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Positron emission tomography for target volume definition in the treatment of non-small cell lung cancer

Konstantin Lavrenkov, Mike Partridge, Gary Cook, Michael Brada

Lung Research Unit¹, Joint Department of Physics², and Department of Nuclear Medicine and PET³, The Royal Marsden NHS Foundation Trust and Academic Unit of Radiotherapy and Oncology⁴, The Institute of Cancer Research, Sutton, Surrey, UK

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Address for correspondence:

Dr Konstantin Lavrenkov
Lung Research Unit
The Royal Marsden NHS Foundation Trust
Downs Road,
Sutton, Surrey
SM2 5PT,
UK

tel: 44 (0)20 8661 3272
fax: 44 (0)20 8661 3127
e-mail: Konstantin.Lavrenkov@rmh.nhs.uk
Abstract

The additional benefit of positron emission tomography (PET) in the initial staging of non-small cell lung cancer (NSCLC) has generated interest in 18F-fluorodeoxyglucose (FDG) PET as a means of defining the extent of primary lung tumour for radiotherapy treatment planning (RTP). A review of published data suggests that PET results in a reduction in the CT-derived GTV for NSCLC primary target volume in 15% of patients. This is principally due to the ability of PET to distinguish tumour from atelectasis. However, the difficulty of tumour edge definition, limited spatial resolution and tumour motion during image acquisition currently limit the accuracy of PET in target volume delineation in NSCLC without adjacent lung consolidation. This is compounded by the lack of data correlating PET with spatial pathology at the primary tumour site. With the current technical limitations it is not established that PET can add accuracy to the CT defined primary target delineation in RTP of NSCLC. It is hoped that advances in PET and combined PET/CT imaging may overcome some of the technical limitations. Future use of PET for primary tumour delineation in NSCLC will also be critically dependent on detailed studies of imaging-pathology correlation.
Introduction

Lung radiotherapy has come of age with considerable research interest in modern techniques of localised treatment delivery. The aim is dose escalation to achieve improved tumour control and survival. Despite many technological advances which have led to more conformal radiotherapy, all is not well. It is possible to harness all available technology to treat not only stationary but also moving targets in the chest with greater accuracy and with more localised treatment. However, this is difficult to do if there is uncertainty where the target is. Although this may be overstating the facts, anyone dealing with radiotherapy of non-small cell lung cancer (NSCLC) is aware of the well publicised issue of inter-observer variation in tumour delineation and the lack of agreement on what is and isn’t tumour on conventional imaging [1, 2]. Into this scenario come new imaging modalities of which 18F-fluorodeoxyglucose (18FDG) positron emission tomography (PET) seems most promising. Judging by titles of some recent publications [3-8], it may be possible to gain an impression that adding 18FDG PET to CT in defining the target volume improves the localisation of the tumour. Is this really the case?

Undoubtedly PET with radio-labelled glucose analogue fluorine-18-fluorodeoxyglucose is a useful staging investigation in patients with non-small cell lung cancer (NSCLC). Can the increased accuracy in defining nodal disease be transferred to improved target volume definition for radiotherapy planning (RTP)? Before being swept by the wave of enthusiasm in favour of 18FDG-PET it
is important to take stock of the present evidence for its benefit in delineating primary target volume in NSCLC.

**18FDG-PET in staging of NSCLC**

There is little doubt that 18FDG-PET helps in staging of NSCLC. PET in combination with chest computerized tomography (CT) increases the accuracy of mediastinal lymph node staging to 92-95% compared to 68-85% for CT alone. The positive and negative predictive values of combined CT and PET imaging are in the region of 95% [9-11]. There are two possible consequences of altered stage following PET for radiotherapy planning. Upstaging due to finding previously undetected regional nodal involvement, which occurs in 10-25% of patients, translates into a larger gross tumour volume (GTV) with potentially undeliverable radical RT because of excessive radiation dose to normal lung [3, 4, 12]. Smaller GTV due to exclusion of suspicious but PET negative lymph nodes, noted in 15-35% of patients, may allow for dose escalation with possible improvement in tumour control and survival [3-8, 12].

**Current use of 18FDG-PET in RTP of NSCLC**

The recently published study of De Ruysscher et al. [13] reported a reduction in GTV derived from combined PET/CT in comparison with CT alone in all 21 patients studied. This translated to a reduction in mean oesophageal and mean lung doses and a reduction in oesophageal V55 and lung V20. This benefit in normal tissue sparing was a consequence of excluding CT suspicious but PET
negative lymph nodes from GTV. The question, however, remains whether PET improves the accuracy in delineating the primary lung tumour.

Six previously published studies reported using $^{18}$FDG-PET for delineation of primary tumor GTV in RTP of NSCLC [3-8]. PET data were incorporated into CT-based RTP planning either by visual comparison or with formal image coregistration. When information about lymph node staging is excluded, the PET-derived primary tumour GTV was reported to be smaller in 13-17% of patients regardless of the method of image fusion. This was largely accounted for by the ability of PET to distinguish tumour from uninvolved distant collapse/consolidation. Nevertheless, there is lack of pathologic data to confirm that atelectatic regions with low FDG-uptake do not contain any tumours. Can FDG - PET help in the definition of the primary lung tumour in patients without adjacent atelectasis? To be able to answer it it is necessary to consider the factors which influence the accuracy of PET derived target volume in the lung.

**Factors affecting FDG-PET accuracy in delineation of primary lung tumour**

*Tumour edge definition*

GTV delineation using CT and PET in patients with NSCLC is subject to major inter-observer variations and this adds considerable uncertainty to the accuracy of target volume definition [12, 14]. Reliable use of PET in primary GTV definition requires a clearly established methodology particularly for quantitative determination of the tumour edge which is typically based on standardized
uptake value (SUV), where threshold (or cut-off value) defined as a percentage of maximum SUV or an absolute SUV value is used.

Reported variability of threshold values (30-55%) for lung lesions of different volumes [14, 15] indicates that there is no standard value applicable for all patients and techniques for individual thresholding need to be defined and standardized. The regression function representing the relationship between the threshold and the mean target SUV cannot be accurately applied to automatically define the primary tumour edge in PET scans because of highly heterogeneous distribution of $^{18}$FDG uptake within the tumour [16]. This demonstrates the limitations for direct translation of phantom model studies to clinical use in RTP of NSCLC. Adequate methodologies are therefore needed to account for heterogeneity of $^{18}$FDG uptake when defining the tumour edge in NSCLC. The “gold standard” method for validating a threshold technique for tumour definition would be comparison with histological specimens; this poses a particular problem in lung cancer, where accurate spatial correlation of excised surgical specimens with imaging is difficult to achieve.

Spatial resolution

The limited spatial resolution of PET significantly contributes to image blur and this is closely linked to the problem of tumour edge definition. Technical developments are likely to lead to improvement of detector and imaging system design [17]. However, the influence of intrinsic tissue factors related to tissue density and atomic structure cannot be eliminated by further hardware advances.
Since positron interactions with matter are influenced by both tissue atomic composition and density, it is expected that a cloud of annihilation points around the positron source vary in shape and size depending on the type of tissue in which the positron transport takes place. There are large differences in positron range for various human tissues [18]. For fluorine-18 in a typical whole-body PET scanner spatial resolution losses due to the finite positron range were shown to be around 0.5 mm in soft tissues but up to 1.5 mm in lung. Although this contributes little to the overall system spatial resolution for fluorine-18, it can become significant in lung tissue for isotopes with higher energy positron emission such as oxygen-15 (5.3 mm) and rubidium-82 (10.5 mm). With future generation scanners which aim for system resolution of 3 mm or less, further 1.5 mm uncertainty for fluorine-18 may also become significant.

Tumour motion

Tumour motion as a function of normal respiration presents a major problem for RTP in lung cancer. There are two methods which ensure that the whole tumour is included in the acquired image and is subsequently appropriately treated. A composite tumour volume method takes into account tumour motion without altering it. It either employs slow CT acquisition with a blurred image in all its positions during free breathing cycle, or scans are acquired at both deep inspiration and deep expiration breath hold which includes the tumour at the two extremes of excursion [19]. These methods are relatively easy to implement, but have the disadvantage of needing large GTV to include all tumour positions.
Alternatively, to reduce the impact of tumour motion on primary GTV delineation, CT image can be acquired at a specific phase of respiratory cycle by using either voluntary deep inspiration breath hold [20], or imposed breath hold applying active breathing control device (ABC) when inspiration breath hold is set at reproducible tidal lung volumes [21]. Modern multichannel CT scanners can acquire images synchronously with surrogate signals of respiration with subsequent reconstruction at specific parts of breathing cycle [22].

PET volume acquired over several minutes during free breathing takes into account the whole range of tumour positions. While this has the disadvantage of enlarged GTV as well as the uncertainties of margin definition, it may help in defining the composite volume of the whole respiratory excursion.

Breath hold methods cannot be easily transferred to PET GTV acquisition. PET is a protracted procedure and multiple breath holds may not be tolerated by patients with NSCLC, whose lung function is frequently compromised. Nevertheless, developments in PET technology may allow for either gated image acquisition or reconstruction in a specific phase of the breathing cycle. Such techniques have been tested in small feasibility studies and are some way from routine clinical application [23].
Other PET tracers

$^{18}$F-fluorodeoxythimidine (FLT) used for visualizing proliferating tumour cells [24], and $^{18}$F-fluoromisonidazole (FMISO) [25] and $^{60}$Cu-labelled methylthiosemicarbazone (Cu-ATSM) [26] used as markers of hypoxic areas are currently explored for biologically derived planning to give different doses to areas of hypoxia and high proliferative activity within the tumour [27]. However, these tracers have not been tested for ability to define the tumour margin. The clinical application of these tracers in NSCLC is also subject to the current physical limitations of $^{18}$FDG-PET.

Conclusion

At present, FDG-PET is useful in defining nodal extension for RTP in NSCLC. It may also help in distinguishing tumour from distant atelectasis and consolidation. In the absence of atelectasis adjacent to the primary tumour, there is no evidence to suggest that PET helps in the delineation of CT defined primary lung tumour volume. The uncertainties of tumour edge definition, spatial resolution and tumour motion do not allow for routine use of PET for contouring of primary GTV in RTP of NSCLC. Further developments in PET imaging may overcome some of the problems. Ultimately, the impact of PET-based RTP will require evaluation in large-scale prospective studies.
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References


