Impact of PET-CT imaging on staging and conformal radiotherapy treatment planning for non small cell carcinoma of lung

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Abstract

Introduction: Lung cancer is the most common cancer in the world and accounts for nearly 13% of all new cancer diagnoses in both sexes combined and currently is the leading cause of cancer related deaths worldwide**.** Due to dismal overall survival, all efforts should be made to improve the diagnosis and treatment to lung cancer patients. So the aim of this study is to explore the possibility of using fused CT-PET images for accuracy of staging and three dimensional radiation treatment planning in regard delineation of target in patients of carcinoma lung (NSCLC) who are referred to us for radical radiotherapy.

Materials and Methods: It's a hospital based prospective study in which 16(n) cancer patients who had biopsy proven NSCLC and were referred to us for radical radiotherapy.

Results: The mean age was 65 yrs, 81.25% (13) patients are male and 18.75 % (3) are female. PET-CT imaging changed the staging in 4 patients (25%), metastatic disease found in 2 patients (12.5%). The registration of fused images of PET with planning CT scan decreased the gross tumor volume (GTV) in 10 patients (71.42%), decreased volume in 4 patients (28.58%). The 3D-CRT planes were modified in 5patients (35%).

Conclusion: Our findings extend the conclusion of observational studies in which FDG-PET has already been used to improve cancer staging and the definition of GTV for radiation treatment planning. It showed 25% change in staging, 12% detecting distant metastasis and 35% alteration in radiotherapy treatment plan. PET-CT should be routinely used for staging and if feasible it should be incorporated in radiotherapy treatment planning.

Keywords: NSCLC, PET-CT, 3D-CRT.

Introduction

Lung cancer is the most common cancer in the world and accounts for nearly 13% of all new cancer diagnoses in both sexes combined[1,2] and currently is the leading cause of cancer related deaths worldwide.[3] The lung cancer incidence in India is 2-14.6 per 1,00,000 in males and 0-3.7 per 1,00,000 in females.

The global rise in lung cancer incidence, and the fact that the overall 5-year survival of patient with this disease is less than 15%, underscore the magnitude of the lung cancer epidemic.

Non small cell lung cancer (NSCLC), is the most common type of lung cancer and refers to a group of commonly observed pulmonary neoplasm that are typically associated with cigarette smoking and share the common property of not being responsive to small cell carcinoma treatment protocols. The treatment options for NSCLC depend on stage, extent of cancer and may consist of surgery, radiotherapy, chemotherapy and or biologic therapy.

Definitive radiotherapy alone or chemo-radiotherapy is indicated for approximate 40% of patients presenting with newly diagnosed NSCLC. This patient population consists of two groups: patient with localized lesions that are potentially resectable but are medically inoperable and the patient with larger unresectable tumors (T3-4N0-1 orT1-4 N2-3). An additional small group of patients are those with recurrent NSCLC confined to thorax after surgical resection.

The success of radiotherapy in such tumors solely depends on the selective delivery of adequate dose to target with minimal irradiation of surrounding structures. Due to complex anatomical structure and its proximity to some critical organs such as heart, esophagus, spinal cord etc pose as a challenge for delivering radiotherapy in lung cancer. It has been generally accepted that a dose response relationship exist between local tumor control and radiation dose. Higher the dose of radiation superior the local control.

Dose escalation has been tried by varies means and all treatment delivery methods such as Three Dimensional conformal Radiotherapy (3D-CRT), Intensity Modulated Radiotherapy (IMRT) with or without Gating, SRS/SRT, Neutron therapy, brachytherapy, intraoperative therapy etc, have a single objective: to achieve therapeutic objective while sparing uninvolved structures. Thus a radio-therapeutic intervention must deliver a lethal dose to the target volume while maintaining subclinical dose to the surrounding healthy tissues.

The success of radiotherapy relies on knowing exactly where the tumor is in 3-D space within the body and its relationship with the surrounding structures of the body. Traditionally treatment planning for these patients has been based on CT scan alone. In many cases, CT scan provides excellent morphologic

information but lack the ability to distinguish between benign and malignant disease or biological activity, also cannot rule out metastatic disease in normal size lymph node.

18 F-fluoro-deoxy-2-glucose (FDG), Positron Emission Tomography (PET) scan is a functional imaging technique that visualizes the distribution of a glucose analog in vivo. Many tumor cells have an increased rate of glycolysis, leading to a increased uptake of FDG. In lung cancer staging, PET imaging with FDG has proven to be more sensitive and specific than CT or MRI in detecting mediastinal lymph node involvement.[4-6] In a meta-analysis, PET scan's mean sensitivity and specificity of 0.79 and 0.91, respectively, for mediastinal staging of NSCLC. The corresponding values for CT were 0.60 and 0.77, respectively.[7]

The combination of CT and PET scan imaging's has significantly improved the ability to accurately map the distribution of cancer within the chest and newest generation of radiotherapy planning computers has the ability to take full advantage of both study types in the treatment planning process. This is done by co-registering or fusing the images from different planning studies in the three dimensions on the same display. In this way anatomic information provided by CT scan and cancer biological information provided by PET studies are combined in the computer in the view of getting most accurate possible radiation treatment volume with better sparing of surrounding tissues.

The aim of this study is to explore the possibility of using fused CT-PET images for accuracy of staging and three dimensional radiation treatment planning in regard delineation of target in patients of carcinoma lung (NSCLC) who are referred to us for radical radiotherapy.

Materials and Methods

All 16 patients of NSCLC who are referred to us for radical radiation therapy and fulfill other set criteria of patient selection included in this prospective study.

Initial evaluation consisted of a history and physical examination; routine blood investigations, including complete blood count and liver function test; renal functions; chest X-ray; broconscopy, a computed tomography (CT) scan of the chest; pulmonary function tests, PET scan and a CT or magnetic resonance imaging scan of the brain. A CT guided FNAC and or broncoscopic biopsy was done to establish histopathology. We revived the slides in our histopathology department if patients were investigated outside.

Patients are staged according TNM staging classification as per AJCC 2002 staging. Patients who received Neo-adjuvant chemotherapy were evaluated for Radiation therapy 2-3 weeks post chemotherapy. Evaluation included a complete clinical examination, hematological and biochemical parameters, chest-x-ray, and CT Scan of the primary site to assess the extent of residual disease. Patients with mixed pathologic types between NSCLC and SCLC and bronchoalveolar carcinoma were excluded.

In all patients the simulation was done in supine position with neck rest, hands above the head, abducted and normal breathing. Same position is maintained throughout simulation, CT scan, PET scan procedure. The isocenter was chosen for each patient, lasers are marked so that it will help in proper patient positioning and external radio-opaque markers placed for future reference.

During acquisition of the CT images, patients were instructed to maintain steady, shallow breathing,. Spiral CT was performed using a slice thickness of 3.3 mm and inter slice spacing of 3.3 mm throughout the volume containing the tumor and fiducial markers to encompass the entire thorax and upper abdomen. The voxel dimensions in this region were 0.9 mm x 0.9 mm x3 mm.

PET imaging was commenced after 1 hour of injection. Immediately before the PET imaging was begun, patients were asked to urinate and empty the bladder fully. Fiducial markers were secured to the same skin locations as used for CT. The patient was placed in treatment position, using the same neck rest and a flat Perspex top on the PET couch. FDG-hybrid PET images were acquired in 64 gantry steps, 20 seconds/view with an energy window of 20% around 511 KeV.

Acquisition was performed with a matrix size of 128 X 128, as a 1hr 30mins single tomographic study. Transaxial slices were reconstructed using ordered-subsets, maximum likelihood iterative technique. A calculated attenuation correction and a three-dimensional (3D) post reconstruction, low-pass filter were applied to the data, which were then resliced into transaxial, coronal, and sagittal planes for visual assessment. Voxels were cubic, measuring 4.6 mm on each side. Transaxial data were sent via a DICOM protocol to the CT simulation workstation for image co-registration.

Patients were staged as per AJCC TNM staging system based on diagnostic work-up and reevaluation for staging was done after PET scan.

CT and FDG-hybrid PET data sets were co-registered with Focus (Computerized Medical Systems, Version 4.33.02) using an auto fusion, 3D rotation and translation rigid body program, and the fiducial markers. In all cases, the total conjugate deviation between matched points was less than 5 mm. Registration was confirmed by verifying that images of the markers were overlaid in the fused images. Additional visual confirmation of anatomic registration was sought in cases where the myocardium was FDG avid.

For all patients, the gross tumor volume (GTV) and planning target volume (PTV) were defined using

the CT data and PET-CT data. This was done in two separate sessions. For CT planning, the GTVct was the primary tumor on the lung window (width 1600, length -800) and lymph nodes ≥1 cm on mediastinal setting (width 400, length 40),

For CT-PET planning, the anatomic sites of the pathologic zones on the PET scan were delineated on the CT scan. This was done using a visual fusion technique (33). The localization of the abnormal lymph nodes on the PET images was correlated with the lymph node zones on the CT images.

If the PET scan was negative in the mediastinum and the CT scan was positive, the mediastinum was considered not to harbor cancer cells and was not included in the CT-PET GTV. The volumes of primary tumor and abnormal lymph node areas were assessed by CT only. When the lymph nodes were abnormal on PET but negative on CT, the corresponding anatomical location of particular lymphnode within the mediastinum was taken as the GTV, to avoid the problems of tumor size determination on PET.

The PTV was defined as the GTV with a 1-cm margin in all directions for both CT- and CT-PET–based treatment planning. No elective nodal RT was done. The body surface and lungs were contoured automatically by the treatment planning system. For the calculation, normal tissue parameters were defined.

After contouring, both data sets are transferred to CMS planning system (Computerized Medical System, XiO TPS, Version 4.33.02), a three-dimensional conformal treatment plan was done using the PTVct and PTVct-pet for all patients, both to deliver 60 Gy in 30 fractions to the PTV, according to the International Commission on Radiation Units and Measurements Report 50 guidelines.

Dosimetric values were calculated on the basis of dose–volume histograms and dose distributions on each axial CT plan for both CT- and CT-PET–base planning.

For the tumor and pathologic lymph nodes, we analyzed the GTV and PTV. For the lung, the V20 and MLD were analyzed as predictors of radiation pneumonitis.[27,46] For the esophagus, the volume of the esophagus receiving 45 Gy (V45), Dmax and mean esophageal dose were analyzed as predictors of early and late esophageal toxicity.[90,35] For spinal cord, the volume receiving 45 Gy (V45), maximum dose received (Dmax), mean dose received.

All patients were analyzed and results are expressed as the mean ± standard error of the mean. Statistical differences between paired parameters from CT vs. CT-PET plans were evaluated with the Wilcoxon signed rank test for statistical analysis. Differences were considered to be significant when the two-tailed p-value was <0.05.

Results

We analyzed 16 patients who are biopsy proven NSCLC and referred to us for radical radiotherapy. After studying the various aspects of the patients included in our series the following observations were made.

Table 1: Patient demographics and clinical characteristics

Median Age (years)	**Range (years)**
64.75	54-82
Sex	**Number of patients (%)**
Male	13(81.25)
Female	3(18.75)
Kornafsky score	
70-80	8(50)
80-90	6(37.5)
90-100	2(12.5)
Weight loss	
Yes	7(43.75)
No	9(56.25)
Personal habits of patient	
Smoking	12(75)
No smoking	4(25)
Alcohol	6(37.5)
Stage of cancer	
IIB	3(18.75)
IIIA	6(37.5)
IIIB	43(43.75)
Histopathology	
SCC	2(12.5)
Adenoca	7(43.75)
Adeno-squamus	1(6.25)
NSCLC (not specified)	6(37.5)
Location	
RUL	5(31.25)
RLL	4(25)
LUL	2(12.5)
LMZ	1(6.25)
LLL	4(25)
Mediastinal LN	
Yes	13(81.25)
No	3(18.75)
History of Chemotherapy	
Received chemotherapy	12(75)
No chemotherapy	4(25)

Patients Characteristics

Impact of CT-PET on staging: Assigned clinical stages at protocol entry (without PET information) include 1 patient with T2N2M0, 3 with T3N0M0, 2 with T3N1M0, 3 with T3N2M0. 2 with T3N3M0, 1 with T4N1M0, 4 with T4N2M0. The addition of PET altered the AJCC TNM Clinical stage in 4 patients (25%) (Table 2). PET identified unsuspected distant metastases (M1 disease) in 2 patients. One had liver metastases, and the other had supracalvicular

lymphnode metastases. Both received palliative radiation therapy.

Table 2: AJCC TNM staging

Patients No.	CT Stage	CT-PET Stage
1	T3N0Mx [IIB]	T3N0Mx [IIB]
2	T3N3Mx [IIIB]	T3N3Mx [IIIB]
3	T4N2Mx [IIIB]	T4N2Mx [IIIB]
5	T3N0Mx [IIB]	T3N0Mx [IIB]
6	T4N1Mx [IIIB	T4N1Mx [IIIB]
7	T4N2Mx [IIIB]	T4N2Mx [IIIB]
8	T4N2Mx [IIIB]	T4N2Mx [IIIB]
9	T3N2Mx [IIIA]	T3N2Mx [IIIA]
10	T3N2Mx [IIIA]	T3N2Mx [IIIA]
11	T2N2Mx [IIIA]	T2N2Mx [IIIA]
12	T3N3Mx [IIIB]	T3N3Mx [IIIB]
14	T3N0Mx [IIB]	T3N0Mx [IIB]
Stage changed:		
4	T3N1Mx [IIIA]	T3N2Mx [IIIA]
13	T3N1Mx [IIIA]	T3N0Mx [IIB]
15	T3N2M0 [IIIA]	T3N2M1 [IV]
16	T4N2M0 [IIIB]	T4N2M1 [IV]

Two patients were excluded from analysis as they had distant metastasis

Impact on Target Delineation:

For all 14 patients, GTV was 123.91 cm³ by CT and 93.67 cm³ by PET ($p < 0.042$). We divided the patients on the basis of increase/decrease the GTV volume. In GTV increase group (10 patients) GTV was 135.34 cm³ by CT and 88.37 cm³ by PET ($P<0.0019$). (Table 3)

For all 14 patients, PTV was 316.51 cm³ by CT and 255.60 cm³ by PET ($p < 0.049$). In GTV increase group (10 patients) GTV was 343.73 cm³ by CT and 239.51 cm³ by PET ($P<0.0019$). (Table 3)

Table: 3: Target Volume Parameters

Target volumes				
Patients no.	**CT**	**GTV (cc) CT- PET**	**CT**	**PTV (cc) CT-PET**
GTV decrease:				
1	29.67	22.05	129.07	96.07
2	35.43	21.6	149.62	110.89
3	354.38	295.97	808.38	718.26
4	234.85	44.3	506.48	169.62
5	39.67	21.72	117.73	75.9
8	139.6	103.3	319.66	240.96
9	149.12	116.11	376.08	298.12
12	37.22	26.78	211.79	114.21
13	290.9	202.93	659.63	446.25
14	42.57	28.97	158.85	124.81
MEAN	135.34	88.37	343.73	239.51
SD	120.56	94.15	242.72	203.58
SEM	38.12	29.77	76.75	64.38
P	p<= 0.0019		p<= 0.0019	
	W+ = 55, W- = 0, N = 10,			W+ = 55, W- = 0, N = 10,
GTV increase:				
6	18.93	36.83	101.09	154.35
7	204.16	206.02	466.88	484.88
10	130.15	142	404.54	455.39
11	97.24	111.44	307.64	348.05
MEAN	112.62	124.0725	320.0375	360.6675
Total (14)				
MEAN	123.41	93.67	316.51	255.60
SD	99.32	80.11	205.87	181.39
SEM	28.71	23.23	57.83	51.47
P	p<= 0.04187		p<= 0.04944	
	W+ = 85, W- = 20, N = 14,		W+ = 84, W- = 21, N = 14,	

Table 4: Summary of FDG-PET impact on stage and target volumes

1.	TNM staging change	4/16	25%
2.	Metastatic disease found	2/16	12.5%
3.	GTV volume decrease	10/14	71.42%
4.	GTV volume increase	4/14	28.58%
5.	3D-CRT plan change	5/14	35%

Conflict of Interest: Nil

Discussion

Carcinoma Lung is unique by virtue of its location, propensity for extensive nodal metastasis and potential for distant dissemination. Despite all these disadvantages it is known to be radiosensitive, and hence radiation therapy has been considered as the prime modality for inoperable carcinoma lung.

Recent interest in use of chemotherapy as neo-adjuvant or adjuvant in concurrent setting along with the radiation therapy has not only proved to be superior for better local control but also for overall control of the disease.

Numerous studies have shown that control of carcinoma lung depends on the radiation therapy dose delivered and therefore higher dose of radiation is expected to offer better local control of the disease.

In our prospective study we examined the impact of fused CT-PET imaging in patients with NSCLC in conjunction with stage and target volume delineation. We proposed a complete 3D-CRT plan for each patient based on fusion of morphologic and metabolic information.

The performance of FDG imaging is clearly superior to those of conventional imaging techniques, especially CT. The indications for FDG imaging in the primary evaluation of lung tumors are multiple, and include characterization of an isolated nodule and initial staging of lung cancer, especially mediastinal staging. It also allows evaluation of the response to chemotherapy or radiotherapy, and can even represent a predictive factor of local control and survival.[8] Several studies also have shown that FDG plays a role in both predicting and assessing the therapeutic response.[9]

One of the advantages of FDG-PET imaging in radiotherapy when fused with CT image, is to obtain anatomic and metabolic data to help the radiotherapist define the target volume and therefore optimize the treatment planning.[9,10]

The first studies of CT and FDG image fusion for treatment planning were performed in the head and neck tumors and on the brain to target the boost dose. In the lung, Kiffer et al, graphically superimposed a frontal FDG-PET reconstruction into the simulation film. In this retrospective study, they concluded that they would have modified the irradiation fields for 4 of 15 patients if they had taken FDG-PET into account.[11]

The use of FDG-PET has improved staging accuracy in NSCLC. A prospective study of 50 patients by Didier Lardinois resulted in Integrated PET–CT provided additional information in 20 of 49 patients (41 percent), tumor staging was significantly more accurate with integrated PET–CT than with CT alone (P=0.001), PET alone (P<0.001), or visual correlation of PET and CT (P=0.013); node staging was also significantly more accurate with integrated PET–CT than with PET alone (P=0.013). In metastasis staging, integrated PET–CT increased the diagnostic certainty in two of eight patients.[12]

MacManus et al,[13] recently reported that 30% of patients with locally advanced NSCLC became ineligible for curative radiotherapy, because FDG-PET demonstrated either distant metastatic disease or intrathoracic disease too extensive for radical radiation. Eighteen percent of patients became palliative because of previously undetected distant metastases.

In our study, TNM staging changed in 4 patients (25%) of patients. Only 2 patients (12.5%) were found to have distant metastasis by PET. This is likely a reflection of our small sample size, but could also result from the through radiographic staging workup in the protocol.

A few recent studies have used radiation therapy simulation based on both CT and FDG-PET via image fusion. Mah et al, reported 30 patients undergoing definitive radiation therapy for NSCLC.[14] Treatment was significantly altered in 12 patients (40%). The treatment intent became palliative in 7 patients. The PTV was altered to include nodal disease detected by coincidence imaging in 5 patients. The treatment volumes based on CT were judged to be inadequate by comparison to those based on CT and FDG imaging in 17–29% of the cases, depending on the physician contouring the volumes.

We planned the treatment for 14 patients using CT with and without FDG-PET information. The size of the primary tumor and lymph node areas were assessed by CT only and countered as GTV. The margins of 1 cm from the GTV to PTV were used. We omitted the elective nodal RT. In our series, one can see that differences in GTV exist for each plan comparison. (Table: 2) For all 14 patients, GTV was decreased from 123.91 cm^3 to 93.67 cm^3 ($p < 0.042$) and PTV was decreased from 316.51 cm^3 to 255.60 cm^3 ($p < 0.049$). Our findings can be compared with study by Van Der Wel et al.[15] where he reported a decrease in nodal GTV from 13.7 ± 3.8 cm^3 on the CT scan to 9.9 ± 4.0 cm^3 on the PET-CT scan (p=0.011).

Bradley et al. studied differences in GTVs contoured with CT data alone vs. PET/CT fusion

images. Two of 26 patients (8%) were found to have metastatic disease. The addition of PET information altered the inclusion of tumor and/or nodal regions in 14 of 24 patients receiving 3D-CRT. Two of these were decreases due to atelectasis distinguished from tumor by PET.[16]

Our study therefore confirms the results of the literature. Using a dedicated PET-CT scanner, it changes in TNM staging, helps in detecting the metastatic disease and when used fusion imaging for radiotherapy planning it can modify initial treatment plan for 35% of patients.

Study limitations

Some limitation of this study should be noted. No pathologic verification of the lymph nodes was obtained and therefore possibility of risk of geographic misses could not be ruled out. No system was used to take into account the breathing movements of the chest. We, therefore, could not rule out the possibility that, because of motion artifacts, the exact anatomic localization of the target volume might have been blurred. We have not correlated the dosimetric parameters with clinical findings of toxicity.

Conclusion

Carcinoma lung (NSCLC) is a radiosensitive tumor because of which radiotherapy is considered as the primary modality for inoperable tumors. However the proximity of critical organs remains as a stumbling block for dose escalation to achieve better control of the disease. Newer methods of conformal radiotherapy such as 3D-CRT, IMRT and Stereostactic RT, have been used successfully although each has promises and pitfalls.

In new era of conformal radiotherapy, 3D-CRT has been successfully used in various anatomical sites including lung and the dose escalation is possible to some level with acceptable normal tissue toxicity.

The molecular and functional imaging has "arrived," amongst them FDG-PET imaging is based on tracer principle and FDG uptake strongly correlates with presence of cancer. It has become a reimbursable procedure in developed countries for diagnosis and staging of NSCLC, to detect nodal and other metastases and to usefully guide to biopsy procurement. Because CT is now the major imaging platform for radiotherapy planning, the acquisition of PET image on a similar digital image array allows for rapid fusion of metabolic and anatomic information. Increased dose can be targeted to the metabolically active regions of the GTV, and nonviable CT images can be excluded, making these merged images useful for conformal radiotherapy ushering a new era of physiologic or biologic conformity.

In this study we explored the possibility of using fused CT-PET images in patients with NSCLC and its impact on staging, target delineation. Our findings extend the conclusion of observational studies in which FDG-PET has already been used to improve cancer staging and the definition of GTV for radiation treatment planning. It showed 25% change in staging, 12% distant metastasis and 35% alteration in plan.

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