Prediction of radiation pneumonitis: dose-volume histogram analysis in 62 patients with non-small cell lung cancer after three-dimensional conformal radiotherapy

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The purpose of the study was to determine the relation between the incidence of radiation pneumonitis (RP) and available parameters from a dose-volume histogram (DVH) in patients with non-small cell lung cancer (NSCLC) who underwent three-dimensional conformal radiotherapy treatment.

Between January 1999 and August 2003 in the Greatpoland Cancer Center, 62 patients with NSCLC were treated using three-dimensional conformal radiotherapy (3D CRT). All patients were treated 5 days per week with daily fractionation of 2 Gy to total dose of 60 Gy. All patients were available for analysis for symptomatic RP. Radiation pneumonitis was graded according to the RTOG/EORTC morbidity scoring classification. Logistic regression analysis was performed to test the association between RP and the following DVH parameters: mean lung dose (MLD), volume of lung receiving ≥20 Gy (V_{20}) and ≥30 Gy (V_{30}) and normal tissue complication probability (NTCP). Additionally, correlation of the following clinical factors such as: age, sex, tumor site, performance status (KPS), and additional therapy (chemotherapy) with incidence of the RP were performed. Moreover, correlation between DVH parameters were tested using Spearman method.

Thirty out of 62 patients (48%) developed RP grade 0 or 1 (0 grade – 12%, 1 grade – 36%) and 32 (52%) grade 2 or 3 (2 grade – 47%, 3 grade – 5%). In the logistic regression analysis, all DVH parameters were associated with RP (p in range from 0.004 to 0.007). The strongest association was observed for NTCP and V_{30} (p=0.004). On the other hand, a weak association was found for V_{20} (p=0.007). The correlations between all DVH parameters for lung were sufficient (r Spearman in range from 0.87 to 0.93). The best correlation among DVH parameters were observed between V_{20} and NTCP (r=0.93, p<0.001). On the other hand, the least but sufficient association was found for V_{30} and V_{20} (r=0.87, p<0.001). There was no association between clinical factors and RP.

NTCP and V_{30} parameters were the best predictors of symptomatic radiation pneumonitis for patients after three-dimensional conformal radiotherapy of non-small cell lung cancer.

Key words: NSCLC, radiotherapy, radiation pneumonitis, dose volume histogram

Patients with non-small cell lung cancer (NSCLC) with a locally advanced, unresectable disease have a poor prognosis for survival. Data obtained from prospective trials suggest that clinical benefits can be achieved from the multimodality or molecular targeted therapies [3, 9, 12, 15, 17, 36, 37, 46, 52, 53]. However, it is also very important to improve the efficiency and quality of the individual components of therapy such as three-dimensional conformal radiation treatment (3D CRT).

Within the past several years the development of 3D CRT technology has started a new era in radiation treatment planning [1, 18, 20, 40]. The improvement of target delineation, dose escalation and reduction of normal tissue complication are the basic goals for 3D CRT [2, 7, 11, 14, 21, 27, 32, 50]. A powerful tool used in the 3D CRT verification is a dose volume histogram (DVH). It presents a dose distribution in organs at risk (OAR) and at a target. It includes basic values describing the dose distribution, for example

median, modal and mean dose in the lung. DVH is also required to estimate the normal tissue complication probability (NTCP). However, DVHs obtained from 3D CRT, are not easy to interpret. Therefore, only some parts of the information are often used in clinical practice, e.g. mean dose or the lung volume receiving more than 30 Gy [22, 26, 33].

One of the major dose-limiting organ in 3D CRT are the lungs. In particular, symptomatic radiation pneumonitis occurs in up to 20% of patients irradiated to conventional dose [26]. EMAMI et al [13] published reference values, based on limited clinical lung tolerance data. They reported the tolerance values for lungs radiotherapy using one-third, two-third and whole irradiated organ, when clinical symptomatic pneumonitis was used as the end-point. After this work, other authors have been estimating the specific DVH parameters referring to the risk of symptomatic pneumonitis. This paper reviews our results referring to the relation between the incidence of radiation pneumonitis (RP) and specific DVH parameters, and clinical parameters in patients with NSCLC, who underwent three-dimensional conformal radiotherapy.

Material and methods

Eligibility. Between January 1999 and August 2003, 62 patients with NSCLC were treated by 3D CRT. All 62 patients were available for analysis for RP, 35 out of 62 patients were classified as IIIA clinical stage of disease and remaining 27 patients as IIIB. Thirty-nine out of 62 patients received two chemotherapy cycles (PE: Cisplatin, Etoposide) before radiotherapy. For all analyzed patients histopathological verification was performed. Patient characteristics (age, sex, performance status, clinical stage) and pathologic subtypes are shown in Table 1.

Initial evaluation and 3D CRT. For all patients the following evaluation was performed: posterior-anterior (PA) and lateral chest X-rays, upper abdomen tomography for liver and adrenal glad assessment, bronchoscopy, spirometry and electrocardiogram. For other pathology subtypes brain CT and bone scintigraphy were performed in case of clinical suspicions. In 29 cases mediastinoscopy was performed. Brain tomography (CT) was performed in all patients with histology diagnosis of adenocarcinoma. All patients were treated with 3D radiotherapy treatment in conventional fractionation with 2 Gy daily fraction to total dose of 60 Gy. CT scans were performed from upper abdomen to apex of the lung for tumor and OARs (such as lung, spinal cord and heart) identification. CT scans were obtained during quite respiration with 1 cm distances between next and previous slices. Patients were immobilized on the couch with arms above the head. Typically lung patient's CT data set consisted of 30 slices. We prepared treatment plans including contouring and planning process using CadPlan v.3.1.2 software developed by the Varian Medical Systems. Planning target volume (PTV) was defined as gross tumor volume (GTV) with 1.5 cm margin and elective irradiated lymph nodal with 1 cm margin according to ICRU-50 [23]. The lungs volume was defined on CT, and then outlined at the CadPlan workstation, and presented as a single organ. 6 MV therapeutic energy and three-field technique with wedges and multileaf collimator (MLC) or custom blocks were used in treatment planning process. In each case, dose calculation method was performed using equivalent TAR algorithm. The physician at the CadPlan workstation fixed MLC or custom blocks shapes. Anterior-posterior/posterior-anterior wedge orientations were used for all patients. For 20% of analyzed cases cranial-caudal/caudal-cranial wedge orientations were also used. Digitally reconstructed radiograph (DRR) was prepared for each beam during the planning process. For all patients dose-volume histograms for PTV, GTV and OAR were performed. Accepted dose in PTV ranged from 95% to 105% of prescribed dose. Spinal cord did not absorb higher dose than 75% of the prescribed dose in all cases. The esophagus was included in the high dose area for 24 patients, but the maximal irradiated length was not longer than 13 cm in each case. Treatment plans were sent from CadPlan workstation to the accelerator (Clinac 2300CD) using radiotherapy management system Varis v.1.4d. All prepared plans were verified before the treatment at the simulator, and during the treatment using portal checks. DRR, portal and simulator checks were compared with each other to establish the accuracy between patient's position during the planning and the treatment process. Moreover, during the treatment, the dosimetry *in vivo* was performed for all patients.

Follow-up evaluation. First examination was performed one month after treatment and next with 2-month intervals in first year, and 3 months interval in second year. Chest X-rays were done for each visit of patients. Time of the follow-

Table 1. Patients characteristics. Age presented in years, other data (points: 2–6) presented in numbers of patients and in percent of all patients

Age:	from 48 years to 72 years (median age: 62 years)	
Tobacco use:	All patients 62 (100%)	
Gender:	Male	50 (80%)
	Female	12 (20%)
Histopathology:	Squamous cell carcinoma	36 (57%)
	Adenocarcinoma	12 (20%)
	Large cell carcinoma	2 (3%)
	Unclassified NSCLC	12 (20%)
Clinical stage:	IIIA	35 (57%)
	IIIB	27 (43%)
Karnofsky Performance Status:	≥80	55 (89%)
	<80	7 (11%)

up for patients ranged from 6 months to 48. The mean time of follow-up for living patients was 24 months. Diagnosis of pneumonitis was based on clinical symptoms such as: cough, dyspnea, and eventually fever. Pneumonitis was graded according to the RTOG/EORTC late lung morbidity scoring criteria [43]. We divided patients into two groups: the first group with 0 or 1 grade, the second consisted with patients with 2 or 3 grade. We did not observe 4-grade pneumonitis.

Statistical analysis. Logistic regression analysis was performed to test the association between RP and DVH parameters such as: mean lung dose (MLD), volume of lung receiving >20 Gy (V_{20}) and >30 Gy (V_{30}) and normal tissue complication probability (NTCP) calculated with Lyman-Kutcher-Burman method. Additionally clinical factors such as: age, sex, tumor site, performance status (KPS) and additional therapy (chemotherapy) were analyzed for association with the RP. Tobacco use was not included in the analysis because all patients smoked. Radiobiological parameters (n=1, m=0.3) obtained by KWA et al [26] were used for NTCP calculation. Moreover, correlations between DVH parameters were tested using Spearman method. All tests were two-sided and aperformed at $\alpha<0.05$ significance level.

Results

Thirty patients (48%) developed RP grade 0 or 1 (0 grade – 12%, 1 grade – 36%) and 32 (52%) grade 2 or 3 (2 grade – 47%, 3 grade – 5%).

Means and standard deviations for first group pneumonitis (0–1 grade) were for MLD 17.9 ± 3.9 Gy, for V_{20} $32.6 \pm 8.8\%$, for V_{30} $22.8 \pm 7.3\%$, for NTCP $10.4 \pm 4.8\%$, for GTV 121.2 ± 76.9 cc. In second group (2–3 grade) we observed that means and standard deviations were for MLD 24.4 ± 2.4 Gy, for V_{20} $44.8 \pm 6.7\%$, for V_{30} $36.5 \pm 5.7\%$, for NTCP $27.1 \pm 7.9\%$, for GTV 159.5 ± 59.7 cc.

In the logistic regression, all DVH parameters (MLD, V_{20}, V_{30}, NTCP) were associated with RP (p: range from 0.004 to 0.007). The highest association was observed for NTCP and V_{30} (p=0.004) and the lowest for V_{20} (p=0.007). There was no association between clinical factors and RP. Moreover, we did not observe any association between GTV and RP. Table 2 presents results of the performed analysis using logistic regression method.

The correlations between all DVH parameters for lung

Table 2. Logistic regression analysis of association between radiation pneumonitis and dose-volume histogram parameters and clinical factors. Significance level α=0.05.

Variable		Grade 0 or 1	Grade 2 or 3	p-value
			mean ± standard deviations	
% of total lung volume received dose >20Gy (V_{20})		32.6 ± 8.8	44.8 ± 6.7	0.007
% of total lung volume received dose >30Gy (V_{30})		22.8 ± 7.3	36.5 ± 5.7	0.004
Mean lung dose (MLD) (Gy)		17.9 ± 3.9	22.4 ± 2.4	0.005
Normal tissue complications probability (NTCP) (%)*		10.4 ± 4.8	27.1 ± 7.9	0.004
Gross tumor volume (cc)		121.2 ± 76.9	159.5 ± 59.7	0.064
			median age	
Age (years)		62	60	0.686
			No of patients (percent of all)	
Gender	male:	23 (37%)	27 (43%)	
	female:	7 (11%)	5 (9%)	0.927
Karnofsky Performance Status	≥80:	28 (45%)	27 (43%)	
	<80:	2 (3%)	5 (9%)	0.765
Additional treatment	chemotherapy:	18 (29%)	21 (34%)	
	surgery:	5 (8%)	4 (7%)	
	none:	7 (11%)	7 (11%)	0.636
Clinical Stage	IIIA:	17 (28%)	18 (29%)	
	IIIB:	13 (20%)	14 (23%)	0.809
Localization	upper:	14 (23%)	23 (37%)	
	middle/lower:	16 (25%)	9 (15%)	0.527
Histopathology	squamous cell ca:	19 (31%)	16 (26%)	
	other ca:	11 (17%)	16 (26%)	0.701

* V_{eff} and NTCP were calculated with Lyman-Kutcher-Burman method and presented in percents.

Table 3. Correlations between DVH parameters. Spearman method, significance level α=0.05.

Parameters	V_{20}	V_{30}	MLD	GTV	NTCP
V_{20}	–	r=0.866* p<0.001*	r=0.929 p<0.001	r=0.162+ p=0.377+	r=0.930** p<0.001**
V_{30}	r=0.866* p<0.001*	–	r=0.903 p<0.001	r=0.303+ p=0.091+	r=0.904 p<0.001
MLD	r=0.929 p<0.001	r=0.903 p<0.001	–	r=0.273+ p=0.131+	r=0.899 p<0.001
GTV	r=0.162+ p=0.377+	r=0.303+ p=0.091+	r=0.273+ p=0.131+	–	r=0.273+ p=0.130+
NTCP	r=0.930** p<0.001**	r=0.904 p<0.001	r=0.899 p<0.001	r=0.273+ p=0.130+	–

+non correlate data; *least sufficient correlation; **best correlation; V_{20} – % of total lung volume received dose >20Gy; V_{30} – % of total lung volume received dose >30Gy; MLD – mean lung dose; NTCP – normal tissue complications probability; GTV – gross tumor volume.

were sufficient (r: range 0.87–0.93). The best correlations were observed between V_{20} and NTCP (r=0.93, p<0.001) and the least sufficient between V_{30} and V_{20} (r=0.87, p<0.001). There were not any correlations between gross tumor volume and lung DVH parameters in this group (r: range from 0.16 to 0.30). Table 3 shows correlations between DVH parameters.

Discussion

Clinical factors. Classical prognostic factors such as clinical stage and KPS have been well documented and are widely used to make pre-treatment decisions.

FLEMING et al [16], MOUNTAIN et al [35] and WIRGEN et al [49] showed that clinical stage is a good prognostic factor used in therapy selection decision such as surgical resection, radiotherapy or chemotherapy. However, there are no significant associations between RP and clinical stage in our work. Therefore, we suggest that clinical stage is not a significat predictor of pneumonitis.

Numerous data [10, 44, 47] showed that KPS is a significant factor in identifying patients, treated with definitive radiotherapy, who may benefit from additionally performed chemotherapy. However, there are some different opinions referring to significant predictor of pneumonitis for this factor. ROBNETT et al [42] reported that low KPS increases symptomatic RP. On the other hand, BROOKS et al [5] did not find any significant correlations between KPS and RP in a group of 80 patients. Moreover, HERNANDO et al [22] analyzed 201 patients did not find any significant association between RP and KPS. In our work, patients were divided into two groups according to the grade of radiation pneumonitis: 0–1 grade and 2–3 grade. There were no significant association between KPS and RP for both groups of patients.

We did not find any association between RP and other clinical factors such as age and gender. The majority part of reports from literature [5, 22, 24, 39] confirmed it. However, ROBNETT et al [42] reported an increase of the symptomatic RP for women.

Histology of the tumor was another factor analysed for association with radiation pneumonitis. In our work histology diagnosis was grouped into squamous cell carcinoma and other, and then compared with the symptomatic RP. The association between RP and histology was not found. So far, there is a lack of sufficient data from literature describing this issue.

We did not observe any association between RP and tumor localization distributed to upper and middle/lower part of lungs. This is in contrast to GRAHAM et al [19] who found a significant association between RP and tumor (target) site distributed to upper and lower lobes. These authors observed increased risk of pneumonitis grade 2 or higher for lower lobe tumors. The differences in results between Graham's et al and our work were caused by choosing different investigated group of patients for analysis. In our series there is no association between target location and pneumonitis. Graham et al observed an association between target localization and RP of grade ≥2 grouped into 2, 3, 4 grade.

No significant association between RP and additional treatment such as chemotherapy administered before radiotherapy was observed. However, there are some discrepancies in results presented by others authors. For example, LEE et al [28], BROOKS et al [5], ROBERT et al [41] observed an increase of the symptomatic RP for chemotherapy administered before radiotherapy. JEREMIC et al [24], SCHAAKE-KONING et al [45], GRAHAM et al [19] and HERNANDO et al [22] did not confirm it. On the other hand, YAMADA et al [51] observed that concurrent chemotherapy increased symptomatic RP in 60 analyzed patients. The same results were noted by BYHARDT et al [7] in 461 patients. However, ROBNETT [42] did not find a significant association between RP an concurrent chemotherapy.

DVH parameters. The results of radiation pneumonitis prediction using clinical factors are not satisfactory. It emphasizes necessity to look for new RP predictors such as DVH parameters.

At least six other institutions have reported their experience with RP. The University of Michigan group [34, 48] reported 21 Hodgkin's disease patients and 42 NSCLC patients. In this study, authors were looking for the association between RP and NTCP and V_{eff} parameters. They have implemented a dose-escalation trial for NSCLC in which patients were stratified by volume of normal lung irradiation (V_{eff}). Doses escalation to ≥100 Gy was performed in

patients with low V_{eff} [48]. No acute pneumonitis has been observed in this trial. OETZEL et al [38] compared data with MARTEL et al [34] results. Their data of 46 patients with bronchogenic carcinoma showed association between RP and NTCP (performed for lungs as paired and separated organs). The results of MARTEL et al demonstrated a good correlation between NTCP and incidence of the symptomatic RP in patients with Hodgkin's disease. However, the results in patients with NSCLC were not as good as in Hodgkin's disease. MARTEL et al obtained worse results for lungs considered as separate organ than OETZEL et al. GRAHAM et al [19] reported a good association in an univariate analysis between RP (grade≥2) and V_{eff} calculated in paired organs. In comparison between two groups (with and without RP), HERNANDO et al [22] showed that NTCP is a strong predictor of symptomatic RP. Moreover, MARKS et al [33] reviewed the results of 100 patients (67 with NSCLC) after 3D CRT for the development of RP. They also noted that one of the important RP predictors is NTCP. All mentioned earlier results were presented above calculated NTCP according to the LYMAN model [29, 30, 31].

KWA et al [26] presented a study based on the pooled data obtained from five institutions and encompassed together 540 patients. These authors proposed new values for radiobiological parameters used in NTCP calculation according to the Lyman model (n=1 – parameter describing volume dependence, also named as volume exponent, m=0.3 – parameter describing the slope NTCP vs. dose, TD_{50}=30.5 Gy – the dose referring to the volume leading to 50% complication probability). Old parameters set by BURMAN et al [6] were n=0.87, m=0.18 and TD_{50}=24.5 Gy. These values were deducted from the estimation of lung complication risks by EMAMI et al [13], which were based on the dose estimation without the lung correction. MARTEL et al [34] reported that the TD_{50} value should be corrected to 28 Gy, when tissue heterogeneity correction is applied. It is correct in a situation when dose calculations are based on new, better algorithms (with a shape and homogeneity corrections) implemented in 3D CRT planning systems. The TD_{50} value set by KWA et al is similar to that proposed by MARTEL et al. The consequence of modifications for n and m parameters proposed by KWA et al is that at the low mean dose region, the estimated NTCP values are higher.

In our study we calculate NTCP according to the Lyman model using the LYMAN-KUTHER-BURMAN method [25, 30, 31] and radiobiological parameters obtained by KWA et al [26]. The strong association was observed in our work between RP and NTCP values. Moreover, we observed significant correlation between NTCP and MLD, V_{20}, V_{30} parameters. Other reports confirm our observation. For example, ARMSTRONG et al [2] noted a correlation between V_{25} and NTCP (Lyman model) and the rate of RP (grade≥3) in 31 NSCLC patients. GRAHAM et al [19] observed stronger correlation between V_{20} and V_{eff} than in our case. They showed that only one patient with fatal pneumonitis had low V_{20} and V_{eff} parameters. Others patient with fatal pneumonitis had higher V_{20} and V_{eff} parameters than patients with lower pneumonitis (severe, life-threatening or no complications). However, both presented results are significant in GRAHAM et al report and that of ours.

However, NTCP is a good RP predictor but the majority of commercially available treatment planning systems is unable to calculate NTCP or V_{eff}. It causes difficulties for most 3D radiotherapy treatment planning system users. Correlations between NTCP or V_{eff} parameters and other DVH parameters suggest that simple physic parameters such as MLD, V_{20}, V_{30} are also good predictors for RP.

KWA et al [26] in the analysis of advanced pneumonitis (grade≥2) reported that the mean lung dose was a useful predictor of the risk of pneumonitis. However, they did not compare or evaluate it with other DVH parameters. They noted that MLD is a worse RP predictor than NTCP but its calculation is relatively easier than NTCP. For the similar analyzed group (grade≥2) GRAHAM et al [19] did not confirm it. In our paper we compared two groups with low and high grade of pneumonitis, and we noted a strong correlation between RP and MLD for both groups of pneumonitis. HERNANDO et al [22] and OETZEL et al [38] observed similar results in theirs reports (all grades were grouped into two groups, with and without RP).

In dose-volume relationships the authors show their results for V_{20}, V_{25}, V_{30} and V_{40} parameters. GRAHAM et al [19] presented a strong association between RP (grade≥2) and V_{20} parameter in a univariate analysis. Moreover, they confirmed it in a multivariate analysis and suggested that it is the best predictor for RP. ARMSTRONG et al [2] showed a significant association between RP and V_{25} parameters. A strong association between V_{30} and RP was noted by MARKS et al [33] and HERNANDO et al [22]. Moreover, HERNANDO et al show a significant association between pneumonitis and V_{20} and V_{40} parameters but worse than in V_{30} case. Both authors showed that V_{30} and NTCP are the best RP predictors.

In our work we analyzed V_{20} and V_{30} parameters. We noted a significant association with RP in each case. However, we observed better association for V_{30} parameter. NTCP and V_{30} were also the best RP predictors in our case.

In the analysis, the worst result from all DVH parameters was obtained for the association between GTV and RP. However, BRADLEY et al [4] noted that GTV is the best predictor for the survival in NSCLC patients but in RP case GRAHAM et al [19] did not find any significant association with GTV. Moreover, they did not find any correlations between V_{20} and GTV. No association between RP and GTV and no correlation between GTV and others DVH parameters were either observed in our work.

Conclusion

The identification of prognostic factor based on DVH in NSCLC patients treated with 3D CRT is useful to guide patient management in daily clinical practice and prognoses potential lung toxicity. Our report showed that V_{30} and NTCP parameters were the best predictors of symptomatic RP after 3D CRT in NSCLC patients.

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