RESEARCH ARTICLE

Suggestion for a New Grading Scale for Radiation Induced Pneumonitis Based on Radiological Findings of Computerized Tomography: Correlation with Clinical and Radiotherapeutic Parameters in Lung Cancer Patients

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Abstract

  Background: The objective of this research is the computed axial tomography (CT) imaging grading of radiation induced pneumonitis (RP) and its correlation with clinical and radiotherapeutic parameters. Materials and Methods: The chest CT films of 20 patients with non-small cell lung cancer who have undergone three-dimensional conformal radiation therapy were reviewed. The proposed CT grading of RP is supported on solely radiological diagnosis criteria and distinguishes five grades. The manifestation of RP was also correlated with any positive pre-existing chronic obstructive pulmonary disease (COPD) history, smoking history, the FEV1 value, and the dosimetric variable V20. Results: The CT grading of RP was as follows: 3 patients (15%) presented with ground glass opacity (grade 1), 9 patients (45%) were classified as grade 2, 7 patients (35%) presented with focal consolidation, with or without elements of fibrosis (grade 3), and only one patient (5%) presented with opacity with accompanying atelectasis and loss of pulmonary volume (grade 4). Both univariate and multivariate analysis revealed as prognostic factors for the radiological grading of RP the reduction of FEV1 and the V20 (P=0.026 and P=0.003, respectively). There was also a significant (P<0.001) correlation of radiological grading of RP with FEV1 and V20 (spearman rho 0.92 and 0.93, respectively). Conclusions: The high correlation of the proposed radiological grading with the FEV1 and the V20 is giving a satisfactory clinical validity. Although the proposed grading scale seems relevant to clinical practice, further studies are needed for the confirmation of its validity and reliability.

Keywords: Pneumonitis - radiotherapy - toxicity grading scale - computerized tomography - thoracic imaging

Introduction

  Radiation induced pneumonitis (RP) is a common and explicit complication caused by radiotherapy in patients with breast, lung, oesophagus, lymphoma or other thoracic and mediastinal cancers. Research on the frequency of radiation-induced injury manifestation varies and depends on radiological, clinical or laboratory criteria, and by the stage at diagnosis, set by every researcher (Kocak et al., 2007).

  Also, the manifestation and development of RP depends on parameters such as the patient's age, any pre-existing pulmonary disease, smoking, hereditary and

genetic factors, any previous or simultaneous to radiation chemotherapy and of course, radiotherapy's dosimetric and technical parameters (Tsujino et al., 2003; Barriger et al., 2010; Mehta, 2005; Madani et al., 2007).

  Radiation pneumonitis was first reported by Groover et al. (1922). Ever since, the pathophysiology, the clinical and radiological image of the said disease is analysed in many bibliographical references. Albeit developments in radiotherapy techniques, such as the Three-Dimensional Conformal Radiation Therapy (3DCRT) and the Intensity-Modulated Radiation Therapy (IMRT), which offer greater protection to adjacent healthy tissues and, at the same time, increase the dose absorbed by the tumour target,

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the frequency of RP has not been eliminated (Bucci et al., 2005; Tsoutsou and Koukourakis, 2006; Guckenberger et al., 2010). Although, some inflammatory mediators such as amifostine (Kouvaris et al., 2007) or Toll-like receptor agonism (Wang et al., 2012) have shown evidence of radioprotection in vitro and in vivo studies, RP clearly remains a radiation dosimetric-related morbidity (Zhang et al., 2012).

The objective of this research is the classification and staging of CT - radiological findings in patients with RP and their correlation with clinical and radiotherapeutic parameters. A new CT grading of radiation-induced injury is proposed: the imaging findings are divided into five scales (grades: 0-4). The clinical parameters under research include the patients' age, any pre-existing chronic obstructive pulmonary disease (COPD), spirometry testing, such as Forced Expiratory Volume in 1 Second (FEV1), and positive smoking history. The radiotherapeutic parameters regard the percentage of the pulmonary parenchyma's volume, which was irradiated with over 20 Gy (V20).

Materials and Methods

In this report, the chest CT films of 20 patients with non-small cell lung cancer who have undergone radiotherapy were reviewed. The radiation method used was 3DCRT with a daily dose of 2 Gy to a total dose of 60-66 Gy. Gross tumour volume (GTV), clinical target and planning target volume (CTV, PTV) contouring and 3D dose distribution were created in two treatment planning systems (Plato Sunrise v.2.7 and ONCENTRA, Nucletron Veenedal, Netherlands). The GTV was confirmed either by PET scan or CT studies with enhanced contrast media. The PTV was created by adding a 1-cm expansion in the axial plane and a 2-cm expansion in the longitudinal plane taking account the organ movements. Treatment was delivered with a 6 MV linear accelerator. None of the patients had undergone chemotherapy. Also, data as to the clinical picture of the patients and the clinical stage of the radiation-induced injury were not analysed. Follow-up of the patients continued in the 2nd Radiology Department in ATTIKON Hospital as well as at the Computerized Tomography Department of 251 Hospital of Military Air Force.

Chest CT scans were performed before radiation therapy, and three, six, and nine months following radiation therapy. The described findings were classified according to the proposed RP grading based on CT staging (Table 1). In cases where the CT film showed findings of different grades, the dominant finding was taken under consideration and the patient was classified accordingly.

The demographic data of the patients were reviewed, as well as any pre-existing COPD, positive smoking history and FEV1 value.

Statistical analysis

All the correlations were performed with the spearman correlation coefficient; the potential impact of age, performance status (PS), FEV1, V20 and COPD to the radiological grading or RP was assessed with the linear

multivariate regression analysis. The significance level was set at 0.05. The statistical analysis was performed with the SPSS version 10 software (IL, Chicago).

Results

From March 2002 until March 2009, 20 patients (12 men, 8 women, of an average age of 70 years old, range: 62-78) with non-small cell lung cancer came to the Radiation Unit of the Aretaieion University Hospital and the Radiotherapy Department of YGEIA Hospital for further treatment. All patients underwent 3DCRT. The stage of the disease was T3N2M0. None of the patients deceased during the study. Also, none of them had undergone chemotherapeutic schemes.

As already mentioned, patients underwent chest CT scans before radiotherapy and 3, 6 and 9 months after. The CT scans were performed during a routine clinical follow-up and everything was done in accordance with the clinical practice of the radiation oncology unit. The CT films were classified according to the proposed grading (Table 1). RP related CT findings were identified in all of our patients. Three months following the completion of radiotherapy, none of our patients presented with ground glass opacity (grade 1), 1 patient were classified with RP grade 2, consolidation with elements of fibrosis was identified also in 1 patient (grade 3) and none was classified with RP grade 4 (Figure 1, 2).

Six months after the completion of radiotherapy sessions, 1 patient were classified with radiation-induced injury grade 1, 3 patients with grade 2 and 3 and none with grade 4.

Finally, 9 months after radiotherapy, the classification of CT findings was as follows: 2 patients with RP grade 1, 5 patients with grade 2, 3 patients with grade 3, 1 patient with grade 4.

Overall, during the nine months, 3 patients (15%) presented with ground glass opacity (grade 1), 9 patients (45%) were classified with grade 2, 7 patients (35%) presented with clear focal consolidation with or without elements of fibrosis in CT scan (grade 3) and only 1 patient (5%) presented with consolidation with accompanying atelectasis and loss of pulmonary volume (grade 4).

None of our patients presented with recurrence during the study and 2 patients with positive COPD history and 2 smoker patients presented with pulmonary infection that

Table 1. Radiological Grading Scale of Radiation Induced Pneumonitis (RP)

Grade	CT Findings	Time Of Manifestation
0	No Findings.	ACUTE
1	Ground glass opacities without fuzziness of the subjacent pulmonary vessels.	
2	The findings may vary from ground glass opacities, extending beyond the radiation field, to consolidations.	
3	Clear focal consolidation ± elements of fibrosis.	
4	Dense consolidation, cicatrisation atelectasis, aerobronchogram and bronchial extension (traction bronchiectasis), significant pulmonary volume loss, and pleural thickening.	100.0 LATE

6.3

75.0

56.3

50.0

was dealt with successfully with supportive treatment, without affecting significantly the radiological image.

However, it must be reported that 8 of our patients (with an age average of 71 years old), whose axial tomography showed clear consolidation or atelectasis with lung volume loss (grade 3 and 4), had positive COPD history (6 patients) and positive smoking history (5 patients). For these patients, the V20 value was 27%

Table 2. Allocation of CT Imaging Findings

Grade	Number Of Patients			Total
	3 Months	6 Months	9 Months	
0	-	-	-	-
1	-	1	2	3 (15%)
2	1	3	5	9 (45%)
3	1	3	3	7 (35%)
4	-	-	1	1 (5%)

Table 3. Univariate and Multivariate Regression Analysis for RP with the Following Variables: PS, Age, V20, Reduction of FEV1, Smoking and COPD. The Analysis Revealed as Prognostic Factors Only the Reduction of FEV1 and the V20 (2 degrees of freedom, X2=113.6, P<0.001, multivariate)

Variables	Univariate analysis			Multivariate analysis		
	P	Risk ratio	95% CI	P	Risk ratio	95% CI
PS	0.34	-				
Age	0.68	-				
V20	0.026	0.72	0.21-0.94	0.029	0.67	0.18-0.92
Smoking	0.075	-				
Reduction of FEV1	0.005	0.64	0.32-0.89	0.003	0.63	0.33-0.87
COPD	0.76	-				

(Table 2).

Ten patients suffered from chronic obstructive pulmonary disease (COPD) (8 men, 2 women, with an average age of 74 years old) and 12 patients were smokers (8 men, 4 women, with an average age of 72 years old). Following the statistical process of the results, a high correlation of COPD and smoking was found (rho=0.8, P=0.001). Also, a high correlation was found between smoking and low Performance Status (PS) (rho=-0.75, P=0.001).

It was already reported that patients with pre-existing chronic obstructive pulmonary disease (COPD) during CT scanning presented with findings that correspond to radiation-induced injury grade 3 and 4. The emergence of the described radiological image was identified mainly in the 6th and 9th month. Respectively, in the 12 smoker patients, radiation-induced injury took place in the 6th and 9th month following radiation therapy.

In our patients' sample, a 20-25% decrease of FEV1 was measured in 17 patients (11 men and 6 women), 3-4 months following the completion of radiation therapy. Twelve patients were smokers and 10 suffered from COPD. In 7 patients whose V20 was higher than 30%, RP, as scanned in CT films, was of a high grade (2 and 3) and the injury could be diagnosed by imaging during the 6th month following the completion of radiation therapy.

Mainly, the radiological grading of RP was significantly (P<0.001) correlated with the decrease in FEV1 (rho=0.92), yet V20 (rho=0.93) as well.

The statistical process with regression analysis showed

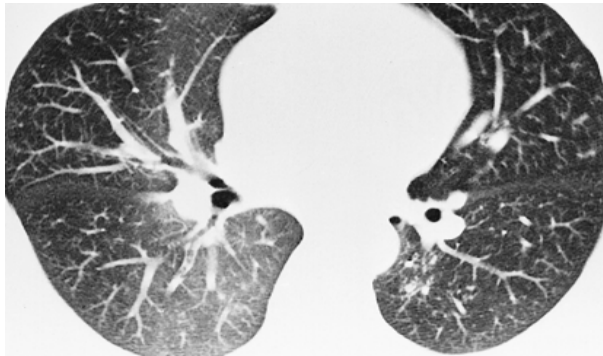**Figure 1. Man, 62 Years Old, with Non-small Cell Lung Cancer: Ground Glass Image at the Posterior Basic Part of the Right Lower Lobe (grade 1)**
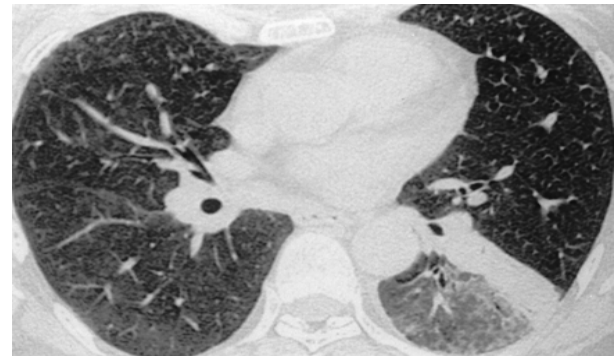

Figure 2. Man, 75 Years Old, with Non-small Cell Lung Cancer: Ground Glass Image at the Superior Segment of the Left Lower Lobe with Accompanying Consolidation at the Left Middle Lobe. Additional elements of obstructive pulmonary disease (grade 3)
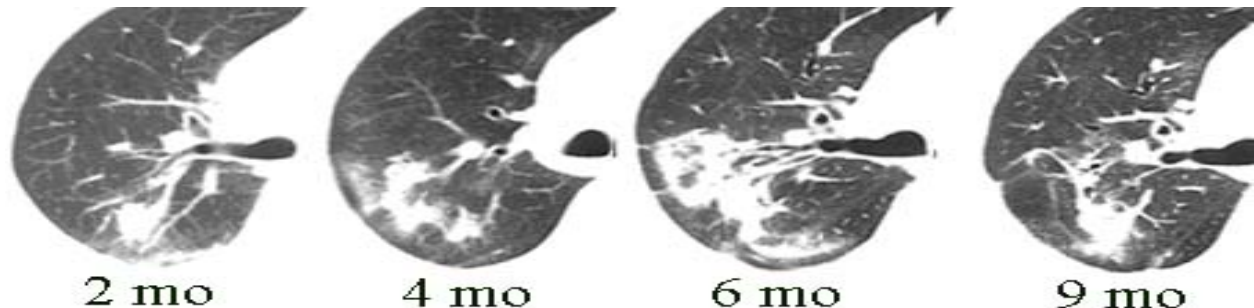

Figure 3. The Development of Radiation Pneumonitis is Evident in Successive Chest CT Post Irradiation. An increase in opacity and fuzzy consolidating elements around the primary injury is changed in the following months into a dense consolidation and scar-like image

that the development of RP was highly correlated with the decrease of FEV1 (P=0.007) and V20 (P=0.046). At the same time, the spearman correlation method indicated that there is a significant correlation between the decrease of the percentage of FEV1 and V20 (r=0.49, P=0.032).

Both, univariate and multivariate regression analysis revealed as independent variables for the radiological grading of pneumonitis the reduction of FEV1 and the V20 dosimetric parameter. The two above variables manage to be predictive for the radiological grading of RP. The results are shown in Table 4.

Discussion

Although new radiotherapeutic techniques are applied, such as the Three-Dimensional Conformal Radiation Therapy, which definitely induce decreased radiation toxicity to adjacent healthy tissues, the radiation-induced lung injury remains a recurrent complication of radiation on the pulmonary parenchyma (Tarbell et al., 1990; Tsoutsou and Koukourakis, 2006; Kocak et al., 2007). Clinically, radiation-induced lung injury is divided into two phases: the early phase of RP and the late phase of radiation-induced fibrosis. However, the most sensitive radiodiagnostic method in order to follow its development from one phase to the next is the computed axial tomography (CT) (Libshitz and Shuman, 1984; Ikezoe et al., 1988).

The present research proposes a new approach to RP through staging based on CT imaging findings (Table 1). International bibliography does not refer to an exact classification-staging of radiation-induced lung injury's CT imaging following a 3DCRT on the pulmonary parenchyma (Libshitz and Shuman, 1984; Koenig et al., 2002; Aoki et al., 2004). The staging that this research refers to was supported by the imaging features of both the early and the late radiation-induced injury (Figure 3). At the same time, the objective of the therapeutic management of patients with RP is to stop the development of the disease towards the ultimate and irreversible phase of pulmonary fibrosis. We believe that a CT imaging staging of RP will contribute to the diagnosis of the disease at its early presentation resulting in more effective treatments (Gross, 1977; Roswitt and White, 1977).

In our patients' sample, a chronically gradual emergence of the radiation-induced pulmonary injury's radiological image was observed. In the 3rd month, only 2 patients (10%) were presented with findings that corresponded to grade 2 and 3 RP, respectively. In the next CT-based review, during the 6th month, 7 patients (35%) were classified with grade 1, 2 and 3 RP and in the 9th month 11 patients (55%) were presented with grade 1, 2, 3 and 4 RP. This development of the radiological image conforms to other studies as well. In effect, Aoki et al. (2004) identified elements of radiation-induced injury in the chest CT in 2 to 6 months following radiation therapy, Ikezoe et al. (1988) in 16 weeks, and Koenig et al. (2002) from the 3rd month following the chest wall's radiation.

Overall, throughout our research, most of our patients presented with ground glass opacity that extended beyond the radiation field, or consolidations also (grade 2, 45%

of the patients), or definite consolidations as well, with or without elements of fibrosis (grade 3, 35% of the patients).

Although a pulmonary infection may radio-diagnostically complicate the image of radiation-induced injury, our 2 patients' image suffering from lower respiratory system infection remained clear (Salinas and Winterbauer, 1995). It should be mentioned that the present research did not estimate the clinical picture of the patients and the proposed CT grading was not correlated with it. Also, our patient's sample did not include other cancers, such as breast and oesophagus cancer and our patients had not undergone chemotherapy.

We deem that a prospective study, which will examine all the factors that clearly affect the manifestation and emergence of radiation-induced pulmonary injury and correlate them with the proposed CT grading, is necessary. The second part of our report concerns the evaluation and the correlation of factors, such as any pre-existing pulmonary disease, smoking history, FEV1, and V20, with the radiological manifestation of RP.

It has been reported that a pre-existing pulmonary disease predisposes the patient to manifestation of RP (Robnett et al., 2000; Inoue et al., 2001). In our patients' sample, 10 patients suffered from COPD. Six of them (60%) presented with severe radiation-induced injury (grade 3 and 4), while RP manifested in these patients during the 6th and 9th month. It is also known that smoking creates a predisposition for chronic pulmonary disease and COPD (Hernando et al., 2001; Miller et al., 2004). Twelve of our patients were smokers and a high percentage of them (41,67%) was classified as high graded RP (3 and 4). At the same time, radiation-induced injury was identified during the 6th and 9th month following the completion of radiation therapy. The correlation of COPD and smoking was high, which resulted to rho: 0.8, P<0.001. Also, a correlation was identified between smoking and patients' low Performance Status (PS), which resulted to rho equal to -0.75 (P=0.001). All the above support the fact that pre-existing pulmonary disease, as well as smoking, predispose the patient to the manifestation of high graded radiation-induced damage.

The FEV1 is a useful index to evaluate RP (Ghafoori et al., 2008). Most studies find a decrease in spirometric parameters following chest radiation therapy (Choi and Kanarek, 1994; Abratt and Willcox, 1995; Miller et al., 2003; Borst et al., 2005). FEV1 reductions are measurable from 3 to 6 months following radiation therapy (Myers et al., 2005).

The conclusions of our study are similar: a decrease in FEV1 by 20-25% in 17 patients (85%), who were mostly patients with pulmonary disease or/and smokers, from 3 to 4 months following chest field radiation.

The percentage of the pulmonary parenchyma's volume that was radiated with more than 20 Gy (V20) was correlated with the manifestation of radiation-induced pulmonary injury (Graham et al., 1999; Hernando et al., 2001; Claude et al., 2005). Toxicity increases when V20 is increased and the patients' symptoms become louder (Graham et al., 1999). In the present study, results were similar to other bibliographical references (Graham et al., 1999; Hernando et al., 2001; Claude et al., 2005). In

7 patients out of our sample, with V20 exceeding 30%, radiation-induced injury was identified in CT films during the 6th month and was graded as grade 2 and 3.

Also, the development of RP was correlated with the decrease of FEV1 (P=0.007), yet also of V20 (P=0.046). At the same time, it was shown that there is a high correlation of the decrease in the percentage of FEV1 and V20, (r=0.49, P=0.032). Our observations confirm V20 as a significant factor of predisposition for the manifestation of RP in accordance with relevant publications (Claude et al., 2005; Piotrowski et al., 2005; Kong et al., 2006; Uno et al., 2006; Schallenkamp et al., 2007; Ramella et al., 2010; Kimura et al., 2012; Kumar et al., 2012).

The suggested scale is simple and according to the multivariate analysis, there is a significant impact of V20 and FEV1 to the radiological grading of RP (Table 4). This seems to have a clinical validity, since these two above factors manage to predict well the radiological grading of RP. Although our sample was not efficient in terms of the small number of patients, the present study necessitates a perspective trial with more patients and sufficient power analysis, which would investigate any further significant correlation of the radiological grading of RP with clinical and chemotherapeutic parameters, as well as with additional radiotherapeutic parameters. Although in our study the PS was not significantly related with the grading of RP, mainly due to the small number of patients, it should be mentioned that the concurrent chemo-radiotherapy should be under multidisciplinary evaluation in cases of poor PS (de Cos Escuín et al., 2007). At last but not least, the V20 associated with the radiological grading of RP is also significantly related with the optimization of target volumes in thoracic radiotherapy coming definitely from the implementation of PET-CT in the clinical practice (Morarji et al., 2012).

In conclusion, albeit our patients' small and non-randomized sample, we believe that the proposed CT grading of radiation-induced injury on the pulmonary tissue can be clinically applied and that the imaging findings of RP can be graded as to their severity, thus, distinguishing patients and giving direction to their oncologic treatment. More prospective studies with sufficient number of patients stand in need for the validation of the proposed grading scale for RP. However, it should be emphasized that the proposed scale might be a "common language" in terms of a multidisciplinary approach of patients who undergo thoracic irradiation.

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