PET-CT and CT Alone Comparison for Target Volume Definition in Radiation Treatment in Patients with Lung Cancer

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Abstract—

Purpose: The aim of this study was to evaluate the possible role of fused images (anatomical CT and functional FDG-PET), acquired with a combined PET-CT scanner, in delineating gross tumour volume (GTV) and clinical target volume (CTV).

Materials and Methods: Twenty-nine patients with small cell or non-small cell lung cancer were studied. CT and FDG-PET images were obtained in treatment position in a combined PET/CT scanner. FDG-PET and CT images were transferred to a workstation for contouring. Gross Tumor Volumes (GTV) and Clinical Target Volumes (CTV) were defined first using the CT data alone and then using the registered CT and FDG-PET data. For each patients two three Dimensional Conformal Radiotherapy (3DCRT) plans were made and they were compared with respect to the GTV, CTV, mean lung dose and volume of normal lung receiving ≥20 Gy ($V_{lung20Gy}$)

Results: Out of these 29 patients, PET clearly changed GTV in 17 patients. PET increased CTV in 7 patients. Additional unsuspected regional nodal disease was included in these patients. In 16 patients with atelectasis, decrease in CTV led to reduced radiation dose to the lung. Likewise, with additional PET information, CTV was enlarged and values of MLD and $V_{lung20Gy}$ were increased in 5 patients.

Conclusion: The use of PET/CT images in radiotherapy is helpful in defining tumor location more precisely, possibly sparing more normal lung tissues and also helpful in differentiating tumor from atelectasis lung. The increasing availability of combined PET/CT units will facilitate the use of this technology for radiation treatment planning.

Keywords— Lung Cancer, Image Fusion, PET/CT, Target Definition, Treatment Planning.

I. INTRODUCTION

Development of new imaging techniques in order to image and define target volumes and critical organs more accurately in the field of radiation therapy has been widely investigated. ^{18}F-Deoxyglucose positron emission tomography (FDG-PET) has been frequently used as a functional imaging method in the field of oncology in recent years. FDG-PET is valuable in staging, in detection of the recurrences and in the evaluation of response to treatment. It is generally the preferred method to evaluate pulmonary nodal status, to stage mediastinal disease and to detect distant metastases in patients with verified or suspected small or non-small cell lung cancer (1, 2). PET provides significant information to the clinician to locate the tumor much more precisely and to stage the disease more accurately (3). Three dimensional conformal radiation therapy is based on computerized tomography (CT). CT shows anatomical structures clearly and helps in creation of 3-dimensional anatomy. CT images are not distorted geometrically and show electron density using 3 dimensional dose calculation algorithm. CT is useful in the delineation of the critical organs in 3 dimensional planning systems and can also give physical density information in Hounsfield units. In contrast, CT is not good enough in the delineation of nodal disease (1). It also can not provide any information about tumor activity which is one of the most important prognostic factors in radiation therapy (3).Recent studies have shown that FDG-PET is superior to CT in showing mediastinal nodal status. Sensitivity of PET in defining the nature of lung nodules was 93-100%, while its specifity was 52-88% and its accuracy was 92-94% in a study performed by Patz *et al.* (4). In the detection of mediastinal disease, sensitivity, specifity and accuracy of PET were reported to be 76-92%, 81-100% and 80-100%, respectively. Sensitivity of CT was 56-65%, while its specifity was 73-87% and its accuracy was 77-82% (1, 4). CT was inferior to PET in detecting mediastinal disease. With the use of new technologies with the capability of registration of CT and PET images (see Figure 1), target volumes [Gross Tumor Volume (GTV) and Clinical Tumor Volume (CTV)] can be delineated with a higher accuracy. It was shown that these volumes could be different when contoured separately (5-16, 17 and 18). It was shown in several studies that treatment plans might be changed in 20-35% of the cases when the metabolic information taken from PET was added on the anatomical information taken from the

CT imaging (7, 9, 11, 13 and 16). Metabolical tumor mapping derived from the combination of anatomical and metabolical images using PET/CT is very effective in defining GTV and CTV dimensions and shapes. Until recently, PET and CT images were taken separately and they were then combined using special software programs (5-18). Newly developed PET/CT devices enable us to receive both functional and anatomical images in the same session.

In our study, we aimed to determine the value of PET/CT imaging, which also gives us functional information, in defining target volumes.

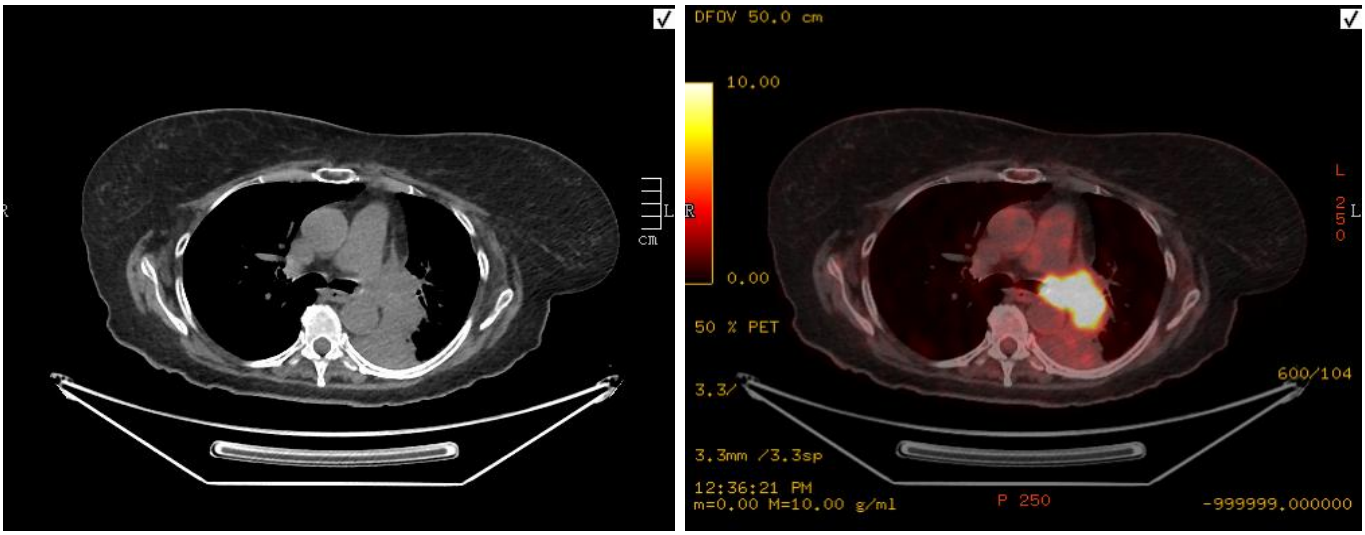


FIG. 1. REGISTRATION OF CT AND PET IMAGES.

II. MATERIALS AND METHODS

2.1 Patients

Twenty-nine patients with small cell or non-small cell lung cancer (24 male, 5 female), treated in our center between September 2005 and June 2008, were included within our study. Median age of the patients was 49. In 19 of the patients (65.5%), primary tumor was located in the right lung while it was in the left lung in 10 cases (34.5%). Vacuum beds (MED-TEC) were prepared in supine position with the hands above the head a day before taking the images in PET/CT simulator. MED-TEC flat planning couch was used in PET/CT device in order to assure the same position in the treatment room. A laser positioning system was also installed in the PET/CT room. Three fiducial markers were placed on torso in order to determine reference slice on CT data.

2.2 PET-CT data acquisition

According to our PET/CT protocol, patients fasted for six hours before undergoing scanning, and blood sugar levels were checked to ensure that there was no hyperglycemia (levels< 200 mg/dL). To prevent muscular radiotracer uptake, we instructed the patients to avoid strenuous activity and to sit without speaking in a dimly lit room before the examination and after injection of the radioisotope. A dose of 370-555 MBq (10-15 mCi) of F-18 FDG was intravenously injected 60 min before imaging. In addition, 1000 mL of oral contrast agent (sodium amidotrizoate/ meglumin amidotrizoat, 76%) were administered, 10 min before and 30 min after injection of F-18 FDG. Simulation was performed by radiation therapy technicians who were especially trained for this trial. PET and CT images were performed with a Siemens Biograph Duo LSO combined PET/CT scanner. PET/CT images were acquired during regular breathing. CT images were acquired by using a matrix of 512×512 pixels and a pixel size of about 1 mm. CT images were then obtained as 3 mm thickness through the entire thorax. After CT acquisition, the patient proceeded, with immobilization devices, directly to the combined PET unit. Scanning was performed from the base of skull through the mid thigh. PET images were acquired by using a matrix of 128×128 pixels, with a slice thickness of 5 mm. The final imaging resolution for clinical practice was about 6.5 mm. CT-based attenuation correction of the emission study was employed. The PET images were reconstructed by the iterative method ordered subset expectation maximization with a filter of 5 mm.

2.3 Image registration and contouring of PET-CT data set

PET and CT images were then transferred in DICOM format to CMS FocalSim computer. Dicom formatted images were sent from PET/CT device to the computer where images were registered, and target, critical organs countered. Before registration of CT and PET images, normal tissues were contoured on the CT data set using contouring software (FocalSim, CMS). Normal tissue contours included the right lung, left lung, esophagus (from the carina to the esophago-gastric junction) and spinal cord. The lungs were contoured automatically by contouring computer. After the normal tissues were contoured, images were registered using image fusion options on FocalSim computer. Using combined PET and CT scans, patient position errors were minimized. In order to reduce errors which might occur due to incorrect registration of PET and CT scans, patients were scanned at the same position. Registration accuracy was verified by using the body contours of PET and CT, which is well-defined on both image types.

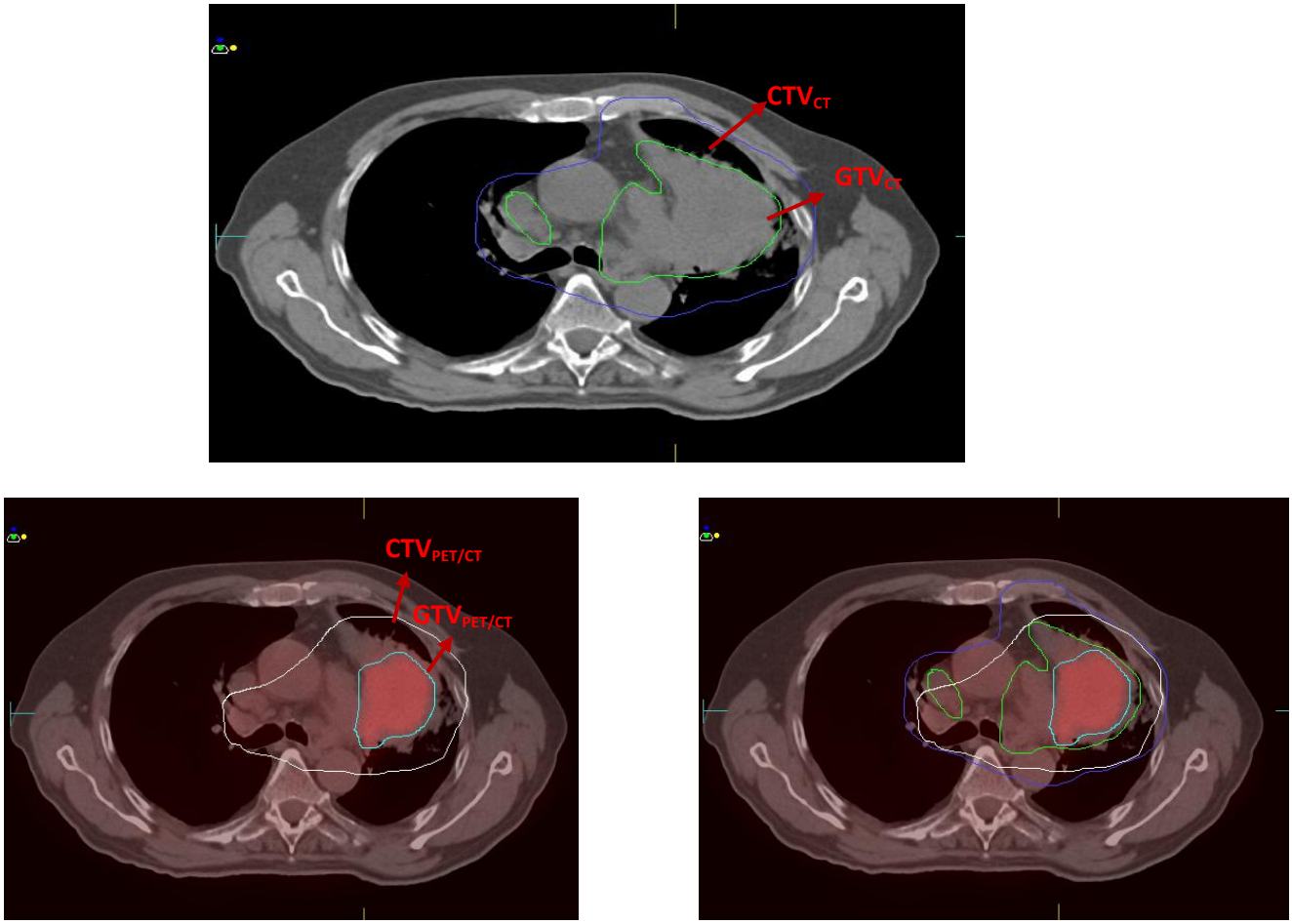


FIG. 2. (A) GTV_{CT} and CTV_{CT} CONTOURED BY USING CT SCAN ONLY (WITHOUT PET DATA). (B) $GTV_{PET/CT}$ and $CTV_{PET/CT}$ CONTOURED BY USING COMBINED PET AND CT DATA. (C) CONTOURED CTV AND GTV VIEWS TAKEN FROM CT ALONE WERE REGISTERED WITH VIEWS TAKEN FROM PET/CT.

In all patients, the gross tumor volume (GTV) and clinical target volume (CTV) were defined using the CT data and PET-CT data. The same experienced radiation oncologist contoured the volumes in two sessions independently, in order to avoid personal differences. GTV_{CT} and CTV_{CT} were contoured using CT without PET [Figure 2 (a)], and then contoured by combining PET and CT images [Figure 2 (b)]. Contoured CTV and GTV views taken from CT alone were registered with views taken from PET-CT were shown in Figure 2 (c). The images, $GTV_{PET/CT}$-$CTV_{PET/CT,}$ acquired through the PET, were evaluated by an experienced nuclear medicine specialist.

2.4 Treatment planning and evaluations of plans

Treatment planning was performed in two steps. For CTV_{CT} and $CTV_{PET/CT}$, 5mm margin was given in all directions, in order to determine PTVs (PTV_{CT} and $PTV_{PET/CT}$). Conformal beams were then generated for all beams using multi-leaf collimators and virtual treatment planning was performed. Radiotherapy planning was performed using CMS XiO computerized treatment planning system (Version 4.2.2), with inhomogeneity corrections based on Clarkson algorithm. The treatments were delivered using 18MV photon linear accelerator (Siemens, Impression). A three dimensional conformal treatment plan (Fig. 3) was prepared, with a prescribed dose to the PTV_{CT} and $PTV_{PET/CT}$ of 60 Gy in 30 fractions according to International Commission on Radiation Units and Measurements (ICRU 62) (19). Dosimetric values were calculated on the basis of dose-volume histograms and dose distributions on each axial CT slice for both CT and PET/CT based planning. Both treatment plans for each patient were compared with respect to GTVs, CTVs and normal tissues (lung) receiving radiation. GTV_{CT} and CTV_{CT} were compared to $GTV_{PET/CT}$ and $CTV_{PET/CT}$. For the lung, healthy lung volumes which received ≥20 Gy ($V_{lung20Gy}$) and MLD (Mean Lung Dose) doses were also analyzed.

2.5 Statistical Analysis

For statistical analysis, to compare target volumes, the volumes of normal lung receiving ≥20 Gy ($V_{lung20Gy}$) and Mean Lung Dose (MLD) obtained using CT alone and PET/CT, the paired *t* test was used. *P* values less than < 0.05 were considered to be statistically significant. GTV, CTV, MLD and $V_{lung20Gy}$ data are reported as mean ± 95% confidence interval. $CTV_{Left\ Lung}$, $CTV_{Right\ Lung}$ data are reported as mean ± 99% confidence interval.

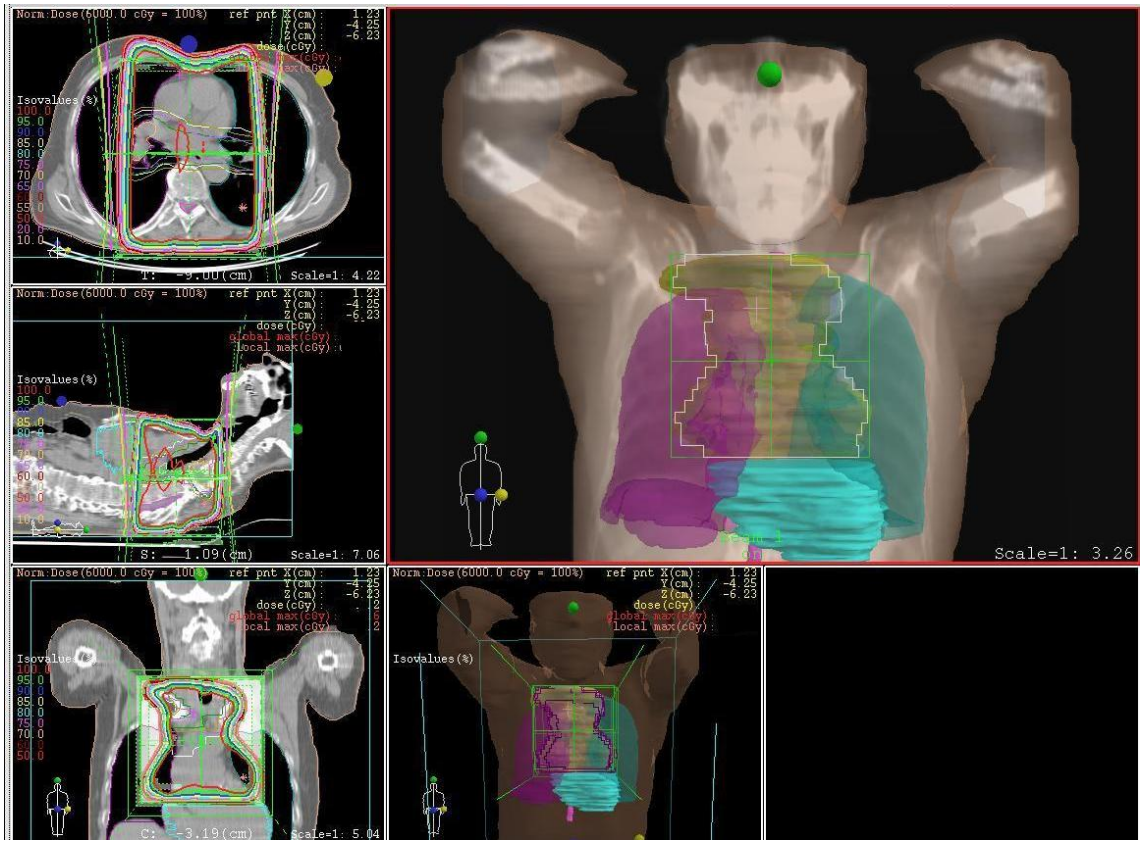


FIG. 3. THREE DIMENSIONAL CONFORMAL TREATMENT PLANS.

III. RESULTS

All patients included in our current study received definitive 3-DCRT (Three Dimensional Conformal Radiation Therapy) planned with the PET/CT fused images. GTV_{CT}, $GTV_{PET/CT}$, healthy left and right lung doses (Mean Lung Dose - MLD) and the volumes of normal lung receiving ≥20 Gy ($V_{lung20Gy}$) were given in Table 1 for 29 patients. In 90% of our patients (26/29), GTV_{CT} was found to be larger than $GTV_{PET/CT}$. In 69% of the patients (20/29), CTV_{CT} was found to be larger than $CTV_{PET/CT}$. In only one patient, there was no difference between CTVs. In the first, 21st and 26st patients, $GTV_{PET/CT}$ was larger than GTV_{CT} and $CTV_{PET/CT}$ was also proportionally larger than CTV_{CT}. In the patient #6, GTV_{CT} was found to be greater than $GTV_{PET/CT}$ although there was no difference between CTVs. GTVs and CTVs for CT and PET/CT comparison

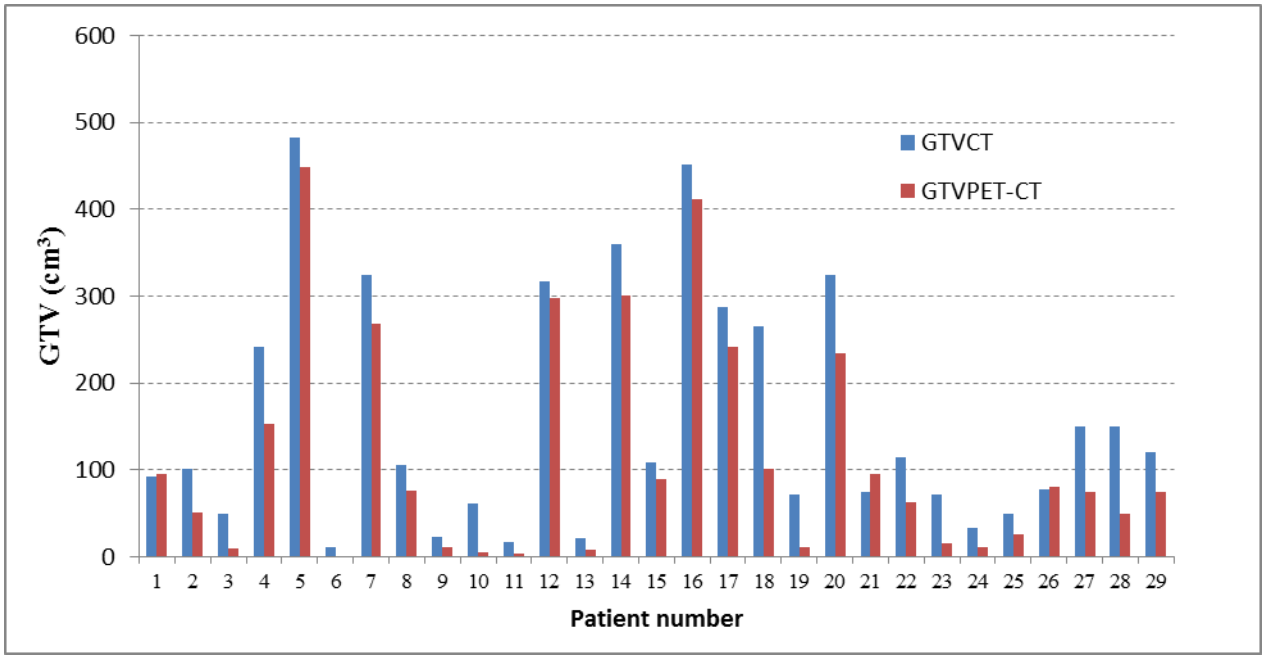
were shown in Figure 4 (a) and (b). Of these 29 patients, PET clearly changed GTV in 24 patients and minimal change (<%17) in GTV was observed in 5 patients. PET increased CTV in 8 patients. Additional unsuspected regional nodal disease was included in these patients. In 19 patients with atelectasis, decreases in CTV led to reduced radiation doses to the lung. Likewise, with additional PET information, CTV was enlarged and values of MLD and $V_{lung20Gy}$ were increased in 4 patients. Tumor location was in the right lung in 19 patients and in the left lung in 10 patients in this study. The mean doses and volumes exceeding 20 Gy were compared for healthy lungs in CT alone and PET-CT images. In Figure 5 (a), two different treatment plans and their DVHs were compared according to CT and PET/CT for healthy right lung in patient #9. GTV and CTV were found higher on CT than on PET/CT. Therefore, the dose of right lung was found to be higher based on CT alone information. DVH comparisons of the patient #12, who had right lung cancer, were shown in Figure 5 (b). CTVs were higher in PET/CT than CT alone. Therefore, the dose of left lung was found to be higher based on PET/CT information. Although $CTV_{PET/CT}$ was higher than CTV_{CT}, healthy left lung MLD (Gy) and $V_{lung20Gy}$ were lower than CT in patients #1, #21 and #26 [Figure 5 (c)]. The difference did not reach statistical significance. Dose and volume correlations were also analyzed in order to observe statistical distribution. Statistical results are given in Table 2, 3, 4 and 5. Differences between GTV_{CT} and $GTV_{PET/CT}$ were statistically significant while no statistical differences were detected between CTV_{CT} and $CTV_{PET/CT.}$ Healthy MLD doses and $V_{lung20Gy}$ doses were also analyzed. In the right sided lesions, differences between healthy MLD dose and $V_{lung20Gy}$ doses were not statistically significant while statistical significance was observed in healthy MLD doses and $V_{lung20Gy}$ in left sided lesions.

TABLE 1
MEAN LUNG DOSES AND $V_{lung20Gy}$ (%) FOR 29 PATIENTS

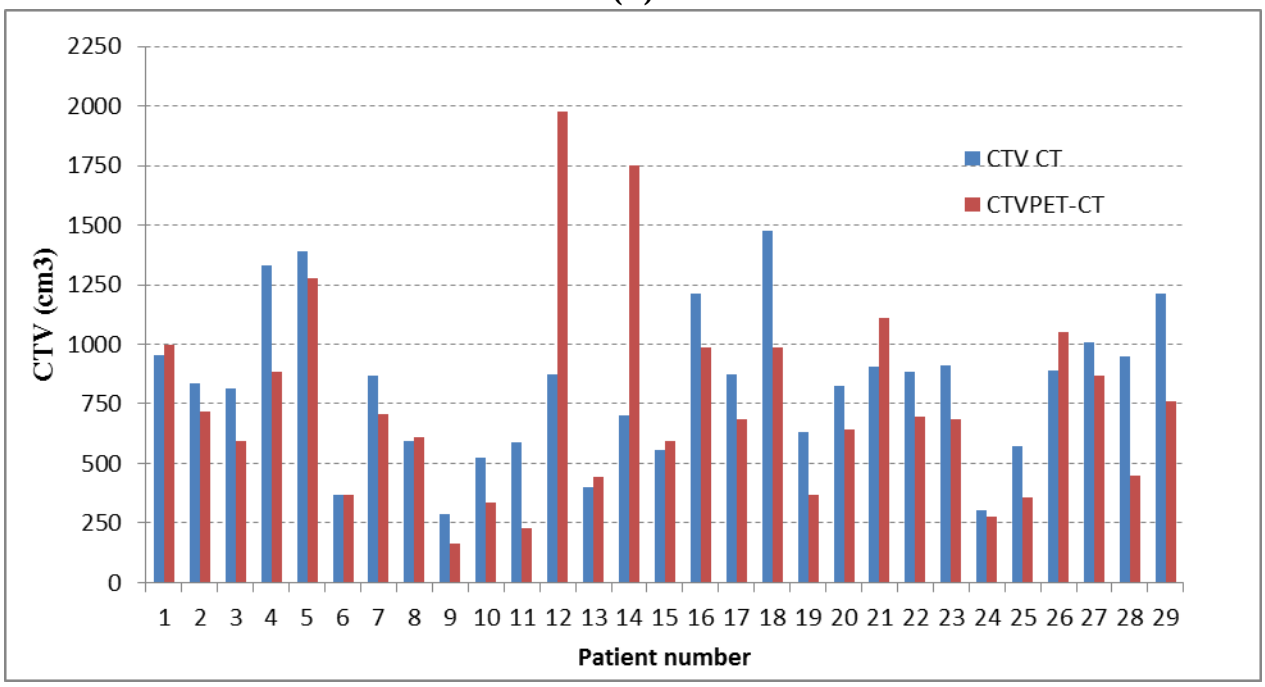
	Target volumes				Normal Tissue (Healthy Left Lung)				Normal Tissue (Healthy Right Lung)			
	GTV (cm^3)		CTV (cm^3)		MLD (Gy)		$V_{lung20Gy}$ (%)		MLD (Gy)		$V_{lung20Gy}$ (%)	
Patients	**CT**	**PET/CT**	**CT**	**PET/CT**	**CT**	**PET/CT**	**CT**	**PET/CT**	**CT**	**PET/CT**	**CT**	**PET/CT**
1	93	95	952	1000	1851	1789	33	32	-	-	-	-
2	101	51	835	717	-	-	-	-	1727	1403	32	27
3	50	10	817	595	1360	988	25	18	-	-	-	-
4	241	153	1332	885	2089	1450	37	26	-	-	-	-
5	483	449	1390	1277	1736	1153	31	21	-	-	-	-
6	11	1	368	368	1243	1243	23	23	-	-	-	-
7	325	269	866	708	-	-	-	-	1184	1203	21	22
8	106	76	593	609	1074	1141	19	20	-	-	-	-
9	23	11	290	166	-	-	-	-	1526	337	27	6
10	61	5	523	336	879	572	17	11	-	-	-	-
11	17	3	586	226	-	-	-	-	1600	1239	29	22
12	317	298	875	1978	436	1057	7	20	-	-	-	-
13	22	8	402	443	1474	1112	24	19	-	-	-	-
14	360	301	699	1748	415	998	6	18	-	-	-	-
15	108	90	554	596	946	1155	16	19	-	-	-	-
16	452	411	1215	988	1533	1004	33	24	-	-	-	-
17	288	242	874	684	-	-	-	-	1228	1144	26	22
18	266	102	1474	987	1987	1335	35	23	-	-	-	-
19	72	11	633	368	912	601	21	13	-	-	-	-
20	325	234	825	642	1658	1223	42	35	-	-	-	-
21	74	96	906	1112	1758	1699	33	29	-	-	-	-
22	115	63	886	698	-	-	-	-	1655	1399	30	24
23	72	16	912	687	1288	1004	22	21	-	-	-	-
24	34	11	302	274	-	-	-	-	1542	1189	31	21
25	50	26	570	356	-	-	-	-	1698	631	29	7
26	78	80	890	1050	1901	1825	35	34				
27	150	75	1010	870	1420	1088	24	17				
28	151	51	950	450					1645	1321	31	25
29	122	76	1210	760					1625	438	32	11

Abbreviations: **CT= Computed Tomography; PET= Positron Emission Tomography; GTV= Gross Tumor Volume; CTV= Clinical Target Volume; MLD= Mean Lung Dose; $V_{lung20Gy}$= the volumes of normal lung receiving ≥20 Gy.**

Since the difference between PET/CT and CT alone contoured GTVs was statistically significant (p=0.000), while the difference in CTVs (p=0.2818) was not. The differences in MLD (p=0.0062) and $V_{lung20Gy}$ in patients with left lung cancer were found to be statistically significant (p=0.003). While MLD healthy left lung were statistically significant in patients with right lung cancer (p=0.041), $V_{lung20Gy\ were\ not}$ found statically significant (p=0,103) respectively, (Table 2, 3 and 4). CTVs were evaluated separately for left and right lung cancer patients by using PET/CT and CT alone data. The difference in $CTVs_{left\ lung}$ (patients with left lung cancer) between PET/CT and CT alone contoured patients was found to be statistically significant (p=0.001), while the difference in $CTVs_{right\ lung}$ (right lung cancer) was not (p=0,927) (Table 5). These analyses help us to explain the reason for statistically significant difference in MLD and $V_{lung20Gy}$ in patients with left lung cancer.



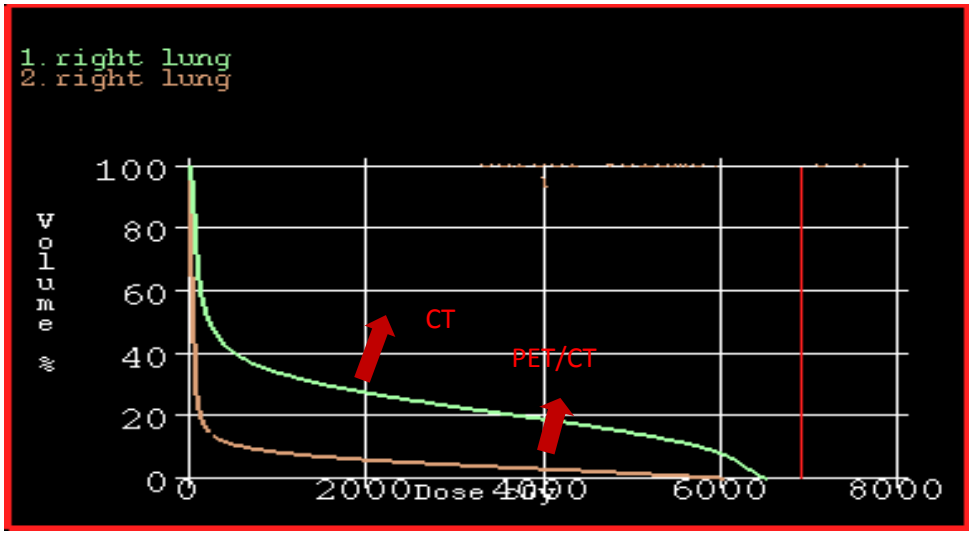
(A)



(B)

FIG. 4. (A) GROSS TUMOR VOLUME (GTV) COMPARISON OF CT AND PET/CT FOR 29 PATIENTS. (B) CLINICAL TARGET VOLUME (CTV) COMPARISON OF CT AND PET/CT FOR 29 PATIENTS.

(A)



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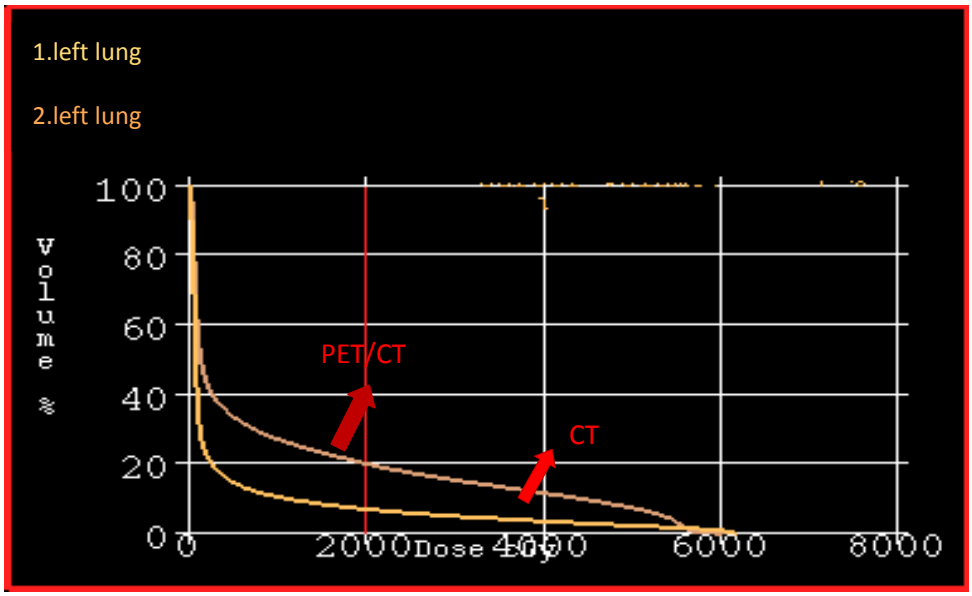

(C)

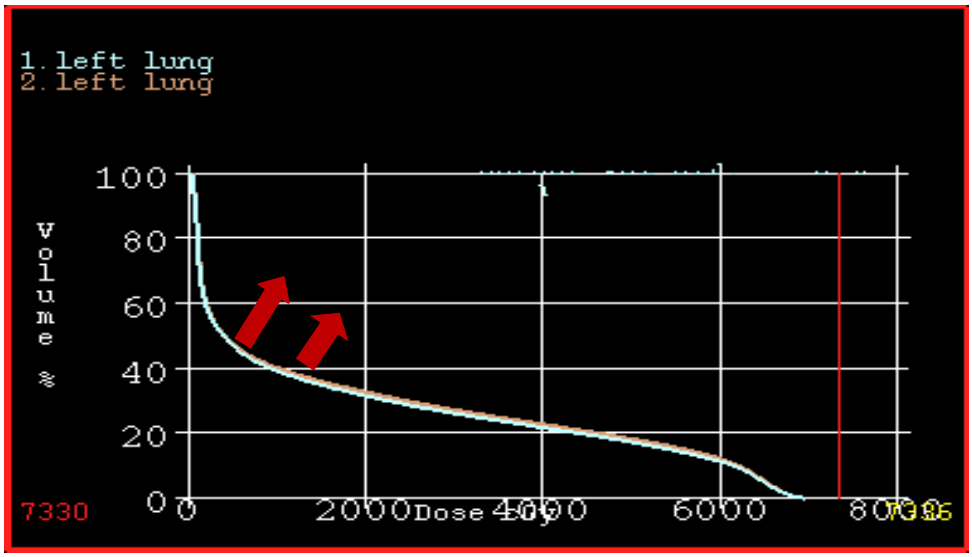

FIG. 5. (A) LEFT LUNG CANCER DVH COMPARISON (PATIENT #9), (B) RIGHT LUNG CANCER DVH COMPARISON (PATIENT #12), (C) RIGHT LUNG CANCER DVH COMPARISON (PATIENT #1 AND #21)

TABLE 2
GTV_{CT}, $GTV_{PET/CT}$ AND CTV_{CT}, $CTV_{PET/CT}$ DIFFERENCES AND STATISTICAL RESULTS

		Average (cm^3)	P <0.05
GTV	CT	157.38	0.0000
	PET-CT	114.21	
CTV	CT	818.59	0.2818
	PET-CT	744.07	

TABLE 3
MLD DIFFERENCES AND STATISTICAL RESULTS

		Average (Gy)	P <0.05
MLD	CT	13,66	0.041
	PET-CT	11,80	
MLD	CT	15,43	0.0062
	PET-CT	10,30	

*** MLD: Mean Lung Dose**

TABLE 4
$V_{lung20Gy}$ (%) DIFFERENCES AND STATISTICAL RESULTS

		Average (%)	P <0.05
$V_{lung20Gy}$ (%) (Healthy Left Lung)	CT	25,42	0.06
	PET-CT	22,26	
$V_{lung20Gy}$ (%)	CT	28,8	0.003
	PET-CT	18,7	

TABLE 5
$CTV_{Left\ Lung}$ AND $CTV_{Right\ Lung}$

Patients		Average (cm^3)	P <0.01
$CTV_{Left\ Lung}$	CT	736.9	0,001
	PET-CT	503.9	
$CTV_{Right\ Lung}$	CT	861.6	0,927
	PET-CT	870.5	

IV. DISCUSSION

In conformal radiotherapy, it is essential to determine exact dimensions of the tumor. Radiation treatment with CT based planning allows more precise determination of volumes. Lymph nodes and areas of metastatic involvement may not be determined easily by CT scan [1, 2]. In recent years, the importance of treatment planning using PET increased in lung cancer. In three dimensional conformal radiation treatments, radiation oncologists frequently use CT, MR, and ultrasonography in order to determine the target volumes. Although it can not be replaced with the standards mentioned above, PET can show the metabolic activity of the lesions and may cause changes in GTVs and CTVs. Bradley *et al.* reported that GTV was changed in 14 of 24 patients (58%) when PET was used for planning [6]. In 3 of 24 patients, PET differentiated atelectasis volumes and GTV decreased due to more accurate imaging of the tumor. Eleven of 24 patients, GTV were increased by using PET. Vanuytsel *et al.* [7] reported that target volume was changed in 45 of 73 patients (62%). In another study performed by Messa *et al.* [15], at least 25% variations in CTVs were observed between PET and CT in 10 of 18 patients. In eight of 18 patients, target volumes were found to be the same. Using PET for planning was shown to alter target volumes in several other studies [8-13, 17]. In addition to mentioned above, using PET/CT in planning changed the stage of patients in many cases [5, 10]. Esophagus and healthy lungs are the dose-limiting organs in the irradiation of lung cancer when conventional radiation treatment techniques are used. In the studies done by De Ruysscher *et al.* [5], Bradley *et al.* [6] and Van Der Wel *et al.* [8], PET/CT simulated PTV was smaller compared to CT simulated volumes. In several studies, determination of GTV differs among the radiation oncologists and variations were larger in CT compared to PET/CT

determined GTVs [13]. In order to avoid the personal differences, GTVs and CTVs were contoured by the same experienced radiation oncologist in our study. In recent years, PET and CT are combined in the same device. This model proves that the evaluation of treatment volume is more accurate in PET/CT combined devices compared to other devices [17]. PET and CT images were taken in separate devices and then fused in many studies indicating that delineation of tumor was better when information taken from the CT which was combined with the functional information taken from PET. Devices combining PET and CT solved most of the problems, due to positioning and timing and the accuracy of the views were increased. [5, 15, 17]. We aimed to increase the quality of system by using PET/CT and decrease the problems due to fusion. In 69% of our patients (20/25), GTV $_{PET/CT}$ and CTV $_{PET/CT}$ derived from the combination of PET and CT were smaller than the values obtained by CT alone. Respectively, healthy lung doses (MLD) and $V_{lung20Gy}$ doses in the plans of 20 patients (9 left lungs, 11 right lungs), in which PET and CT were combined, were observed to be less than the values obtained by CT alone (Patients #2-5, #9-11, #16-20, #22-29). In 10% of the patients (3/29), $GTV_{PET/CT}$ and $CTV_{PET/CT}$ were greater than GTV_{CT} and $CTV_{CT.}$ MLD doses and $V_{lung20Gy}$ were less in GTV $_{PET/CT}$ and $CTV_{PET/CT}$ compared to GTV_{CT} and CTV_{CT} in these patients. The reduction in healthy lung tissues was due to GTV and CTV on the other side of healthy lung (Patient #1, #21 and #26). In 3.4% of the patients (1/29), CTV values were equal in PET/CT and CT alone although GTV contoured using PET/CT was smaller than GTV contoured using CT alone. Due to equality of the treatment volumes, MLD and $V_{lung20Gy}$ were also equal in this particular patient (Patient #6). In 17% of the patients (5/29), GTV was decreased and CTV was increased in PET/CT. In these patients, healthy MLD and $V_{lung20Gy}$ were also increased (Patients #8, #12, #14, #15). In 3.4% of the patients (1/29), healthy lung doses and $V_{lung20Gy}$ were increased although GTV and CTV were decreased in PET/CT due to tumor location (patient #7). In 3.4% of the patients (1/29), GTV was decreased and CTV was increased in PET/CT. Healthy lung doses and $V_{lung20Gy}$ were found to be less since GTV and CTV were not on the side of healthy lung (Patient #13).

In conclusion, using PET/CT images is helpful in defining tumor location more precisely, possibly sparing more normal lung tissue and also helpful in differentiating tumor from atelectasis lung. In comparison to CT only, using combined PET/CT images for radiation therapy planning resulted in significant alterations in 69% of patients. The slightly increasing number of patients did not change the results we found in our previous study [20]. The increasing availability of combined PET/CT units will facilitate the use of this technology for radiation treatment planning.

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