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Positron emission tomography-computed tomography guided radiotheraphy planning in lung cancer

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► ***Original article***

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ABSTRACT

Aims and background: In three dimensional conformal radiotherapy (3D-CRT), treatment planning is based on computerized tomography (CT) images. However, the data obtained from CT may not be sufficient in target delination. The purpose of this study is to show the differences between the radiotherapy (RT) plans which were done with positron emission tomography (PET) fusion or not. ***Methods:*** Patients with lung cancer between February 2009 and January 2012 at our institution were assessed retrospectively. Sixty patients who were treated with 3DCRT, CT simulation images were registrated with PET images. For each patient target volumes were determined and normal tissues were revised. Wilcoxon Signed Rank Test was used to compare the two groups. ***Results:*** For gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV); median volume values, median mean dose values and median maximum dose values were significantly different according to use of PET. About normal tissue doses; mean lung dose (MLD), lung V20, mean and maximum esophagus dose, V50 and V60, mean heart dose and maximum medulla spinalis dose were analyzed. ***Conclusion:*** Within these parameters there were statistically significant difference except in maximum dose of esophagus and V60. In our study, we observed decreased target volumes and higher dose distrubutions for target volumes in PET registrated RT plans. According to these data, it is possible to say that optimal RT plans can be formed for lung cancer by using PET registration.

Keywords: *Lung cancer, PET-CT, image fusion, target definition, radiotherapy planning.*

INTRODUCTION

Lung cancer is the leading cause of cancer death in the world [1]. Surgery is the most effective treatment modality. But surgery can be applied especially in early stage and 20-25% of patients. Concurrent chemoradiation is the main treatment modality for patients with locally advanced lung cancer. Radiotherapy (RT) plays a key role in the curative treatment of lung cancer. Unfortunately, locoregional control is poor in unresectable cancers. In inoperable non-small cell and limited-stage small cell lung cancer high radiation doses are correlated with improved local control [2,3]. Also RT improves local control in postoperative cases with margin positive and involved mediastinal node [4,5]. Therefore, it is important to improve locoregional tumor control which is expected to improve overall survival.

Normal tissue toxicity is dose limiting fact. Also dose-escalated RT combined with chemotherapy is potential for significant toxic effects; like esophagitis, pnemonitis, and bone marrow supression. Therefore, correct target volumes delineation is very important for accurate RT planning. Three-dimensional conformal radiation therapy (3D-CRT) planning

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is based on computerized tomography (CT) scan slices. However, data obtained from CT may not be sufficient for consistent target volume delinetaion [6]. Several contouring techniques are used for delineation purposes and breathing maneuvers are utilized for achieving improved normal tissue sparing in lung cancers [7]. Also interobserver variability has been observed for many tumor sites [8-17]. Positron emission tomography (PET), has been a major innovation in lung cancer imaging and is being used increasingly in RT planning in recent years. With adding PET-CT to RT planning, target area can be detected more accurately and normal tissues protected better.

In this study we aimed to investigate the PET-CT data for RT planning in lung cancer. We retrospectively analyzed 60 lung cancer patients who undervent 3D-CRT and compared their RT plans by using PET fusion. In these patients we wanted to show that there may be differences with PET fused plans.

MATERIALS AND METHODS

Patients characteristics

The clinical records of sixty patients with lung cancer who had undergone external beam RT at the University of Ankara between February 2009 and January 2012 were retrospectively reviewed. There were 54 males and 6 females. They ranged in age from 46 to 83 years, with a median age of 64 years. Of all patients squamous cell carcinoma is the most seen pathologic subtype with 31 patients. Patients who underwent PET-CT for staging and/or treatment planning were included in this study. Patients who had surgery didn't take place. Patients' characteristics are summarized in Table 1.

Table 1. Patients characteristics.

Parameters	n (%)	Parameters	n (%)
Sex		**Weight Loss (n=44)**	
Man	54 (90)	Positive	27 (61.4)
Woman	6 (10)	Negative	17 (38.6)
Performance Score		**Diagnosis**	
0	17 (28.3)	1 SCC	31 (51.6)
1	34 (56.7)	2 Adeno	13 (21.7)
2	8 (13.3)	3 Large Cell	1 (1.7)
3	1 (1.7)	4 Small Cell	15 (25)
Tumour Stage		**Nodal Stage**	
1	7 (11.7)	0	10 (16.7)
2	19 (31.7)	1	5 (8.3)
3	18 (30)	2	36 (60)
4	16 (26.6)	3	9 (15)
TNM Stage		**Tratment Modality**	
1A	1 (1.7)	CRT	29 (48.3)
2A	2 (3.3)	CT + RT	4 (6.7)
2B	7 (11.7)	CT + CRT	23 (38.3)
3A	31 (51.7)	RT	4 (6.7)
3B	19 (31.6)		

CRT: chemoraditherapy CT: chemotherapy RT: radiotherapy

Fourty-nine patients had their PET's before radiotherapy and 11 had after induction chemotherapy. If the patient had stable disease after induction chemotherapy, he/she was included into the study. The mean duration from the date of PET-CT to the start of RT was 26 days. The mean dose of RT was 60 Gy and fraction dose was 2 Gy (table 2).

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Table 2. PET and RT Parameters Values.

Variables	Min; Max	Median (IQR)
Time between PET and RT (Day)	4; 72	26 (25)
SUVmax value	2.5; 36.9	13.1 (12.4)
RT treatment dose (Total dose)	50; 68	60 (7.5)
RT fraction dose (Dose per fraction)	1.8; 2	2 (0.2)

Procedure

Immobilization and CT simulation were performed, as a routine procedure for lung cancer patients receiving 3D-CRT in our department. Patients were immobilized with wing-board. The treatment position is supine with arms up. The patients were scanned in treatment position on Varian Acuity Cone-Beam CT Simulator (Varian Medical Systems, Crawley, GBR) and GE Optima RT 580 CT Simulator (GE Healthcare, Beijing, CHN) using 5-mm slice thickness. Treatments were done with Varian Clinac DHX High Performance (Varian Medical Systems, Palo Alto, USA) lineer accelerator.

Fusion

Patients' PET-CT and CT simulation images were sent to Eclipse planning computer in DICOM format. CT simulation images were overlaid with PET images on planning program. In the fusion process PET and CT images were matched manually with the Eclipse version 10 software program imagefusion option. Outer contour, heart, kidneys, and carina were used as reference. Normal tissue contouring was performed in the same way in both plans.

Target volume delination and organ at risks (OARs)

Gross tumor volume **(**GTV): The GTV includes primary pulomary lesions and metastatic lymph nodes. As a standart procedure in our institute both of the lungs contoured as a single organ and GTV is excluded from it. The GTV was first delinated on CT images (GTVct) and then defined based on PET-CT fusion images (GTVpet). GTVct and GTVpet values obtained from automatic calculation.

Clinical target volume (CTV): The CTV includes the GTV and the subclinical disease region range. The CTV margin to GTV changed from 0.5-1.5 cm depending on pathologic subtype. For squamous cell carcinoma 6 mm, for adenocarcinoma 8 mm margins were standardly used. There were 2 patients which had 1.5 cm margin. Both of thems pathologic subtype was small cell lung cancer. Elective nodal irradiation wasn't done to any patient.

Planning target volume (PTV): The PTV includes the CTV and a margin for uncertainties like organ displacements, patient movements, daily positioning errors. The PTV margin was 0.5 -1.5 cm according to patient clinical situations. Most widely used margin was 1 cm.

Normal tissues and target volume were contoured according to ICRU 50/62 by using Tomocon Pacs 3 and Eclipse External Beam Planning Version 10. Treatment planning was performed using the Elekta and Eclipse Precise Plan treatment planning sytem. Dose constraints to OARs were lung V20<%35, heart V40<%50, spinal cord Dmax<45 Gy, and esophagus V55<% 50.

STATISTICS

Statistical analysis was performed using SPSS 21.0 software. Wilcoxon Signed Rank Test was used to compare the two groups. Parameters were tested in univariate analyses with a P value <0.05 for statistical significance. Several factors i.e. GTV (mean, min., max. doses, and volume), lung (MLD, V20), esophagus (mean, V50,V55, V60, max. doses), heart (mean, V40) and medulla spinalis (max. doses) were tested. Parameters such as RT dose, normal tissue doses, time between PET and start of RT were expressed as median (Interquatile Range-IQR) value. Z score is the number of standart deviations from a mean data point is. Number and percentage values were given for the parameters such as sex, performance status, pathologic subtype,

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nodal status, and treatment modality.

RESULTS

The GTV-volume and GTV-mean dose values had significant changes with using PET-CT (p=0.007 and p<0.001). The GTVpet volume decreased compared to the GTVct. Median; GTVpet and GTVct volumes were 96.4 cm^3 and 123.5 cm^3, respectively. The GTVpet mean dose increased compared to the GTVct. Median; GTVpet and GTVct mean dose values were 63.2 Gy and 61.9 Gy, respectively. Also GTV maximum (max) dose value was significantly higher with using PET-CT (table 3).

As a result of GTV parameters' changes CTV parameters had differences too. The CTV-volume, CTV-mean dose, and CTV-max dose values were significantly different (p=0.008, p=<0.001, p=0.039). Also PTV-volume and PTV-mean dose were different (p=0.009, p=0.001). The CTV and PTV parameters are summarized in Table 4 and Table 5.

Compared to CT plan parameters, PET plan parameters showed better type of change for organ at risks (OARs). For lung; mean lung dose (MLD) (19.2 Gy / 16.1 Gy) and V20 (36% / 28.5%) were significantly higher in CT plans (p=<0.001) Esophageal mean dose (32.9 Gy / 24.5 Gy), V50 (39.5% / 27.5%), and V55 (24% / 17.5%) were significantly higher in CT plans (p=<0.001, p=<0.001, and p=0.001), while V60 and Dmax were not (p=0.05, p=0.45). Also heart V40 (28% / 19.5%) showed increased percentage in CT plans (p=<0.001). For spinal cord Dmax (44.9 Gy / 41.4 Gy) was higher too in CT plans (p=0.004).

Table 3. GTV parameters values comparing.

GTV	PET planning (+)		PET planning (-)		Test statistics	
	Min; Max	Median (IQR)	Min; Max	Median(IQR)	Z	p
GTV-volume (cc)	6.9; 1408.6	96.4 (144.8)	10.3; 1592.7	123.5 (174.0)	2.716	**0.007**
GTV-mean dose (Gy)	50.1; 71.8	63.2 (8.6)	51.0; 68.3	61.9 (6.1)	5.036	**<0.001**
GTV-min dose (Gy)	43.8; 67.2	58.3 (8.5)	19.3; 64.9	58.1 (8.8)	0.938	0.348
GTV-max dose (Gy)	52.1; 74.8	65.8 (8.6)	52.2; 71.9	64.3 (6.8)	2.529	**0.011**

IQR: Interquartile range

Table 4. CTV parameters comparing.

CTV	PET planning (+)		PET planning (-)		Test statistics	
	Min; Max	Median (IQR)	Min; Max	Median (IQR)	Z	p
CTV-volume (cc)	37.6; 1913.5	265.3 (271.7)	66.5; 2294.9	296.2 (302.7)	2.650	**0.008**
CTV-mean	49.6; 70.8	63 (8.9)	50.2; 66.4	61.3 (6.5)	4.543	**<0.001**
CTV-min	2; 64.5	54.7 (8.4)	19; 63.1	55.8 (10.3)	0.619	0.536
CTV-max	52.6; 75.2	66 (8.6)	52.3; 71.4	64.9 (7.6)	2.061	**0.039**

IQR: Interquartile range

Table 5. PTV parameters comparing.

PTV	PET planning (+)		PET planning (-)		Test statistics	
	Min; Max	Median (IQR)	Min; Max	Median (IQR)	Z	p
PTV-volume	127.5; 2457	587.6 (497.4)	62.6; 3077.6	712.1 (509.6)	2.628	**0.009**
PTV-mean	48.8; 69.5	62.2 (8.7)	50.2; 67.1	60.8 (7.5)	3.314	**0.001**
PTV-min	21.3; 62.7	48.8 (7.7)	17.4; 61.8	47.9 (11.5)	1.215	0.224
PTV-max	52.7; 75.5	65.7 (8.9)	52.5; 71.4	65.5 (6.6)	0.391	0.696

IQR: Interquartile range

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DISCUSSION

Three-dimensional conformal radiotherapy treatment planning is based on CT images; however, the information provided by CT data often can not meet the requirements of target volume delination [6]. In recent years, PET-CT has been increasingly used in RT planning, especially in lung cancer. The delination of target volumes and organs is a very critical step in RT planning [18]. Furthermore, studies have focused on the utility and impact of molecular imaging for both SCLC and NSCLC [19,20]. In this study we have analyzed 60 lung cancer patients' RT planning differences according to use of PET-CT.

SUV is a semiquantitative value that is affected by factors associated with cell proliferation. In retrospective series, SUV value during the diagnosis may be a predictive parameter for disease control and survival. In univariate analysis, threshold for SUV is 5-7, 10, 15, and even 20 [21]. But in Shervin's study no difference was found for disease free or overall survival [22].

One of the major issues is the elapsed time between PET-CT and CT simulation. In Shervin's study, median duration of this period was 38 days and there was a non-significant improvement in survival if this period is <30 days [22]. The mean duration from the date of PET-CT to the start of RT was 26 days.

Although it is important to meet the requirements of target dose distrubution, protection of normal tissues is also important. Complications of RT caused by very large irradiated volume or very high dose to OARs should be avoided. Deniaud-Alexandre et al. delinated GTV in 92 non-small cell lung cancer (NSCLC) patients by PET-CT and found that the GTVpet was reduced in 23% of patients and increased in 26% of them compared to GTVct, also 21 patients had a GTV change of ≥ 25% [6]. In our study 31 (52%) of 60 patients had a GTV change of of ≥ 25%. The GTV of patients reduced in 24/60 (40%) patients and increased in 7/60 (12%). Bradley et al. contoured the GTV from CT and PET-CT data sets in 26 NSCLC patients and found that, in three patients with atelectasis, the GTV and PTV obtained from PET-CT images were significantly reduced compared to those obtained from CT images, the MLD decreased from 14.83 Gy to 12.93 Gy and lung V20 decreased from 25.33% to 21.33%. They also discovered that the MLD and mean esophageal dose increased with the increase in the GTV in 11 patients whose target volumes increased as a result of additional detection of metastatic lymph nodes [23]. Also in Erdi's study 7/11 patients showed an increase in PTV with the use of PET-CT. In three of seven patients, PTV had less dose than the prescription dose (30-95 cm^3 of PTV received a dose less than 10% of the prescription dose) [24]. Lower doses to the PTV raises the risk of locoregional and distant recurrences further. However, higher doses may cause toxicity in normal tissues. Samples of GTV and PTV's changes are shown in Figure 1 and 2.

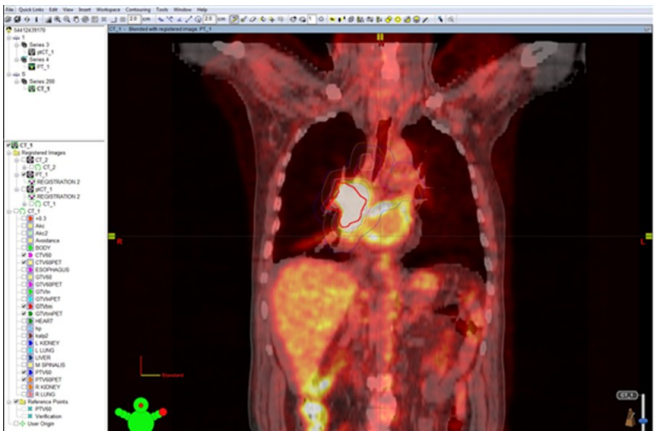


Figure 1. Representation of PET and CT simulation fused planning coronal slice from a patient with a mass in right hilar region. Red line is the GTV which is delineated with CT images (GTVct). PET-CT alters RT target volumes. GTVct can be seperated from focus of intense. GTVct has a smaller volume than GTVpet.

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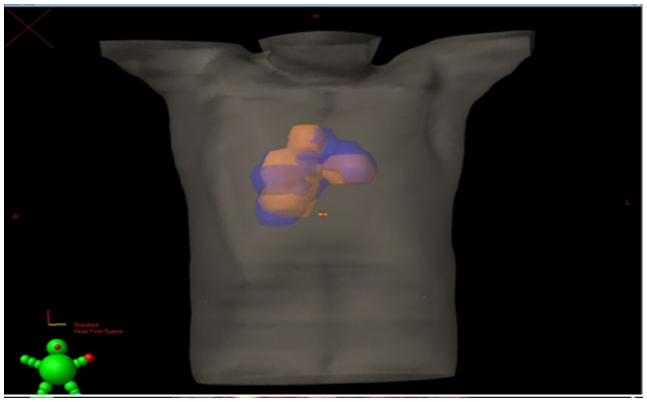


Figure 2. Three dimensional view of PTVs. PTV with blue colour belongs to CT guided delineation. PTV with orange belongs to PET-CT guided delineation. In this patient, PTVpet has a smaller volume than PTVct.

Shervin investigated elective nodal failure as a result of involved field IMRT in 60 limited stage SCLC patients. Only one patient in 30 with recurrence was isolated elective failure [22]. In De Ruyysher's study with the use of PET-CT elective nodal failure was 3% [25]. In Intergroup 0096 study, 2-year overall and disease-free survival rates were 47% and 29% respectively. Also in RTOG 9311 study failure rate was 8% in NSCLC patients [26]. No patients received elective nodal irradiation in our study.

In our study; median volume values of GTV, CTV, and PTV were significantly lower in PET planning. This means that the irradiation is performed from a smaller area. Median dose values of GTV-mean and GTV-max were significantly higher in PET planning, while GTV-min was not significantly different. Also median dose value of PTV-mean was significantly higher in PET planning.

Severity of acute radiation-induced lung injury is associated with irradiated volume. V20 is the most frequently used parameter in the evaluation of treatment plans. Graham et. al. found that V20 and MLD were associated with grade ≥2 acute radiation damage in the univariate analysis. However, in multivariate analysis, only V20 was shown as independent predictive factor [27]. In our study, V20 and MLD values were significantly lower in PET planning. The parameters and remained results for radiation esophagitis are variable. Algara has found that V50 is the most valuable predictive factor [28]. However, Topkan showed that V55 is the parameter associated with esophagitis [29]. In Kim's study, V60 is stated as an important factor for grade ≥3 acute radiation esophagitis [30]. We showed that median values of esophagus mean dose, V50, and V55 were significantly lower in PET planning. Maximum dose is the main parameter to predict radiation myelitis. Median value of maximum spinal cord dose was significantly lower in PET planning in our study. Also median median values of heart mean dose and V40 were obtained significantly lower in PET planning.

Most of the PET-CT guided planning studies include small number of patients. In addition, most of them are dosimetric studies as our study. Histological or clinical outcome assesment study number is a very small amount. Limitations of our study include the small number of patients, manual registration during the planning (as a result of software program) and lack of treatment and toxicity outcomes. Treatment and toxicity results of these sixty patients were designed as another trial topic.

CONCLUSION

In our study, we observed decreased target volumes and higher dose distrubutions for target volumes in PET registrated RT plans. According to these data, with today's technology facilities, it is possible to say that optimal RT plans can be formed for lung cancer by using PET registration.

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***Conflicts of interest*:** *Declared none.*

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