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PHYSICS CONTRIBUTION

PREDICTIVE MODELS FOR PULMONARY FUNCTION CHANGES AFTER RADIOTHERAPY FOR BREAST CANCER AND LYMPHOMA

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Purpose: To propose multivariate predictive models for changes in pulmonary function tests (ΔPFTs) with respect to preradiotherapy (pre-RT) values in patients undergoing RT for breast cancer and lymphoma.
Methods and Materials: A prospective study was designed to measure ΔPFTs of patients undergoing RT. Sixty-six patients were included. Spirometry, lung capacity (measured by helium dilution), and diffusing capacity of carbon monoxide tests were used to measure lung function. Two lung definitions were considered: paired lung *vs*. irradiated lung (IL). Correlation analysis of dosimetric parameters (mean lung dose and the percentage of lung volume receiving more than a threshold dose) and ΔPFTs was carried out to find the best dosimetric predictor. Chemotherapy, age, smoking, and the selected dose-volume parameter were considered as single and interaction terms in a multivariate analysis. Stability of results was checked by bootstrapping.
Results: Both lung definitions proved to be similar. Modeling was carried out for IL. Acute and late damage showed the highest correlations with volumes irradiated above ~20 Gy (maximum $R^2 = 0.28$) and ~40 Gy (maximum $R^2 = 0.21$), respectively. RT alone induced a minor and transitory restrictive defect ($p = 0.013$). Doxorubicin-cyclophosphamide-paclitaxel (Taxol), when administered pre-RT, induced a late, large restrictive effect, independent of RT ($p = 0.031$). Bootstrap values confirmed the results.
Conclusions: None of the dose-volume parameters was a perfect predictor of outcome. Thus, different predictor models for ΔPFTs were derived for the IL, which incorporated other nondosimetric parameters mainly through interaction terms. Late ΔPFTs seem to behave more serially than early ones. Large restrictive defects were demonstrated in patients pretreated with doxorubicin-cyclophosphamide-paclitaxel. © 2012 Elsevier Inc.

Chemotherapy, Dose-volume histograms, Lung definition, Pulmonary function tests, Threshold doses.

INTRODUCTION

Lung is a dose-limiting organ in irradiation of the thorax, but at the same time, it is part of the target in lung cancer patients. In non-small-cell lung cancer, locoregional recurrences and development of distant metastases are still problematic, and the prognosis remains poor (1). Recent studies suggest that local control can be improved with radiotherapy (RT) dose escalation (2). Thus, good predictors of radiation-induced lung damage are needed to enable safe dose escalation.

Various research groups have been working on predictors of radiation-induced lung damage (3–19). Some of these studies being conducted with lung cancer patients (13, 16–18). However, these patients are not an ideal population for the study of the effects of RT on the remaining normal lung, as the underlying malignant diseases may cloud the interpretation of toxicty (20). Results may be even more confounding when lung cancer patients and those with healthy lungs are pooled (3–6, 11). Even when effort has been put into analyzing exclusively non-lung cancer patients (7–10, 12, 14, 15, 19), there is still no consensus on the choice of a function of the dose-volume distribution to describe the toxicity, whether it is simple (*e.g.*, threshold dose) or complex (*e.g.*, mean lung dose [MLD] or a normal tissue complication probability model) (21).

It is not clear whether the dose-volume data of the whole (*i.e.*, paired organ) or just the involved (*i.e.*, single organ) lung is most relevant in correlating with a defined endpoint.

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Some studies do even not specify which definition of the lung was assumed. Other studies were carried out before the arrival of three- dimensional planning systems, and, in those cases, dose-volume information was not available for each particular patient but instead a sort of dose-volume histogram (DVH) representative of the radiation technique was derived. However, even when all this information is explicitly given, results are not conclusive (3, 4, 20).

A nonstandardized approach to scoring lung toxicity may explain the different results (22). It might also be the case that no unique definition of the normal lung exists, as this might depend on several factors such as (*a*) type of thoracic irradiation (unilateral or bilateral) and (*b*) chosen toxicity endpoint (*e.g.*, changes in lung function or in the radiological density).

Modeling in terms of dosimetric parameters remains challenging due to the lack of clear definitions of both normal tissue volume and toxicity endpoints and the confounding factors such as pre-existing disease, chemotherapy, and other patient factors (16, 23–27).

Against this background, a prospective study was designed aiming to identify good predictors for a well-defined set of endpoints (changes in lung function, chest radiographies, clinical symptoms, and others) in a group of healthy lung patients (*i.e.*, no lung cancer patients). DVHs were generated for two definitions of the lung. Thus, a comprehensive set of treatment (RT and chemotherapy) and patient (age and smoking habit) factors could be investigated to search for significant predictors of lung injury. This study focuses on changes inpulmonary function tests (ΔPFTs). The impact of the covariates on other collected endpoints was studied separately.

METHODS AND MATERIALS

From January 2002 to July 2006, all patients referred to the radiotherapy unit at Clínica Alemana for breast cancer (BC) or lymphoma (L) irradiation were invited to participate in the study. Seventy-three patients gave informed consent. Sixty-six patients (51 BC and 15 L patients) were included in the analysis (1 patient resigned before receiving RT, 5 patients refused follow-up, and 1 patient had an incomplete lung scan) (Table 1). None of the smokers gave up smoking during the 12 months of follow-up. Patients had pre-RT (baseline) and post-RT (1-, 6-, and 12-month) clinical assessments (hereafter referred to as C_b, C_1, C_6, and C_{12}, respectively) and PFTs. This study was approved by the hospital's ethics committee, and all patients gave written informed consent.

RT techniques

BC patients were divided into local breast RT (LBR) and locoregional breast RT (LRBR) groups. The LBR group was treated with tangential wedged photon fields to the breast. Prescription dose was 50 Gy in 2.0 Gy/fraction. An electron or photon boost (10–16 Gy in 2.0 Gy/fraction) to the tumor bed was given in cases of partial mastectomy.

LRBR patients received irradiation of the mammary gland (or chest wall), as in the LBBR group, and the regional lymph nodes. The internal mammary node fields were a combination of photon and electron beams. Additionally, a photon anterior beam was used for the supraclavicular and axillary lymph nodes, matching the edges of the adjacent tangential fields. A post-axillary boost was sometimes required. Prescribed dose to treatment volumes was 50 Gy in 2.0 Gy/fraction.

L patients were treated with the mediastinal involved-field technique (anteroposterior and posteroanterior beams covering the tumor plus a margin of up to 2 cm, defined by custom blocking). Prescription dose was 36 Gy with fraction sizes from 1.5 to 2 Gy/fraction.

Treatment plans were based on computed tomography data sets with interscan spacing of 5 mm. The first 24 radiation treatment plans were performed with the Target (version 1.2.0) treatment planning system (Prism Microsystems, Elstree, UK). The other 42 plans were carried out on XIO (CMS-Elekta).

DVHs

Two definitions of lung organ were considered and accounted for in the analysis: the "whole lung" (paired organ) and the IL (paired or single organ, depending on the type of irradiation). For unilateral BC patients, the IL was just the ipsilateral lung (contralateral lung dose was negligible). For patients with both lungs irradiated (*i.e.*, L or bilateral BC patients), the IL included both lungs (*i.e.*, coinciding with the paired lung organ definition).

First, lung volume was outlined as two different structures, and two separate DVHs, one for each lung, were generated (0.5-Gy dose intervals). Then, a composite DVH of both was created, accounting for the paired organ definition (Fig. 1). Biologically equivalent DVHs (BDVHs) were computed that corresponded to doses delivered in 2-Gy fractions, using an α/β ratio of 3 Gy. Thus, four different DVHs were available for each patient.

Dosimetric factors considered were the MLD and the percentage of lung volume receiving more than a threshold dose d, termed V_d, for both the DVH and the BDVH. Thus, the following parameters were computed: $\{MLD, V_d\}$ and $\{MLD_b, V_{db}\}$ and $\{MLD^i, V_d^i\}$ and $\{MLD_b^i, V_{db}^i\}$ for the paired lung and the IL, respectively. Where b indicates, biological correction, i stands for irradiated, and $d \in [0, 60]$ Gy, every 0.5 Gy.

Chemotherapy treatment

Table 1 summarizes the chemotherapy regimens. Adjuvant chemotherapy regimes, when prescribed pre-RT, concluded at least 3 weeks before it. Chemotherapy regimens for BC patients were diverse but all had in common doxorubicin and cyclophosphamide (AC). All patients in the L group, except 1, received a regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), either alone or in combination with other drugs, and they were considered to be in the same chemotherapy group. Regarding the exposure and timing to chemotherapy administration, three independent variables were considered: pre-RT AC (ACpre), post-RT AC (ACpost), and pre-RT CHOP/ABVD (CHOP_ABVD). All variables were coded as no = 0, yes = 1 (Table 1). The classification of patients into three groups was a balance between sensible stratification and the size of the groups (which limits the statistical power).

PFTs

Given the difficulty of carrying out the assessment of differential lung function, more accessible PFTs were performed. Dynamic or forced parameters (forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and the FEV_1/FVC ratio) were measured with spirometry. Static parameters (total lung capacity [TLC], residual volume [RV], and the RV/TLC ratio) were measured by using the helium dilution technique. Diffusing capacity

Table 1. General statistics of the patient population grouped by chemotherapy exposure/timing

Group	No. of patients	Age	Gender	No. of smoking patients (%)	No. of patients receiving RT	Chemotherapy regimen(s) (no. of patients)
ACpre	27	49.0y (32-65)	27F 0M	11 (41)	27 LRBR	AC (9) FAC (3) AC + paclitaxel (13) AC+ paclitaxel + epirubicin (1) AC+ CMF (1)
ACpost	8	40.6y (15-75)	8F 0M	1 (13)	5 LRBR 3 LBR	AC+ CMF (1) AC + paclitaxel (1) AC (6)
CHOP_ABVD	15	32.5 (15-75)	7F 8M	1 (7)	15 L	ABVD (6) CHOP (2) CHOP + rituximab (3) ESHAP + MINE + BFM (1) ABVD + ESHAP(1) CHOP + ESHAP + MINE + rituximab (1) (1) ABVD + COP (1)

Abbreviations: AC = doxorubicin, cyclophosphamide; CMF = cyclophosphamide, methotrexate, 5-fluorouracil ; FAC = 5-fluorouracil , doxorubicin, cyclophosphamide; ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; ESHAP = etoposide, methylprednisone, cytarabine, cisplatine; L = lymphoma; MINE = ifosfamide, mitoxantrone, etoposide; COP = cyclophosphamide, vincristine, prednisone; BMF = methotrexate, cytarabine, ifosfamide, vinblastine.

The number of smokers and the type of RT (LBR, LRBR, or L) are shown. Note that there are patients who received chemotherapy both pre- and post-RT. Grouping by chemotherapy was chosen because the RT treatment is better described by the three-dimensional dose-volume distribution. Only patients who were active smokers during the year before RT treatment were ranked as smokers.

of carbon monoxide (*D*L,CO), alveolar volume (Va), and the *D*L,CO/Va ratio were measured using the single-breath method (Va is conceptually a static parameter). *D*L,CO was corrected for hemoglobin.

Values were adjusted by sex, age, and height and expressed as a percentage of predicted reference values (28). Thus, the FEV_1/FVC, RV/TLC, and *D*L,CO/Va ratios do not have units.

Endpoint definition

ΔPFTs were calculated at C_1, C_6, and C_{12} relative to the baseline according to the following expression:

$$\Delta PFT_i(\%) = \frac{PFT_{baseline} - PFT_i}{PFT_{baseline}} \cdot 100 \quad i = 1, 6, 12m \qquad \text{Eq. 1}$$

Statistical analysis

The purpose was to model the ΔPFTs as a function of treatment (dosimetric parameters and chemotherapy) and patient factors. Interaction terms between them were also considered independent variables. Age was not included as a single factor because PFT outcomes included age correction. The latter did not exclude age from being analyzed as interacting with other parameters. Third-order interactions were not considered.

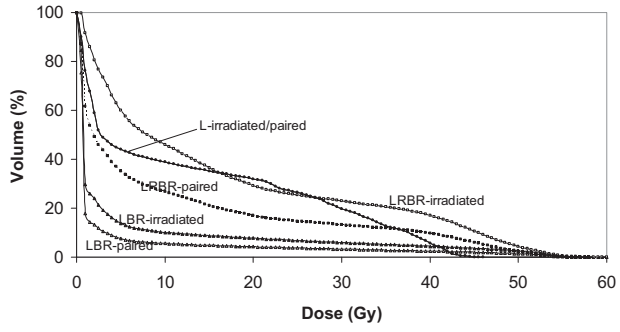

Fig. 1. Mean values of the cumulative physical DVH of the IL and the paired lung (*i.e.* whole organ) for each of the three treatment groups are shown. For the L group, both definitions coincide.

Multiple regression analysis was used to assess the impact of the independent variables on (*a*) baseline PFTs (PFT_b) (Eq. 2) and (*b*) ΔPFTs (Eq. 3).

$$PFT_b = PFT_0 + a_1 * CHOP\_ABVD + a_2 * ACpre + a_3 * smoking + a_4 * CHOP\_ABVD * smoking + a_5 * ACpre * smoking + a_6 * CHOP\_ABVD * age + a_7 * ACpre * age \qquad \text{Eq. 2}$$

$$\Delta PFT_i = b_{1*}D + b_2 * CHOP\_ABVD + b_3 * ACpre + b_4 * ACpost + b_5 * D * CHOP\_ABVD + b_6 * D * ACpre + b_7 * D * ACpost + D * (b_8 * smoking + b_9 * age) + CHOP\_ABVD * (b_{10} * smoking + b_{11} * age) + ACpre * (b_{11} * smoking + b_{12} * age) + ACpost * (b_{13} * smoking + b_{14} * age) \qquad \text{Eq. 3}$$

for i = 1 and 12

PFT_0 in Eq. 2 represents the PFT_b average value for the non-smokers who did not undergo chemotherapy pre-RT. The models for ΔPFTs (Eq. 3) should predict no changes in the case of no treatment. Pearson's correlation coefficients were calculated to measure the strength of the associations between each ΔPFT_i and {MLD, V_d}. *D* was chosen as the dosimetric parameter showing the highest significant association. This full model assumes that changes are due either to RT (b_1) or chemotherapy (b_2 to b_4) treatment factors and interactions between themselves (b_5 to b_7). The model also includes interactions between (*a*) patient factors and (*b*) RT (b_8 and b_9)/chemotherapy (b_{10} to b_{14}) factors.

All independent variables (including interaction terms) were first tested with a univariate regression analysis. Only significant (2-sided p values ≤ 0.05) univariate associations with the corresponding dependent variable were included in the multiple regression models (Eq. 2 and 3). To evaluate the stability of results (*i.e.*, whether or not associations remained statistically significant), multivariate models including the bootstraping (BS) command with 1,000 samples were applied. Statistical analysis was performed using SPSS version 18.0 software (Chicago, IL).

RESULTS

All 66 analyzed patients had baseline data, 59 patients had C_1 assessments, 40 patients had C_6 assessments (not available for 17 patients due to machine breakdown), and 56 patients had C_{12} assessments. One patient died 2 months after RT due to disease progression, and another died after the C_6 assessment for causes unrelated to cancer. During the follow-up period, some patients failed to comply with the investigations.

Regarding lung toxicity, all patients (except 1) remained asymptomatic or had very mild cough/dyspnea at 1 year after RT; 35.8% of patients presented some grade of radiological abnormality, and 1 patient developed clinical pneumonia that was reversed with antibiotics.

IL versus *paired lung*

Figure 2 shows the significant Pearson's correlation coefficient (R^2) between dose-volume parameters (for both definitions) and ΔPFTs. The first result is that none of the considered dose-volume parameters is a perfect predictor of the outcome (maximum R^2 is 0.29). Thus, other confounding factors (see Eq. 3) must be important in explaining the measured outcome.

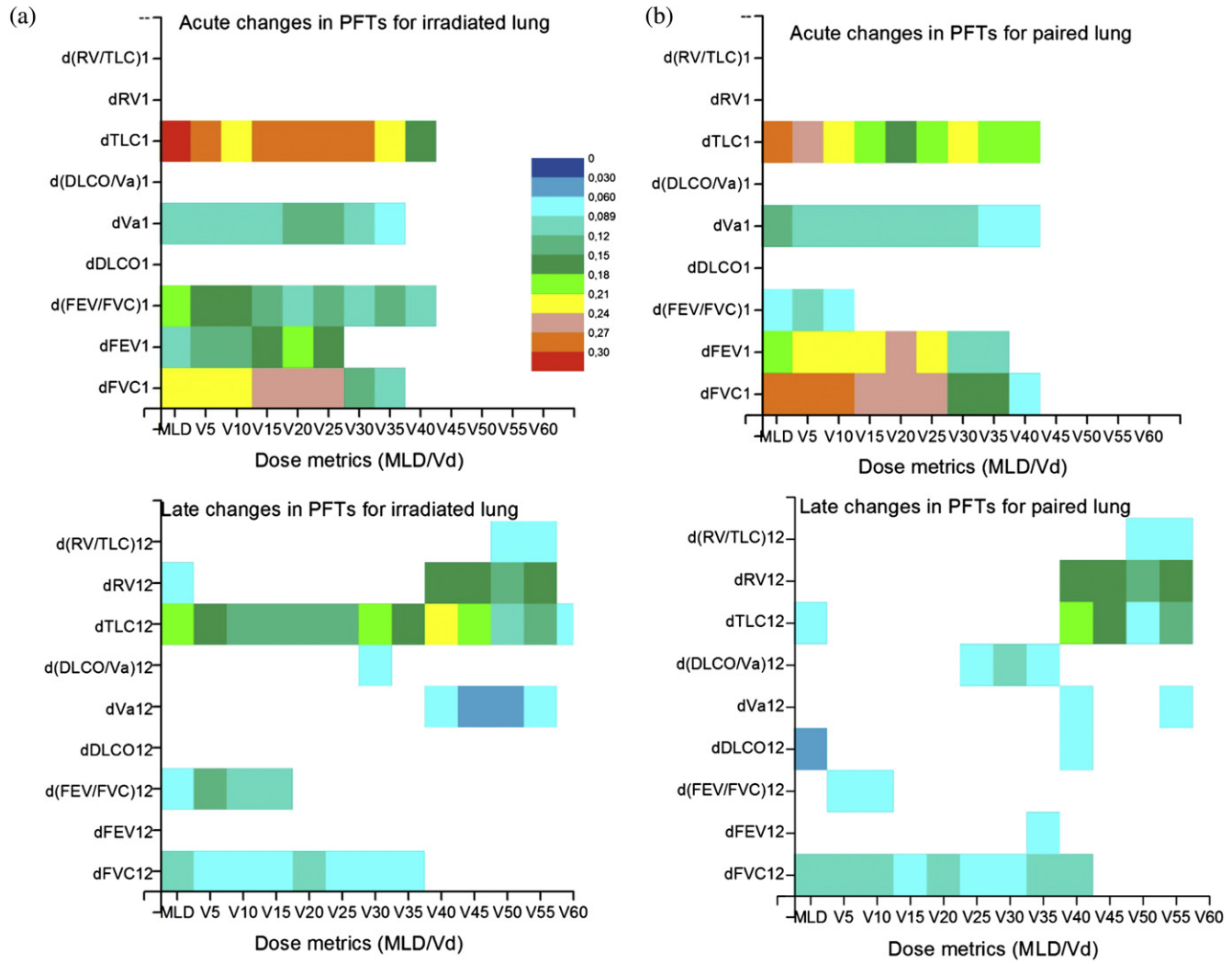

Fig. 2. Strength of the correlations (R^2 parameter) between dosimetric parameters (*i.e.*, {MLD,V_d}) and the ΔPFT_i is shown. Only significant correlations (*i.e.*, $p < 0.05$; 2-sided) have been plotted. The complete matrixes of {ΔPFT_i, MLD} and {ΔPFT_i, V_d}, with $i = 1$ and 12 and $d \in [0, 60]$ Gy every 0.5 Gy, were tested using Person's correlations. (a) It corresponds to the IL and (b) to the paired organ definition. For the sake of clarity, acute and late changes have been plotted separately for each lung definition. Equivalent plots for the BDVHs were generated, but they did not improve the correlations found for the DVHs without the biological corrections.

Additionally, none of the two definitions clearly stands out from the other in terms of showing stronger correlations with outcome (*e.g.*, both average and maximum values of R^2 in Fig. 2a and b were the same). However, a fewer more significant correlations were obtained for the IL (*i.e.*, there are more colored squares in Fig. 2a than in b). Thus, we selected the IL for our modeling exercise (it is also usual that the reference dosimetric constraint corresponds to the ipsilateral lung). BDVH followed the same behavior without major differences in the strength of the correlations. The superscript *i* will be omitted from here onward.

Another result is that the strongest correlations between dosimetric parameters and acute changes appear at intermediate dose levels ($V_d \sim V_{20}$) (maximum $R^2 = 0.28$). The same thing happens in late dynamic parameter changes. For the other late changes, higher dose levels ($V_d \sim V_{40}$) (maximum $R^2 = 0.21$) show the strongest associations. The $< R^2 >_{MLD}$ value was lower than the $< R^2 >_{V20}$ and $< R^2 >_{V40}$ values for acute and late effects, respectively.

Consequently, V_{20} was selected as the dosimetric parameter generally showing the strongest correlation with all acute ΔPFTs and with late changes in dynamic parameters. V_{40} was selected for the other late changes. Thus, *D* was represented by either V_{20} or V_{40} during the modeling exercise (see Eq. 3). (Associations were tested for V_ds every 0.5 Gy. In some cases, the strongest correlation did not happen at either V_{20} or V_{40} but very close to one of them. If the exact V_d with the strongest association had been chosen, it would have made the clinical use of the models rather unpractical, with different dosimetric parameters for each PF.)

Baseline (pre-RT) PFTs values

Coefficients for the resulting full regression model for PFT_b*s* (Eq. 2) are presented in Table 2.

ΔPFTs outcomes

ΔPFTs were computed (Eq.1) to quantify relative changes in lung function at C_1 (ΔPFT_1), C_6 (ΔPFT_6), and C_{12} (ΔPFT_{12}). As ΔPFT_6 data were scarce, analysis was restricted to C_1 and C_{12} (representing acute and long-term changes, respectively). Broad distributions for ΔPFTs were obtained (Standard deviations of up to 18%).

Results of multivariate regression model and BS analysis are presented in Tables 3 and 4, respectively. For each model, acute and late ΔPFTs are shown separately.

DISCUSSION

Two definitions of the lung have been considered: the whole lung and the IL. It is possible to argue that the best definition of the organ depends on the endpoint under analysis. For example, changes in radiological density and in PFTs could be better described by the irradiated and paired organ definition, respectively. Counterintuitively, no major differences between the two definitions were found. However, a fewer more significant correlations were observed for the IL definition, which was finally selected for this analysis.

Baseline PFTs

There is an age-dependent impact of the ABVD/CHOP regimens on FVC and FEV_1 (0.5% decrease per year of age; *i.e.*, restrictive deficit) and on *D*L,CO (0.2% decrease per year of age). For example, for a 32-year old L patient, a decrease in dynamic parameters and a *D*L,CO of 16% and 6%, respectively, is expected. It is well known that bleomycin is associated with pneumotoxic effects (30). Conversely, AC-paclitaxel regimens (Table 1) associated with BC treatment seemed not to significantly affect PFT_b. However, severe late changes were observed (see below).

Additionally, a statistically significant decrease (∼ 9%) was found in *D*L,CO and in the *D*L,CO/Va ratio for smokers, suggesting some damage in the alveolocapillary surface, as it has been also described previously (8, 14).

Changes in PFTs outcomes relative to baseline values

Univariate analysis revealed that threshold doses depend on the phase of the injury. In the multivariate analysis,

Table 2. Results of the multiple regression analysis of PFT_b*s* relative to the independent variables considered in Eq. 2

	PFT_0(% or nu)		a_3 (smoking) (% or nu)			a_6 (CHOP_ABVD * age) (%/year or 1/year)		
PTF_b		95% CI		95% CI	*p*		95% CI	*p*
FVC (%)	110.3	(104.8–115.8)				−0.5	(-0.9–0.0)	0.035
FEV1(%)	109.2	(105.1–113.2)				−0.6	(-1.1 to -0.2)	0.007
*D*L,CO (%)	76.3	(72.1–80.4)	−8.8	(−15.9 to −1.7)	0.015	−0.2	(−0.4–0.0)	0.046
*D*L,CO/Va (nu)	76.6	(73.2–80.1)	−9.3	(−18.3 to −0.3)	0.044			

Abbreviations: CI = confidence interval; ABVD = doxorubicin, bleomycin, vinblastin, dacarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.

Only coefficients of statistically significant explanatory variables are shown. Values a_3 and a_6 represent the impact of smoking and the administration of CHOP/ABVD regimes (combined with age) on the baseline values of PFTs, respectively. Note that coefficient units depend on PFT_bs units (*i.e.*, percentage for all except for the *D*L,CO/Va ratio, with no units [nu]). According to Eq. 2, negative values for a_3 and a_6 mean a decrease in the baseline PFT.

most of the single factors (*i.e.*, dose-volume and chemotherapy) did not retain significance, only interaction terms did so. This was expected as no strong correlations between changes in PFTs and dose-volume parameters had been found (Fig. 2). Consequently, other confounding factors (Eq. 3) should be important in explaining the measured outcome. In fact, only ΔFVC_1 retained the significance found with V_d as a single factor. This represents a note of caution for the conclusions arising from univariate analysis or even multiple regression models, which do not account for variable interactions.

Acute effects

Predictive models show that incidental irradiation of the lung to intermediate dose levels (*i.e.*, 20 Gy) is associated with an acute restrictive phenomena that can be explained by loss of lung volume (Table 3). Specifically, a decrease of FVC at C_1 assessment of 0.4% per 1% of volume irradiated above 20 Gy, irrespective of whether the patient received chemotherapy, was obtained. Patient age modifies the slope of the acute dose-volume-dependent decrease in RV. Significant decreases in Va and RV, which are also compatible with restrictive effects, have been found (Table 4) with the BS analysis.

In the smokers group, our model for the *D*L,CO/Va ratio predicts an increase of 8% for a typical V_{20} of 20% (this association did not hold up under BS analysis). Previous studies have suggested that smoking depresses the frequency and/or magnitude of effects (7, 9, 23, 32, 33). We had found that smokers exhibited baseline PFTs compatible with some damage to the alveolocapillary surface (lower values for *D*L,CO and the *D*L,CO/Va ratio). This situation was reversed after RT. This could be explained by an anti-inflammatory reaction to radiation, but it deserves further investigation to understand the underlying mechanisms.

Typically, there is a high-level correlation among dose-volume parameters (34) (in our case, the association between V_{20} and MLD had an $R^2 = 0.86$). By factoring in the slope of the regression model between both parameters ($V_{20} = 2.02 * MLD$), we found that our prediction for an early decrease in FVC and Va (BS analysis) was remarkably similar to that found by Theuws et al. (8) at 3 months after RT (slope = 0.8 for FVC in both studies and 0.6 for Va in our study and 0.9 for Va in their study). We did not find, however, that the V_d was an independent prognostic factor for the early decrease in FEV_1 and *D*L,CO, as in other studies (8, 29, 31).

Late effects

Our study shows late ΔPFTs associated mainly with factors involving not only V_d*s* but also chemotherapy and smoking habits (*e.g.*, the acute restrictive effects, only explained by V_{20}, have not been observed at C_{12} assessment). The exposure to AC-paclitaxel before RT was an independent prognostic factor for a severe late restrictive effect (more than 40% decrease in TLC at C_{12}). The magnitude of the damage is only slightly affected by age but is independent of the dose-volume distribution. There is evidence of severe pneumotoxic effects associated with the administration of taxanes (35), and this deserves more investigation. Interestingly, the effect of the same AC-paclitaxel regimen, when administered post-RT and in association with V_{20}, generated a decrease in FEV_1 (*i.e.* suggesting an obstructive effect). Both associations were confirmed by BS analysis.

Additionally, we found an increase in both RV and the RV/TLC ratio, which depended on V_{40}, for the L patients. Only the latter association held up in BS analysis, implying an increase on the order of 38% (for an average V_{40} of 5%) for the RV/TLC ratio. This result is difficult to

Table 3. Regression coefficients of significant associations found in multiple regression analysis

C_1 assessment	b_1 (nu) (V_{20})			b_8 (nu) (V_{20} * smoking)			b_9 (1/y) (V_{20} * age)		
ΔPFT_1 (%)		95% CI	*p*		95% CI	*p*		95% CI	*p*
ΔFVC_1	0.4	(0.1–0.8)	0.013						
$\Delta(DL, CO/Va)_1$				−0.4	(−0.7 to 0.0)	0.035			
ΔRV_1							0.004	(0.001–0.006)	0.003

C_{12} assessment	b_3 (%) (ACpre)			b_5 (nu) (V_{40} * CHOP_ABVD)			b_7 (nu) (V_{20} * ACpost)			b_8 (nu) (V_{20} * smoking)			b_{12} (%/y) (ACpre * age)		
ΔPFT_{12} (%)		95% CI	*p*		95% CI	*p*		95% CI	*p*		95% CI	*p*		95% CI	*p*
ΔFVC_{12}										−0.2	(−0.4 –0.1)	0.013			
$\Delta FEV1_{12}$							0.3	(0.1–0.5)	0.003						
$\Delta DL, CO_{12}$				1.0	(0.0–1.9)	0.041									
ΔTLC_{12}	42.3	(4.0–80.6)	0.031										−0.8	(−1.6–0.1)	0.031
ΔRV_{12}				−9.6	(−16.9– 2.3)	0.011									
$\Delta(RV/TLC)_{12}$				−7.7	(−12.9 –2.6)	0.004									

Table data show regression coefficients of the significant associations (*i.e.*, $p < 0.05$) found in the multiple regression analysis (Eq. 3). Units for the different parameters are in brackets. nu = no units. According to the definition of the ΔPFTs in Eq. 1, positive regression coefficients imply a decrease in the PFT with respect to the baseline value and vice versa. The impact of the independent variable in a particular ΔPFT must be evaluated taking into account both the regression coefficient (b_i) and the value of the independent variable (single or as raw products).

Table 4. Regression coefficients of significant associations found in multiple regression analysis including BS commands

C_1 assesment	b_1^{BS}(nu) (V_{20})		b_9^{BS} (1/y) (V_{20} * age)	
ΔPFT_1 (%)	*p*			*p*
ΔVa_1	0.3	0.02		
ΔRV_1			0.004	0.006

C_{12} assesment	b_3^{BS} (%) (ACpre)		b_5^{BS} (nu) (V_{40} * CHOP_ABVD)		b_7^{BS} (nu) (V_{20} * ACpost)		b_8^{BS} (nu) (V_{20} * smoking)		b_{12}^{BS} (%/y) (ACpre * age)		b_{13}^{BS} (%/y) (ACpost *smoking)	
ΔPFT_{12} (%)		*p*		*p*		*p*		*p*		*p*		*p*
ΔFVC_{12}							−0.2	0.006				
$\Delta FEV1_{12}$					0.3	0.001						
$\Delta(FEV1/FVC)_{12}$											−7.0	0.002
ΔTLC_{12}	42.3	0.027							−0.8	0.025		
$\Delta(RV/TLC)_{12}$			−7.7	0.024								

The 95% CI (top) have been ommitted, in this case, for clarity.

evaluate in the context of drugs, which might cause bronchiolitis obliterans and volumes irradiated to high doses.

Regarding smokers, the association found between changes in FVC_{12} and V_{20} held up under the BS analysis (increase of 0.2% per V_{20} [%]) and also showed that in those who additionally received AC post-RT, the FEV1/FVC ratio increased, regardless of any dosimetric parameter.

Over time, successively lower V_d*s* values have been found to be associated with pulmonary damage (16, 18, 20). Schallenkamp et al. (18) suggested that the so-called low-dose region (*i.e.*, $d < 20$ Gy) should be kept to a minimum. A recent editorial (27) raised the same concerns. We have also found significant associations between ΔPFTs and low threshold doses. However, we disagree on the interpretation of these results. On the one hand, provided the technique is fixed, there is a high-level cross-correlation between the V_d*s* (34). On the other hand, when the dose increases, the range of V_d*s* for each dose level narrows, and the proportion of variation in ΔPFTs, explained by V_d, is expected to decrease (*i.e.*, R^2 decreases as V_d increases). This might partially explain the better correlations found by other studies for the low-dose levels, but to our understanding, it is unwise to extract conclusions about the significance of volumes irradiated to low doses. Our dose distributions were not clustered (*i.e.*, three different RT techniques), which allowed the exploration of a larger dose-volume domain giving more power to the predictive ability of the models. However, the validity of our results is restricted to low-grade toxicity predictions. Further investigation would be needed in order to evaluate our models for higher grades of toxicity.

CONCLUSIONS

In our cohort of patients, and regarding univariate correlations between dosimetric parameters and ΔPFTs, no major differences between paired lung and IL definitions have been found. None of the dose-volume parameters was a good single predictor. However, V_d showed stronger associations than MLD. It was also observed that V_d values were phase injury-dependant (*i.e.*, whether early or late), suggesting that late ΔPFTs could be more serial than early ones. Our multivariate regression models show that in order to minimize the acute restrictive phenomena, V_{20} should be kept to a minimum, irrespective of chemotherapy regimens. In general, this RT-induced complication resolved 1 year after treatment. A late large restrictive effect, regardless of the dose-volume distribution, which had not manifested early, was observed in patients who had received pre-RT AC-paclitaxel. Another finding was a late increase on both RV and the RV/TLC ratio of L patients, depending on V_{40}; this is difficult to evaluate clinically because of the drugs and radiation interaction. Temporal interaction of chemotherapy and radiation and the response smokers to radiation should be further investigated.

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