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A Prospective Study to Evaluate Clinical Radiation Induced Pneumonitis in Lung Cancer Patients and its Dose Response Relationship with Radiotherapy

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Abstract

Purpose: This study was initiated to evaluate incidence, grade and dosimetric correlation of Clinical Radiation Induced Pneumonitis (RIP) (≥ grade 2) in lung cancer patients undergoing radical radiotherapy.

Methods and Materials: From August, 2012 to November, 2013, 85 lung cancer patients received curative 3D CRT. On follow up 14 patients developed symptomatic pneumonitis (≥ Grade 2 as per RTOG Toxicity criteria). They underwent CT thorax/PET-CT at 3 monthly follow-up which were co-registered with planning CT images. Changes in lung density were graded as patchy, discrete and solid consolidation and contoured. Isodose surface enveloping these contours and mean doses received were noted.

Result: At a median follow up of 12.5 months, incidence of clinical ≥Grade 2 RIP was 16.5%. Inclusion of mediastinum in the target volume and higher stage of disease were found to be indicators of increased risk of ≥Grade 2 RIP. Lung volumes showing patchy/discrete consolidation decreased from 3rd to 6th month and then plateaued while solid consolidation appeared at 6 months, increased at 9 months but then decreased at 12 months. Percentage isodoses encompassing grade 2 radiological RIP were between 80-85% and mean doses were between 45-48Gy. However for grade 3/4 RIP corresponding values were 90-95% and 50-54Gy.

Conclusion: Incidence of ≥Grade 2 RIP with conformal RT was 16.5%. V20 alone may not be a sufficient predictor for RIP and one should consider conformal RT planning to restrict even higher isodoses beyond the PTV.

Keywords: Radiation oncology; Pneumonitis; Lung cancer; Conformal radiotherapy

Introduction

Lung cancer is the most common cancer and the leading cause of cancer mortality worldwide [1]. About 30-40% patients present in locally advanced stage (Stage III) wherein concurrent chemoradiation (ChRT) is the standard of care in patients with good performance status [2]. Even with loco-regional disease, the prognosis of lung cancer remains poor because of inadequate control at the primary site after radiation therapy as the tolerance of the normal lung tissue, limits the dose that can be delivered [3]. Clinical RIP is an interstitial pulmonary inflammation that can develop in about 17% patients receiving thoracic irradiation [4]. Despite recent technological advances in radiation therapy (RT) such as three-dimensional (3D) conformal RT and intensity-modulated RT and even 4D RT (although 4DRT is not being practiced in most of the centres in our country), radiation pneumonitis (RP) remains an important dose-limiting toxicity in thoracic RT [2]. Symptomatic patients present with dyspnea, low grade fever and cough (usually non-productive). Acute RIP usually occurs within 1-8 weeks after radiation therapy [5]. Chronic radiation damage occurs due to permanent damage to endothelium and Type 1 pneumocytes leading to pulmonary fibrosis and typically manifests 9-12 months after radiation therapy mainly. Compared to clinical pneumonitis, radiographic pneumonitis is much more common and has been found to occur in 50 - 60% of patients following lung irradiation [5].

There have been studies attempting to provide a dose–volume effect for the development of RIP inconventionally fractionated radiotherapy [6-9]. However the details about the severity, extent and evolution of radiation pneumonitis have not been described very well [5,10,11]. The aim of this study was to find out the incidence, grade and dosimetric correlation of Clinical RIP (grade 2 or more) in lung cancer patients undergoing radical radiotherapy with concurrent chemotherapy.

Methods and Materials

From August, 2012 to November, 2013, a total of 85 patients with lung cancer received 3Dconformal radiation therapy (3D CRT) with or without chemotherapy. They were treated with curative intent using conventional fractionation and in accordance with the existing

institutional protocols. This study received approval from the institutional ethics committee and is registered at ctri.nic.in

Treatment planning

All patients underwent free breathing radiotherapy planning CT scans in supine position. 3D volume definitions were done in accordance with International Commission Radiation and Measurements (Report No. 62). GTV included the primary tumour (GTV Primary) and involved lymph nodes (GTV Node).Lymph nodes were considered tumour if they demonstrated increased FDG uptake or measured >1 cm in short-axis dimension on CT. FDG-PET avidity overrode the standard CT criteria for abnormality (e.g., a lymph node that was <1 cm on CT but had abnormal FDG uptake on PET was included in the GTV). No elective nodal irradiation was carried out. The CTV primary was defined as a 0.7 cm 3D expansion of the GTV primary to account for microscopic extension. The CTV nodes were defined as 0.5 cm 3D expansion GTV nodes. Editing of CTV was done respecting normal barriers (bone, vessel, pleura) if not invaded. The minimal PTV margin was 0.7 cm and was further tailored based on fluoroscopy impression of tumour movement during simulation. 3D-CRT plan for each patient was created using typically three to four beam angles with or without non-coplanar beam arrangement. Dose prescription was 60 Gy/30# for NSCLC and 50 Gy/25# for SCLC. The dose-volume constraints for the lungs were set as follows: V20 <30%, V30 < 20% and mean lung dose < 20 Gy. All lung volumes for dosimetry were calculated for Total bilateral Lungs-PTV. The maximum dose of 45 Gy was allowed to the spinal cord.

Suitable patients with NSCLC received paclitaxel and carboplatin in a concurrent setting (six cycles given once a week) while SCLC patients received Cisplatin and Etoposide (four cycles given three weekly). After completion of treatment, patients were followed up at three monthly intervals for the 1st year and 6 monthly thereafter. At each follow-up detailed history regarding symptoms and thorough clinical examination were carried out. Their clinical response as well as toxicity was recorded by the treating physician. A diagnosis of radiation induced pneumonitis (RIP) was based on clinical symptoms of cough, shortness of breath, possible fever, and correlation with radiologic findings. RIP was graded according to the RTOG Lung Radiation Morbidity Scoring Criteria [12]. During the period of this study a total of 85 patients were treated with radical concurrent chemo-radiation at our centre. Amongst these 85 patients 14 were found to have symptomatic pneumonitis on follow up and only these symptomatic patients underwent CT scan of the thorax or whole body PET-CT at every three months follow-up, as per approval from the institutional ethics committee. Given below is the Figure 1 showing the study procedure.

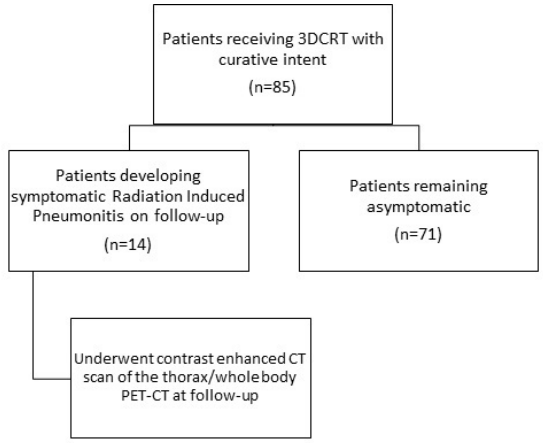

Figure 1: Flow diagram showing the study procedure.

Follow up image analysis

The follow up CT Thorax/PET-CT images of the 14 patients were transferred to the treatment planning system where they were co-registered with the original planning CT. The registration of the image sets were done using a point-based matching algorithm in order to obtain a three dimensional (3D) congruence. The reference image was converted into a distance image in which each voxel has a value proportional to the distance to the nearest feature voxel, so that the mismatching of features from two image data sets could be expressed as a function of the transformation parameters. The external surfaces of the lung extracted from both the transmission images were used as input to obtain the transformation matrix. Fine tuning was accomplished by manual translational and rotational adjustments to match the follow-up CT scan with the planning CT scans. While matching, topmost priority was given to carina (along with the lower portion of trachea) following which vertebral bodies were matched. At times, aorta was also considered as well as natural calcifications.

Radiological interpretation of images

The follow-up CT scans were evaluated by a team including a diagnostic radiologist as well as radiation oncologists for any change in lung density as compared to treatment planning scan (viz. homogenous increase in density, patchy/discrete/solid consolidation) and were graded based on the radiological scoring pattern proposed by Libshitz et al. [13]. The volume of lung having differential pattern of density changes were contoured (using lung L/W settings (i.e. level -600 Hounsfield Units (HU), window 1600 HU) and mediastinum L/W settings (i.e. level 40 HU, window 400 HU)) by the team of radiation oncologists and verified by the radiologist as Grade II, Grade III and Grade IV RIP on the follow-up scans.

These contours (radiological grades) were copied onto the planning image set and making use of dose colour wash and dose-volume histogram of the original plan the following parameters for these contours representing radiological grades of toxicity were noted:

Isodose surface enveloping these individual contoured radiological grade changes with the best fit (in percentage).

Mean doses (in Gy) received by each of these regions.

Results

The patient characteristics are shown below (Table 1). The cohort of patients was predominantly males with a median age of 57 years (range, 36–71 years), 8 out of 14 were smokers and median KPS of 70. Three patients had pre-existing lung disease (chronic obstructive pulmonary disease). The median overall treatment time was 44 days and majority completed treatment within 50 days. The average Mean Lung Dose was 15.14 Gy (range, 7.2-25.7 Gy) while the mean V20 was 19.8% (range, 3.9-35.1%). The dosimetric characteristics are detailed in the table below (Table 2). All the patients except one received chemotherapy. Chemotherapy was withheld in that single patient in view of poor general condition. Two SCLC patients received chemotherapy in the neo-adjuvant setting with Cisplatin and Etoposide. Among the NSCLC patients, 9 received concurrent chemoradiotherapy with Paclitaxel and Carboplatin (median number of cycles received being 6) while one received only concurrent Carboplatin.

Characteristics	Distribution	
Patient Characteristics		
Sex	Male	10 (71.4%)
	Female	4(28.6%)
Age at Diagnosis (years)	57(median)	(36-71 years)
	<60	10 (71.4%)
	≥60	4(28.6%)
Karnofsky performance status	≥70	13 (92.9%)
	<70	1(7.1%)
Smoking	Yes	8(57.1%)
	No	6(42.9%)
Pre-existing Pulmonary Disease	Yes	3(21.4%)
	No	11 (78.6%)
Tumour Characteristics		
Histologic finding	Squamous cell carcinoma	5(35.7%)
	Adenocarcinoma	4(28.6%)
	Small cell carcinoma	4(28.6%)
	NSCLC -not otherwise specified	1(7.1%)
Cancer stage	IIA or IIB	3(21.4%)
	IIIA or IIIB	11 (78.6%)
T Stage	T1	1(7.1%)
	T2	2(14.3%)
	T3	4(28.6%)
	T4	7(50%)
N Stage	N0	4(28.6%)
	N1	1(7.1%)
	N2	7(50%)

Table 1: Patient, tumour and treatment characteristics.

Characteristics	Distribution	Range
Total Lung Volume	2738 cc (mean)	1319 - 4187 cc
Total Dose of RT	60 Gy (median)	50 - 60 Gy
Overall Treatment Time	44 days (median)	36 - 61 days
GTV volume	165 cc (mean)	31- 427 cc
CTV volume	288 cc (mean)	52- 734 cc
PTV volume	514 cc (mean)	159- 1095 cc
Mean Lung Dose	1675 cGy (median)	717 - 2568 cGy
Lung - PTV volume	2394 cc (median)	1318 - 3952 cc
Ipsilateral Lung - PTV volume	874 cc (median)	32 -2927 cc
V20	21.7% (median)	3.9 - 35.1%
V5	52.3% (median)	23.7 - 65.0%
V55	7% (median)	0 - 29.8%

Table 2: Dosimetric characteristics.

At a median follow up of 12.5 months (range: 3-22 months), 14 out of 85 patients were found to have symptomatic Radiation Induced Pneumonitis (RIP) i.e. ≥ Grade 2 RIP as per RTOG toxicity criteria (Incidence of clinical RIP being 16.5%). Amongst symptomatic patients, at three months of completion of treatment, 8 patients out of the total 14 developed Grade 2 RIP while the remaining 6had mild symptoms of cough or breathlessness i.e. Grade 1 RIP. At 6 months 11 patients had been followed up and all of them had ≥ Grade 2 RIP. 1 had progressed to Grade 3 RIP at 6 months. At 9 months, 9 patients had completed follow-up. The single patient with Grade 3 RIP still persisted with Grade 3 while the others continued to have Grade 2 RIP. At the end of one year, 7 patients had completed follow-up. That one patient persistently had Grade 3 RIP while another one progressed to have Grade 3 RIP. The symptomatic patients were managed with oral steroids, bronchodilators and antitussives.

- The pattern of radiological change in one such patient at different time intervals is shown in Figure 2. The frequency of clinical RIP over a period of one year is shown below in Figure 3.

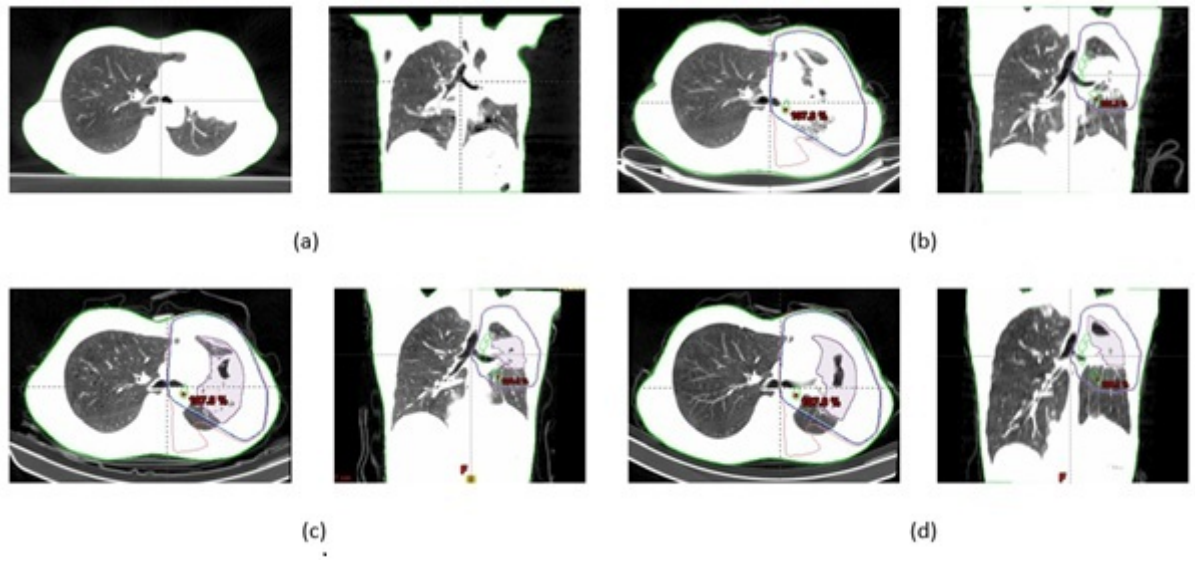

Figure 2: A 58 year old gentleman with NSCLC stage III B a) before radiation therapy (RT), b) at 3 months after RT, c) at 6 months after RT, and d) at 12 months after RT. Dark green, light green, blue and pink lines represent 107%, 95%, 90% and 80% isodoses respectively.

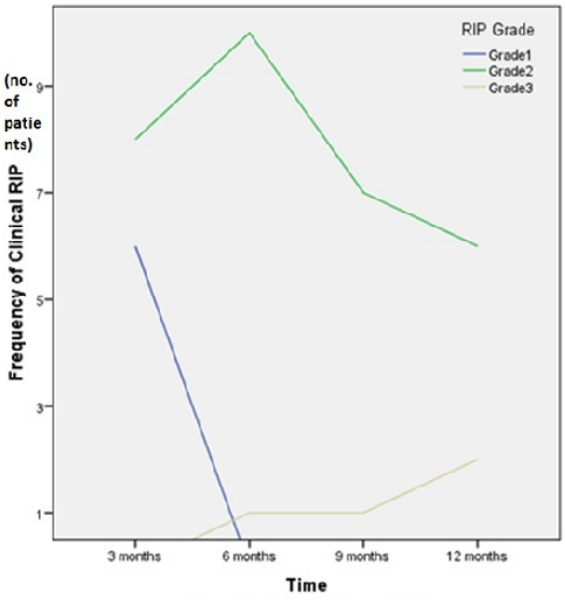

Figure 3: Frequency of clinical RIP in course of time.

All the 14 patients underwent follow up CT/PET-CT imaging at 3 months; 10 at 6 months and 7 at 9as well as 12 months. These images were fused with the planning image set and after proper co-registration of the respective images; the affected volumes were contoured on each CT slice. The details of the varying grades of radiological RIP volumes are shown below in Table 3.

Characteristics	Mean (%) (Min-Max)	
At 3 months	Isodose encompassing RIP Grade 2 volume	80.1 (63.9- 91.4)
	Isodose encompassing RIP Grade 3 volume	93.4 (84 - 99.6)
	Isodose encompassing RIP Grade 4 volume	0 (0)

	Isodose encompassing RIP Grade 2 volume	77.8 (70.3 - 85.9)
	Isodose encompassing RIP Grade 3 volume	91.8 (86.8 - 98.2)
At 6 months	Isodose encompassing RIP Grade 4 volume	96.7 (93.2 - 99.4)
	Isodose encompassing RIP Grade 2 volume	85.5 (71.8 - 102.2)
	Isodose encompassing RIP Grade 3 volume	92.1 (81.7 - 100.9)
At 9 months	Isodose encompassing RIP Grade 4 volume	94.6 (91.1 - 99.6)
	Isodose encompassing RIP Grade 2 volume	85.6 (71.9 - 100.6)
	Isodose encompassing RIP Grade 3 volume	93.1 (82.2 - 101.2)
At 12 months	Isodose encompassing RIP Grade 4 volume	95.3 (91.5 - 99.3)

Table 3: Radiological RIP dosimetric characteristics.

The isodoses encompassing the respective grades of RIP were found out using the dose color wash and the dose-volume histogram. The details of the isodoses encompassing the various radiological changes as well as the mean doses received by the aforementioned volumes at different time points are described below in Table 4.

	Characteristics	Mean (cGy) (Min-Max)
	Mean Dose received by RIP Grade 2 Volume	4651.8(2180.1- 6281.2)
At 3 months	Mean Dose received by RIP Grade 3 Volume	5484.9 (4527 - 6092.8)
	Mean Dose received by RIP Grade 4 Volume	0(0)
	Mean Dose received by RIP Grade 2 Volume	4592.6 (3813.1 - 5845.4)
At 6 months	Mean Dose received by RIP Grade 3 Volume	5180.4 (4404 - 6142.5)
	Mean Dose received by RIP Grade 4 Volume	5384.3 (4512.5 - 6101.4)
	Mean Dose received by RIP Grade 2 Volume	4566.4 (2085.7 - 6153.9)
At 9 months	Mean Dose received by RIP Grade 3 Volume	5115.6 (2855 - 6111.1)
	Mean Dose received by RIP Grade 4 Volume	5166.5 (3306 - 6050)
	Mean Dose received by RIP Grade 2 Volume	4855.6 (3883.3 - 6186)
At 12 months	Mean Dose received by RIP Grade 3 Volume	5018.6 (2029.5 - 6058.1)
	Mean Dose received by RIP Grade 4 Volume	5174.6 (3452.8 - 6052.4)

Table 4: Isodoses encompassing the various radiological changes.

Among these 14 patients, one died of disease at 11 months after completing treatment; 7 patients are alive with disease while the other six are clinically controlled. The patients who developed disease progression or recurrence were managed with palliative chemotherapy.

Discussion

This study had a dual objective. The first was to determine the grade and prevalence of post radiotherapy (or chemoradiotherapy) pneumonitis in our patients. The more important objective was dosimetric correlation of the zones of radiographic changes of pneumonitis with the corresponding dose received by those zones.

Incidence and severity of RIP has been shown to depend on a number of factors. These include total dose of radiation, dose per fraction, volume of lung irradiated (like volume of the lung exposed to doses of 20 Gy or higher i.e. V20), mean lung dose (MLD), location of tumor, inclusion of mediastinum or hilum in treatment volume, certain chemotherapeutic drugs (viz. Actinomycin D, Cyclophosphamide, Vincristine, Bleomycin, Taxanes), underlying pulmonary disease, pre-treatment performance status and age of the patient, H/O smoking, H/O surgical intervention [4,5,11,14-19]. In case of acute RIP, radiographic changes are usually confined to radiation portal and CT scan findings include: homogenous slight increase in attenuation or ground-glass opacity, patchy consolidation or non-uniform discrete consolidation. For chronic RIP, CT scan shows solid consolidation and bronchiectasis. These radiological changes may be sub-clinical, but have been shown to correlate strongly with histologic and physical endpoints in a preclinical study [11,15]. As per existing literature; the incidence of symptomatic clinical RIP is around 17% among patients receiving thoracic irradiation [4] while the incidence of radiological RIP is around 60% [5]. The incidence of clinical RIP (Grade 2 or more) was 16.5% which is at par with current literature [4]. Of these, 14.1 % had Grade 2 RIP and only two patients (2.4%) ended up with Grade 3 RIP.

Patients with mediastinal lymph nodal involvement (N2 disease) have been found to be at an increased risk of developing symptomatic RIP as is evident in current literature [20]. In this study, at the end of 3 months, 7 out of 9 patients with N2 disease developed Grade 2 RIP while the same occurred only in 1 among 5 patients without mediastinal lymphadenopathy – this was statistically significant (p=0.036). Contouring the volumes showing radiological changes of RIP was another big challenge because of the possibility of infection, locally recurrent neoplasm, lymphangitis, and carcinomatosis. In general, filling-in of radiation therapy–induced bronchiectatic change and opacity with a convex lateral border were considered as radiologic signs of recurrent tumour [21]. It was observed in our study that Grade

2 and 3 radiological changes of RIP i.e. patchy and discrete consolidation appeared by 3 months following completion of radiotherapy. However, solid, dense consolidation was visible in select cases only after 6 months following RT. The volumes of both Grade 2 and Grade 3 RIP showed a pattern – their volume decreased from 3rd to 6th month and then gradually plateaued as is evident from Table 5. This, however, was not the case with the volume showing Grade 4 radiological RIP. It first appeared at 6 months, increased at 9 months but then again decreased at 12 months. Traditionally, the lung's response to irradiation is described as having latent phase, occurring immediately and up to 3 months after irradiation; an exudative phase, also known as radiation pneumonitis, occurring from 3 to 6 months after irradiation; and a final fibrotic phase, occurring from 6 months after irradiation onward. Grade 2 and 3 radiological pneumonitis are more representative of exudative phase so they appeared at 3 months and stabilized after 6 months while grade 4 radiological pneumonitis represents the fibrotic phase which appeared after 6 months and stabilized after 9 months. The volumes showing grade2/3 RIP had gradually progressed to grade4 changes from the 3rd month till 9th month while radiation induced fibrosis ensued. Thereafter as fibrotic changes continued and got organized it led to shrinkage of lung volume and traction bronchiectasis. This volume loss might be the reason behind the apparent decrease in the volume showing Grade 4 RIP. Also, all patients with symptoms of RIP received oral steroids which is known to cause tissue remodelling and might have altered the pattern of fibrosis in these patients. Moreover, one important point that should be mentioned here is that in spite of having a V20 of<35% in all these 14 patients, they still went on to develop radiation pneumonitis which perhaps signifies the fact that a single parameter is not a sufficient predictor of radiation pneumonitis and multiple factors should be considered together for this predictive assessment. All 14 patients had symptomatic radiation pneumonitis 2=grade3 and 12=grade 2). Correlation between clinical and radiological pneumonitis, whether exists could not be carried out as routine imaging was not done in asymptomatic patients. However symptomatic patients with Grade 3clinical pneumonitis had greater component grade 4 radiological changes. The isodoses encompassing the respective volumes of radiological RIP showed that the mean of the isodoses gradually increased in an ascending order with increased grade of RIP i.e. lesser magnitude of isodoses encompassed lower grades of RIP while higher values of isodose surfaces encircled higher grades of RIP and this relationship was maintained at all time frames. This was an expected result because with conformal radiotherapy techniques, beams are delivered from different angles resulting in accumulation of dose around the target with low dose areas near the periphery. As such higher grades of radiological changes are expected around the target which shall be covered by higher isodose surfaces. Our study is the first of its kind bringing out this correlation between dose received by particular zone of the lung and the subsequent development of pulmonary changes. The percentage isodoses encompassing grade 2 changes were between 80-85% while the corresponding mean doses were between 45-48Gy. However for grade 3 and grade 4 radiological changes 90-95% isodoses with mean doses of 50-54Gy was encompassing the volume. So some kind of dose response was appreciated with higher doses corresponding to higher grades of radiological density changes (pneumonitis). This has implications in 3DCRT planning, as the aim is to reduce dose to adjacent normal lung outside PTV and a greater conformity thereby leading to a good conformity index .During planning and evaluation high dose regions outside PTV (both irradiated and treated volume as defined by ICRU50) should be minimized as this would decrease the incidence of both symptomatic clinical and radiological pneumonitis. The mean dose received by these volumes also show a similar pattern – mean dose received by the volume with Grade 2 RIP was less than the mean dose in case of Grade 3 RIP which in turn was again less than that with Grade 4 RIP. This is well in accordance with the available evidence – pulmonary damage rarely occurs with total doses below 20 Gy [22], commonly occurs with doses between 30 to 40 Gy and almost always occurs with total doses above 40 Gy [23]. So higher doses are more likely to cause more severe radiological RIP. Both patients who developed grade 3 clinical RIP had received doses of 60Gy/30# while none of the patients receiving 50Gy developed grade 3 clinical RIP. Both clinical grades 3 RIP had large volume grade 4 radiological RIP after 9 months.

Characteristics		Mean (cc)	Minimum (cc)	Maximum (cc)
At 3 months	RIP Grade 2 Volume	26.5	0	149.8
	RIP Grade 3 Volume	142.3	0	314.8
	RIP Grade 4 Volume	0	0	0
At 6 months	RIP Grade 2 Volume	6.8	0	39.7
	RIP Grade 3 Volume	81.5	0	196.5
	RIP Grade 4 Volume	150.4	0	340.7
At 9 months	RIP Grade 2 Volume	15.6	0	67.4
	RIP Grade 3 Volume	48.6	1.8	159.1
	RIP Grade 4 Volume	184.9	0	808.7
At 12 months	RIP Grade 2 Volume	18.8	0	72.7
	RIP Grade 3 Volume	51.7	0	136.4

	RIP Grade 4 Volume	139.4	0	564.7

Table 5: Radiological RIP volume characteristics.

Conclusion

Incidence of symptomatic radiation pneumonitis at our centre (Grade 2 or more as per RTOG Toxicity criteria) in the current era of conformal radiation therapy was 16.5%. However, radiological changes, as seen on CT imaging of the thorax, occur in a higher proportion.

Our findings suggest that V20 alone may not be a sufficient predictor for RIP and one should consider conformal radiotherapy planning to restrict even higher isodoses beyond the PTV.

References

1. http://globocan.iarc.fr/factsheets/cancers/lung.asp.
2. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, et al. (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non small-cell lung cancer. J Clin Oncol 28: 2181-2190.
3. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, et al. (2010) Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 76: S70-76.
4. Graham MV, Purdy JA, Emami B, Harms W, Bosch W, et al. (1999) Clinical dose volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 45: 323-329.
5. Palma DA, Senan S, Haasbeek CJ, Verbakel WF, Vincent A, et al. (2011) Radiological and clinical pneumonitis after stereotactic lung radiotherapy: a matched analysis of three dimensional conformal and volumetric-modulated arc therapy techniques. Int J Radiat Oncol Biol Phys 80: 506-513.
6. Bush DA, Dunbar RD, Bonnet R, Slater JD, Cheek GA, et al. (1999) Pulmonary injury from proton and conventional radiotherapy as revealed by CT. AJR 172: 735-739.
7. Ikezoe J, Morimoto S, Takashima S, Takeuchi N, Arisawa J, et al. (1990) Acute radiation induced pulmonary injury: computed tomography evaluation. Seminars in ultrasound CT and MRI. AJR 11: 409-416.
8. Koenig TR, Munden RF, Erasmus JJ, Sabloff BS, Gladish GW, et al. (2002) Radiation injury of the lung after three-dimensional conformal radiation therapy. AJR 178: 1383-1388.
9. Kong FM, Haken RT, Eisbruch A, Lawrence TS (2002) Non-small cell lung cancer therapy related pulmonary toxicity: an update on radiation pneumonitis and fibrosis. Seminars in oncology 32: S42-54.
10. Choi YW, Munden RF, Erasmus JJ, Park KJ, Chung WK, et al. (2004) Effects of radiation therapy on the lung: radiologic appearances and differential diagnosis. RSNA 24: 985-997.
11. Jenkins P, Welsh A (2011) Computed tomography appearance 312 of early radiation injury to the lung: correlation with clinical and dosimetric factors. Int J Radiat Oncol Biol Phys 81: 97-103.
12. Cox JD, Stetz J, Pajak TF (1995) Toxicity criteria of the Radiation Therapy Oncology Group(RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31: 1341-1346.
13. Libshitz HI, Shuman LS (1984) Radiation-induced pulmonary change: CT findings. Journal ofcomputer assisted tomography 8: 15-19.
14. Das S, Rathod S, Mnshi A, Agarwal J (2013) Being lax with taxanes can be taxing! Int J Radiat Oncol Biol Phys 86: 14-15.
15. Guckenberger M, Heilman K, Wulf J, Mueller G, Beckmann G, et al. (2007) Pulmonary injury and tumor response after stereotactic body radiotherapy (SBRT): results of a serial follow-up CT study. Radiother Oncol 85: 435-442.
16. Kimura T, Matsuura K, Murakami Y, Hashimoto Y, Kenjo M, et al. (2006) CT appearance of radiation injury of the lung and clinical symptoms after stereotactic body radiation therapy (SBRT) for lung cancers: are patients with pulmonary emphysema also candidates for SBRT for lung cancers? Int J Radiat Oncol Biol Phys 66: 483-491.
17. Munshi A, Krishnatry R, Banerjee S, Agarwal JP (2012) Stereotactic conformal radiotherapy in non-small cell lung cancer - an overview. Clinical oncology 24: 556-568.
18. Sunyach MP, Falchero L, Pommier P, Perol M, Arpin D, et al. (2000) Prospectiveevaluation of early lung toxicity following three-dimensional conformal radiation therapy innon-small-cell lung cancer: preliminary results. Int J Radiat Oncol Biol Phys 48: 459-463.
19. Takeda A, Ohashi T, Kunieda E, Enomoto T, Sanuki N, et al. (2010) Early graphical appearance of radiation pneumonitis correlates with the severity of radiation pneumonitis after stereotactic body radiotherapy (SBRT) in patients with lung tumors. Int J Radiat Oncol Biol Phys 77: 685-690.
20. Makimoto T, Tsuchiya S, Hayakawa K, Saitoh R, Mori M (1999) Risk factors for severe radiation pneumonitis in lung cancer. Japanese journal of clinical oncology 29: 192-197.
21. Takeda A, Kunieda E, Takeda T, Tanaka M, Sanuki N, et al. (2008) Possible misinterpretation of demarcated solid patterns of radiation fibrosis on CT scans as tumor recurrence in patients receiving hypofractionated stereotactic radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 70: 1057-1065.
22. Jennings FL, Arden A (1961) Development of experimental radiation pneumonitis. Archives of pathology 71: 437-446.
23. Libshitz HI, Southard ME (1974) Complications of radiation therapy: the thorax. Seminars inroentgenology 9: 41-49.