravenous contrast improves mediastinal nodal detection only marginally but significantly improves hilar lymph node detection\cite{14}. Enhancement characteristics are unhelpful, as necrotic areas are not frequently seen in nodal metastasis from lung cancer. Lymph node enlargement is the most extensively validated sign of metastasis. The size criteria for enlargement vary according to the position in the thorax but simplistically, nodes smaller than 10 mm in the short axis fall within the 95th percentile and should be considered normal\cite{14}. For mediastinal nodes, this gives a sensitivity and specificity of 50% and 65%\cite{15}. Up to 35% of normal-sized mediastinal and hilar lymph nodes can contain tumour\cite{13}.

FDG-PET imaging has emerged as a superior imaging tool for mediastinal lymph node involvement in lung cancer. Co-registration with CT images (PET-CT) further enhances the accuracy, giving the correct nodal stage in 94% of cases, and makes localisation of the involved nodes easier for the clinical oncologist than with standard PET imaging\cite{16}.
5. Partial volume effects. The blurring of the margins of the tumour can often be interpreted as tumour bulk. Normal vessels, notably the central pulmonary arteries, in adjacent sections can be misinterpreted as masses or enlarged lymph nodes. The oncologist may inappropriately include these areas in the GTV, which would result in the irradiation of significantly more of the thorax than is necessary.

6. The pleura. It can be impossible to differentiate between neoplastic involvement of the pleura and reactive pleural effusion or benign pleural thickening. CT signs of parietal pleural invasion include: an obtuse angle of contact; obliteration of the extrapleural fat plane; pleural thickening; and extrapleural soft tissue. The accuracy of CT is limited but alternative imaging modalities may help. MRI has not been shown to be superior to CT in this context. Movement between the pleural layers may be detected using ultrasound scanning or conventional CT or MRI during inspiration and expiration. A diagnostic pneumothorax may be helpful but is not an ideal investigation in a population with significant pulmonary disease. A lack of movement between the pleural layers may be due to tumour invasion but may also be due to benign adhesions. Inclusion of the pleura in the volume may result in a good deal of normal lung being irradiated to a significant dose. Thoracoscopy may be the only reliable way of assessing this problem.

7. Chest wall. Chest wall invasion renders a patient ineligible for radical radiotherapy. CT and MRI are equally unreliable in positively diagnosing invasion unless there is rib invasion or disease outside the intercostal muscles (Fig. 9). The criteria of less than 3 cm of contact and preservation of extrapleural fat will give a greater than 90% sensitivity for no spread beyond the visceral pleura. Pain is probably as reliable as imaging at assessing chest wall invasion.

8. Apices (superior sulcus/Pancoast tumours). Tumours in this area are difficult to treat radically as they have a propensity to invade the chest wall, root of the neck, brachial plexus, subclavian vessels and spine. Radical treatment usually involves a combination of both surgery and radiotherapy. The curvature of the chest makes coronal and sagittal planes ideal for visualisation of neural foramina, vessels and brachial plexus. MRI is therefore considered the optimal imaging modality but multidetector CT imaging may prove to be just as accurate.
Volume definition in radiotherapy for lung cancer

**Figure 6** In (a) the azygous vein is unopacified and gives the impression of bulky mediastinal lymph nodes. The same is true in (b) where the right brachiocephalic is unopacified.

**Figure 7** Lymph nodes in the aortopulmonary window clearly show enhancement in this image. A clinical oncologist may mistake these for vessels and not include them in the treatment volume.

**How the radiologist can help**

Radiologists have both training and experience in differentiating between normal and abnormal tissue on CT scans of the thorax. There are several potential ways in which they may be able to use this knowledge to assist the clinical oncologist in the planning of radical radiation doses in carcinoma of the lung.

1. **Involvement at the point of planning.** Producing the GTVs and PTVs for any treatment plan is the responsibility of the clinical oncologist. However, in our department a consultant radiologist will review the volumes chosen with the oncologist and suggest modifications as appropriate. This also becomes an ideal forum for education of both the oncologist and the radiologist.

2. **Schematic mapping at the MDT.** It is not always going to be possible for the radiologist to be directly involved in drawing the GTV. Multidisciplinary team meetings (MDT) usually involve a review of the patient’s imaging in the presence of the oncologist. This could be an ideal time for a discussion about the radiotherapy target volumes. Other tumour sites have produced a schematic diagram for the radiologist to mark the position of involved lymph nodes or residual tumour bulk. This could be a possibility for thoracic malignancies using the American Thoracic Society and North American Lung Cancer Study Group (ATS/LCSG) lymph node regions as a guide\(^\text{[17]}\), recognising the limitations of CT in differentiating between these nodal stations. The radiological boundaries of lymph node stations have been described using CT scans with the aim of providing guidelines for clinicians and to aid reproducible target volume definition\(^\text{[18]}\).

**Figure 8** The pericardiac recess can easily be mistaken for an enlarged node.
3. Improved education. The technological advances in radiotherapy have been rapid, and the educational emphasis has struggled to keep up. Conventional planning involving simple field arrangements and relying on bony landmarks still forms a large part of our educational programme. Planning from CT scans is increasingly common and with the advent of modern planning technologies it is becoming more and more important for oncologists to know their anatomy in detail and be able to identify structures on cross-sectional images. There is a move to increase the teaching in this area with the proposed introduction of electronic teaching modules and involvement of clinical oncology trainees in reporting sessions, but this is reliant upon the willingness of radiologists to become involved and to understand what the needs of the oncologist are.

4. Structured reporting of diagnostic scans. The report of diagnostic scans forms part of the information assessed by the clinical oncologist when deciding what to include in the GTV. Comments such as ‘slightly enlarged mediastinal lymph nodes’ leaves the oncologist unsure whether they are likely to be involved and if so exactly which mediastinal nodes should be covered by the target volume. The RCR guidelines on reporting of staging scans make a number of recommendations including description of the primary along with dimensions and image numbers, which nodal chains are enlarged and the dimensions, and a statement about non-malignant changes that may be pertinent. The radiologists reporting these scans may not appreciate the importance of this information, so should familiarise themselves with the radiotherapy planning process so that they know what is vital and should be included in a report.

Although, as previously discussed, it is not possible to be 100% accurate in the determination of these parameters, the experienced interpretation of the radiologist is likely to be more accurate than the oncologist.

Conclusion

Technology in radiotherapy is developing rapidly. For these advances to be translated into clinical benefit for the patient, the skills of the clinical oncologist must keep pace with what is required to get maximum benefit from the techniques available. There is little point in producing intricate radiotherapy plans to irradiate complex volumes if the volume chosen by the clinician does not accurately represent the tumour. The radiologist is perfectly positioned to facilitate an improvement in the planning of lung cancers. Choosing the most appropriate imaging modality to answer the clinically important questions relies on the clinical oncologist asking the questions, but the radiologist must educate the oncologist about what questions can be answered and with what level of accuracy. Each centre should devise a strategy between the two departments that will directly or indirectly involve the radiologist in the planning process. The RCR guidelines suggest the identification of a lead clinical radiologist with an interest in cancer imaging and that meetings should occur regularly to discuss the planning of complex cases.

Selecting appropriate patients for radical treatment will reduce unnecessary morbidity of radical treatment for patients who are incurable and increase the overall success rate of radical radiotherapy. Improvement in tumour volume definition will allow the tumour doses to be escalated without increasing the toxicity to critical normal structures. This will hopefully translate into an improvement in local control and overall survival in this group of patients, who currently have such a poor prognosis.

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