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CLINICAL INVESTIGATION **Lung**

PET CT THRESHOLDS FOR RADIOTHERAPY TARGET DEFINITION IN NON–SMALL-CELL LUNG CANCER: HOW CLOSE ARE WE TO THE PATHOLOGIC FINDINGS?

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Purpose: Optimal target delineation threshold values for positron emission tomography (PET) and computed tomography (CT) radiotherapy planning is controversial. In this present study, different PET CT threshold values were used for target delineation and then compared pathologically.

Methods and Materials: A total of 31 non–small-cell lung cancer patients underwent PET CT before surgery. The maximal diameter (MD) of the pathologic primary tumor was obtained. The CT-based gross tumor volumes (GTV_{CT}) were delineated for CT window-level thresholds at 1,600 and −300 Hounsfield units (HU) (GTV_{CT1}); 1,600 and −400 (GTV_{CT2}); 1,600 and −450 HU (GTV_{CT3}); 1,600 and −600 HU (GTV_{CT4}); 1,200 and −700 HU (GTV_{CT5}); 900 and −450 HU (GTV_{CT6}); and 700 and −450 HU (GTV_{CT7}). The PET-based GTVs (GTV_{PET}) were autocontoured at 20% (GTV_{20}), 30% (GTV_{30}), 40% (GTV_{40}), 45% (GTV_{45}), 50% (GTV_{50}), and 55% (GTV_{55}) of the maximal intensity level. The MD of each image-based GTV in three-dimensional orientation was determined. The MD of the GTV_{PET} and GTV_{CT} were compared with the pathologically determined MD.

Results: The median MD of the GTV_{CT} changed from 2.89 (GTV_{CT2}) to 4.46 (GTV_{CT7}) as the CT thresholds were varied. The correlation coefficient of the GTV_{CT} compared with the pathologically determined MD ranged from 0.76 to 0.87. The correlation coefficient of the GTV_{CT1} was the best ($r = 0.87$). The median MD of GTV_{PET} changed from 5.72cm to 2.67cm as the PET thresholds increased. The correlation coefficient of the GTV_{PET} compared with the pathologic finding ranged from 0.51 to 0.77. The correlation coefficient of GTV_{50} was the best ($r = 0.77$).

Conclusion: Compared with the MD of GTV_{PET}, the MD of GTV_{CT} had better correlation with the pathologic MD. The GTV_{CT1} and GTV_{50} had the best correlation with the pathologic results. © **2010 Elsevier Inc.**

Non–small-cell lung cancer, positron emission tomography, computed tomography, PET CT, gross tumor volume, target definition, pathology.

INTRODUCTION

Radiotherapy (RT) is an important component in the curative treatment of non–small-cell lung cancer (NSCLC). Locoregional failure remains a significant problem for patients undergoing definitive RT alone or combined with chemotherapy for NSCLC. With greater radiation doses, it is anticipated that greater tumor control probability can be achieved (1–4). However, the radiation dose delivered to a lung tumor is limited by the toxicity to the surrounding normal tissues. New treatment techniques, such as intensity-modulated RT, stereotactic RT, and image-guided RT, allow additional dose escalation. Those new treatment techniques depend on precise tumor volume delineation, which, again, is dependent on accurate imaging.

The conventional imaging modality for treatment planning is computed tomography (CT). CT provides anatomic information, in addition to the electron densities necessary for dose calculations. Targeting of the gross tumor has been facilitated by the use of CT simulation, allowing for more accurate tumor delineation. Also, multimodality imaging combining anatomic and functional information such as that

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Table 1. Patient and primary tumor characteristics

Characteristic	Value
Patients (*n*)	31
Age (y)	
Median	65
Range	50–85
Gender	
Male	14
Female	17
Site	
LUL	9
LLL	6
RUL	12
RLL	4
Maximal pathologic diameter of primary tumor (cm)	
≤3	20
3–5	9
≥5	2
Median	2.69
Range	1.1–10.0
Histologic type	
Squamous cell carcinoma (including mixed BAC 2)	5
Adenocarcinoma (including mixed BAC 6)	21
Large cell carcinoma	1
BAC	4
Histologic grade	
1	11
2	12
3	5
Not specified	3
Atelectasis	
Yes	1
No	30

Abbreviations: LUL = left upper lobe; LLL = left lower lobe; RUL = right upper lobe; RLL = right lower lobe; BAC = bronchioloalveolar carcinoma.

provided by positron emission tomography (PET) has allowed additional refinement in the treatment planning process, with a significant effect on the planning target volume. PET using ^{18}F-fluorodeoxyglucose (FDG) allows for more precise tumor detection, because it is a functional image based on glucose metabolism instead of structural abnormalities. PET has been shown to result in more accurate staging of NSCLC compared with CT and to provide high-impact and powerful prognostic stratification in staging newly diagnosed NSCLC (5). In an overview of the available data, FDG-PET had 91% sensitivity and 68% specificity in diagnosing primary lung cancer and 83% sensitivity and 91% specificity in mediastinal staging (6) compared with 56–65% sensitivity and 73–87% specificity for mediastinal staging for CT (7).

The standard uptake value (SUV) is often used to delineate tumor on PET. The SUV is defined by the activity per dose injected per body mass, which is proportional to the glucose metabolic rate within the normal range of serum glucose concentration (8). A large degree of uncertainty exists regarding the most appropriate threshold value that should be used to define a PET target volume in NSCLC treatment planning. Different institutions have used varying methods for defining the PET volume, ranging from a ''halo phenomenon,'' to the absolute SUV, to a percentage of the maximal SUV intensity levels, to qualitative delineation, which result in huge alterations in the target volume between CT-based treatment planning alone and CT-PET–based treatment planning (1, 9–11, 12–15).

Similarly, very large volume differences have been found in contouring the gross tumor volume (GTV) using different thresholds for CT. A review of the published data revealed only four studies that had evaluated the ability of CT to define the gross tumor, and its microscopic extension correlated with the histopathologic measurements (16–18). Recently, MacPherson *et al*. (19) reported a poor correlation between the pathologic and radiologic measurements of tumor size in NSCLC.

The present study was a companion study of two Ontario Clinical Oncology Group PET trials of NSCLC. The aim of the present study was to investigate the difference in GTV using different PET intensity levels and CT thresholds and to compare them with the pathologic findings in NSCLC with the goal of determining which window/level and percentage of maximal intensity level correlates with the pathologic findings. The results of the present study will provide new guidelines on the ability of combined PET CT to determine GTV delineation in RT planning for NSCLC.

METHODS AND MATERIALS

Patient and tumor characteristics

Our local institution research ethics board approved the present study. All patients provided written informed consent. Each patient was required to have pathologic confirmation of NSCLC. A total of 31 patients with surgically resectable NSCLC underwent PET CT before surgery between August 2004 and May 2007. The patients and primary tumor characteristics are presented in Table 1.

PET-CT acquisition and image registration

Patients were asked to consume a high-protein, low-carbohydrate diet (to reduce myocardium uptake of FDG) and to avoid vigorous exercise for 24 h before imaging. Patients fasted for ≥6 h before the injection of FDG. The blood glucose levels were checked and recorded. A total of 185–370 MBq of FDG was injected intravenously, depending on the patient's weight. Patients rested for approximately 1 h before imaging. Free-breathing PET and CT images were acquired. The FDG PET CT image was acquired using Gemini PET-CT (Philips Medical Systems, Cleveland, OH) or Discovery PET CT (GE Healthcare). First a topogram was made from the skull to the mid-thigh. Second, CT images (3-mm slices) with an interval of 3 mm typically were obtained from the base of the skull through the proximal thighs without the administration of either oral or intravenous contrast agents.

The PET data were acquired using an acquisition time of 3 min/table position, with a 50% overlap. The data were reconstructed using a three-dimensional row action maximal likelihood algorithm and corrected for attenuation using a CT-derived transmission map. The voxel dimensions were 4 mm on each side.

Once the PET and CT images were acquired, the image data sets were transferred to the treatment planning workstation (Pinnacle, Philips Medical Systems) for image co-registration.

GTV definition and delineation

The CT target volumes were independently defined by a single observer. Target volume definition was performed according to