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CLINICAL INVESTIGATION **Lung**

THE CONTRIBUTION OF INTEGRATED PET/CT TO THE EVOLVING DEFINITION OF TREATMENT VOLUMES IN RADIATION TREATMENT PLANNING IN LUNG CANCER

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Purpose: Positron emission tomography (PET) with the glucose analog [18F]fluro-2-deoxy-D-glucose (FDG) has been accepted as a valuable tool for the staging of lung cancer, but the use of PET/CT in radiation treatment planning is still not yet clearly defined. By the use of (PET/computed tomography (CT) images in treatment planning, we were able to define a new gross treatment volume using anatomic biologic contour (ABC), delineated directly on PET/CT images. We prospectively addressed three issues in this study: (*1*) How to contour treatment volumes on PET/CT images, (*2*) Assessment of the degree of correlation between CT-based gross tumor volume/planning target volume (GTV/PTV) (GTV-CT and PTV-CT) and the corresponding PET/CT-based ABC treatment volumes (GTV-ABC and PTV-ABC), (*3*) Magnitude of interobserver (radiation oncologist planner) variability in the delineation of ABC treatment volumes (using our contouring method).

Methods and Materials: Nineteen patients with Stages II–IIIB non–small-cell lung cancer were planned for radiation treatments using a fully integrated PET/CT device. Median patient age was 74 years (range: 52–82 years), and median Karnofsky performance status was 70. Thermoplastic or vacuum-molded immobilization devices required for conformal radiation therapy were custom fabricated for the patient before the injection of [18]f-FDG. Integrated, coregistered PET/CT images were obtained and transferred to the radiation planning workstation (Xeleris). While the PET data remained obscured, a CT-based gross tumor volume (GTV-CT) was delineated by two independent observers. The PTV was obtained by adding a 1.5-cm margin around the GTV. The same volumes were recontoured using PET/CT data and termed GTV-ABC and PTV-ABC, correspondingly.

Results: We observed a distinct "halo" around areas of maximal standardized uptake value (SUV). The halo was identified by its distinct color at the periphery of all areas of maximal SUV uptake, independent of PET/CT gain ratio; the halo had an SUV of 2 ± 0.4 and thickness of 2 mm ± 0.5 mm. Whereas the center of our contoured treatment volume expressed the maximum SUV level, a steady decline of SUV was noted peripherally until SUV levels of 2 ± 0.4 were reached at the peripheral edge of our contoured volume, coinciding with the observed halo region. This halo was always included in the contoured GTV-ABC. Because of the contribution of PET/CT to treatment planning, a clinically significant (≥25%) treatment volume modification was observed between the GTV-CT and GTV-ABC in 10/19 (52%) cases, 5 of which resulted in an increase in GTV-ABC volume vs. GTV-CT. The modification of GTV between CT-based and PET/CT-based treatment planning resulted in an alteration of PTV exceeding 20% in 8 out of 19 patients (42%). Interobserver GTV variability decreased from a mean volume difference of 28.3 cm^3 (in CT-based planning) to 9.12 cm^3 (in PET/CT-based planning) with a respective decrease in standard deviation (SD) from 20.99 to 6.47. Interobserver PTV variability also decreased from 69.8 cm^3 (SD ± 82.76) in CT-based planning to 23.9 cm^3 (SD ± 15.31) with the use of PET/CT in planning. The concordance in treatment planning between observers was increased by the use of PET/CT; 16 (84%) had ≤10% difference from mean of GTVs using PET/CT compared to 7 cases (37%) using CT alone ($p = 0.0035$).

Conclusions: Position emission tomography/CT-based radiation treatment planning is a useful tool resulting in modification of GTV in 52% and improvement of interobserver variability up to 84%. The use of PET/CT-based ABC can potentially replace the use of GTV. The anatomic biologic halo can be used for delineation of volumes.

Lung cancer, Position emission tomography, Computed tomography, Treatment volumes, Radiation treatment.

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INTRODUCTION

Positron emission tomography (PET) with the glucose analog [18F]fluro-2-deoxy-D-glucose (FDG) is a functional imaging method that has become widely used in oncology. FDG-PET has been shown to have more accuracy than computed tomography (CT) in determining mediastinal lymph node status. A meta-analysis by Toloza *et al.* (1) reported the sensitivity and specificity of PET scan in detecting mediastinal adenopathy to be 84% and 89%, respectively, whereas CT scan assessment proved only 57% and 84%, respectively.

The integration of PET and CT scans allows the simultaneous use of biologic and anatomic imaging data. Lardinois *et al*. (2) reported in 49 patients the added benefit of integrating PET/CT compared to either PET or CT separately or to visual correlation. Integrated PET/CT provided additional information in 41% of cases, beyond that provided by conventional visual correlation of PET and CT. CT scan–based radiation treatment planning may overestimate or underestimate the targeted treatment volumes, because of the inability of CT images to differentiate between neoplastic and benign tissues. With the advent of conformal radiation therapy (CRT) and intensity-modulated radiation therapy, the need for more precise target volumes has become a compelling issue. Gross target volume (GTV) represents the initial gross tumor containing volume that most radiation oncologists contour before the addition of further margins to ensure adequate treatment coverage of subclinical disease, thereby accounting for a final planning target volume (PTV). Whereas in some anatomic disease sites, such as the prostate, contouring CTV is a relatively uncomplicated task, in a lung cancer site, confounding radiologic uncertainties such as small lymph nodes of questionable significance, areas of atelectasis, and operative scarring surround CT scan images, resulting in varying degrees of uncertainty in delineating the target volumes leading to a final PTV. To resolve the issue of uncertainty in treatment planning, PET scan was employed by some (3, 4) to contour biologic target volume in an attempt to refine the final treatment volume.

Initial studies incorporating PET into treatment planning have been reported (5–11). However, most of the data were obtained by the use of separate, nonintegrated PET and CT scanners, a process known to be less than ideal considering the inherent errors associated with patient coregisteration and image restoration. Yet another controversy surrounding PET/CT planning exists in choosing the appropriate treatment planning volume to outline. Some have arbitrarily advocated the FDG-avid volume as the region encompassed by the 50% intensity level relative to the tumor maximum intensity (12, 13), whereas Bradley *et al*. employed the 40% intensity level (14). Paulino and Johnstone (15) suggested in an editorial autocontouring all areas with a standardized uptake value (SUV) of 2.5. The debate has become even more compelling as we enter the era of image-guided radiation therapy. We advocate the use of PET/CT planning to provide a new reference for treatment volume delineation using a method we have conveniently termed ABC (anatomic biologic contour), which in theory replaces traditional contouring methods for GTV and biologic target volume. In a group of lung cancer patients, we prospectively studied the use of fully integrated PET/CT scanning in an attempt to address the following issues:

a. How to contour treatment volumes on PET/CT images.
b. Assessment of the degree of correlation between CT-based GTV/PTV (GTV-CT and PTV-CT) and the corresponding PET/CT-based ABC treatment volumes (GTV-ABC and PTV-ABC).
c. Magnitude of interobserver (radiation oncologist planner) variability in the delineation of ABC treatment volumes.

METHODS AND MATERIALS

PET/CT simulation protocol

We used an integrated PET/CT scanner located in our radiation oncology center. The GE-LSO-based Discovery ST Scanner combines a 16-slice high performance CT scanner in-line with an LSO-based PET scanner. Three cross laser pointers have been integrated with the machine for simulation purposes. Thermoplastic or vacuum-molded immobilization devices needed for CRT are custom fabricated before [18]f-FDG injection. Patients are then injected with a standard dose of 10 mCi [18]f-FDG and are left in the designated "quiet room" in the radiation oncology suite for an uptake period of 30 min. After this time period, patients are escorted to the PET/CT scanner in the adjacent room (10 feet). Patients are placed on the PET/CT machine, which is customized with a flat-top table to replicate the treatment machine. The patients are placed in the treatment position with the use of previously constructed immobilization devices. For the sake of reproducibility, an anterior and 2 lateral reference points are tattooed on the patient using the laser cross marks. A full-body PET/CT scan is then performed. The scan is electronically transmitted to Xeleris and Eclipse treatment planning stations. Coregistration is performed automatically.

Treatment volume determination

For the sake of comparing CT-based treatment planning to PET/CT-based planning, treatment volumes are contoured independently by observers (radiation oncologist treatment planner). While PET data remain concealed to the observer, a GTV (GTV-CT) is first contoured using only the CT data. The GTV-CT is defined per CT data as only the gross tumor and any lymph nodes with a cross-sectional diameter of 1 cm or greater. GTV-ABC is then defined using fully fused PET/CT imaging as the PET visualized enhancing gross tumor and/or any lymph node with an average SUV of 2.5 or greater (regardless of any deficiency in adequate nodal size criteria for malignancy as visualized by CT images alone).

Two independent observers are asked to contour and record both the GTV-CT and GTV-ABC. PTVs were defined by the addition of a 1.5-cm volumetric margin around the GTV-CT (PTV-CT) or around the GTV-ABC (PTV-ABC). Subsequently, the PTVs obtained by both techniques are recorded and compared.

An assessment of the degree of correlation between GTV/PTV-ABC and GTV/PTV-CT is performed, as is a measure of interob-