Is pulmonary function damaged by neoadjuvant lung cancer therapy? A comprehensive serial time-trend analysis of pulmonary function after induction radiochemotherapy plus surgery

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Objective: We have analyzed short- and long-term variations of pulmonary function in locally advanced non–small cell lung cancer after induction chemoradiotherapy.

Methods: Twenty-seven patients with stage IIIA (N2) non–small cell lung cancer underwent resection with radical intent after induction chemoradiotherapy in the period 2003 to 2006. Pulmonary function has been evaluated by spirometry, diffusing capacity of the lung for carbon monoxide, and blood gas analysis before induction chemoradiotherapy (T0), 4 weeks after induction chemoradiotherapy and before surgery (T1), and 1 (T2), 3 (T3), 6 (T4), and 12 months (T5) after surgery.

Results: A 22.80% decrease of diffusing capacity of the lung for carbon monoxide ($P < .001$) was observed at T1. At T2 significant decreases in the following were present: vital capacity, –20.50% ($P < .001$); forced vital capacity, –22.50% ($P < .001$); forced expiratory volume in 1 second, –23.00% ($P < .001$); peak expiratory flow, –29.0 ($P < .001$); forced expiratory flow 25% to 75%, –13.7% ($P = .005$); and diffusing capacity of the lung for carbon monoxide, 43.6% ($P < .001$). However, in the interval between T2 and T5, a progressive improvement of lung function in most parameters was observed, but only diffusing capacity of the lung for carbon monoxide presented a significant increase ($P < .001$). Within the same time gap (T2 to T5), subjects 65 years of age or younger showed an increasing trend for vital capacity, forced expiratory volume in 1 second, total lung capacity, and residual volume significantly different from that of elderly patients, in whom a decrease in these parameters is reported.

Conclusions: An impairment of respiratory function is evident in the immediate postoperative setting in patients with non–small cell lung cancer receiving induction chemoradiotherapy. In the long-term period, a general recovery in diffusing capacity of the lung for carbon monoxide was found, whereas an improvement of forced expiratory volume in 1 second, vital capacity, total lung capacity, and residual volume was detected in the younger population only. (J Thorac Cardiovasc Surg 2010;139:1457-63)

Concurrent radiochemotherapy is the standard of treatment in stage III non–small cell lung cancer (NSCLC). In selected cases a multidisciplinary approach, including induction chemoradiotherapy (IT) and surgery, widened the chances of completeness of the surgical operation and better prognosis.[1–6]

The fact that IT could increase perioperative morbidity and mortality, mainly related to acute respiratory events, is widely evidence based.[7–9] Many studies have analyzed the detrimental effects of radiotherapy (RT) and chemotherapy (CT) on lung function in the short and long term. However, to date and to our best knowledge, a comprehensive and serial (ultra short, short, mid, long, and very long term) analysis of pulmonary function in a homogeneous population of patients with locally advanced non–small cell lung cancer (NSCLC) who underwent an IT-plus-surgery protocol has never been reported. We contend this despite recent reports demonstrating the decrease in diffusing capacity of the lung for carbon monoxide (DLCO) after IT radiotherapy–chemotherapy (RT-CT) as a predictor of postoperative pulmonary morbidity.[10]

PATIENTS AND METHODS

Institutional review board approval has been obtained. The pulmonary function data regarding a cohort of patients with locally advanced NSCLC have been prospectively collected in the setting of an observational study and evaluated in the period from January 2003 to January 2006. Consecutive patients with NSCLC, pursuant a standard staging procedure and

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Abbreviations and Acronyms

CT = chemotherapy
DLCO = diffusing capacity of the lung for carbon monoxide
$FEF_{25\%–75\%}$ = forced expiratory flow 25%–75%
FEV_1 = forced expiratory volume in 1 second
FVC = forced vital capacity
IT = induction chemoradiotherapy
NSCLC = non–small cell lung cancer
$Paco_2$ = arterial blood pressure of carbon dioxide
Pao_2 = arterial blood pressure of oxygen
PEF = peak expiratory flow
RT = radiotherapy
RT-CT = radiotherapy–chemotherapy
RV = residual volume
TLC = total lung capacity
VC = vital capacity

a histologically proven (primitive tumor and homolateral mediastinal nodes) diagnosis of locally advanced stage IIIa (N2), encountered the criteria followed in our institution for the indication of a first step IT RT-CT eventually followed by surgery (lobectomy only) on a comprehensive re-evaluation of the tumor stage after IT (clinical restaging) (Figure 1).

Population Characteristics

From January 2003 to January 2006, we evaluated and treated 62 patients with locally advanced NSCLC. Thirty-four patients showed a downstaging or stable disease and underwent surgery. Of these, 4 patients were treated with pneumonectomy and 3 patients continued treatments in other institutions. Another 28 patients had a progression of disease or had complications during IT treatment and were considered ineligible for surgery. The 27 patients who underwent lobectomy were considered in this study. The mean age of the patients was 62.9 ± 1.6 years and ranged from 40 to 80 years. Main population characteristics are described in Table 1.

Clinical Staging and Restaging: Pathologic Staging

The pretreatment evaluation included physical examination, blood analysis, electrocardiogram, fiberoptic bronchoscopy, computed tomographic scan of the chest, abdomen, and brain, and radionuclide bone scan. The diagnosis of NSCLC was obtained by pathologic and/or cytologic examination of material obtained via endobronchial biopsy or computed tomography–guided fine needle aspiration. Mediastinal involvement was always histologically (via mediastinoscopy) or cytologically (via computed tomography–guided fine needle aspiration) confirmed.

A complete clinical restaging was performed 4 weeks after IT. Redo mediastinoscopy was performed in selected cases.

IT Protocol

The treatment consisted of concurrent CT and RT.

Gemcitabine (350 mg/m^2, or 300 mg/m^2 for patients > 70 years) was administered weekly as a 30-minute intravenous infusion at least 4 hours before RT.

RT was administered with an individualized approach according to the volume and location of the disease, with the requirement that 100% ± 5% isodose should encompass the entire target volume, with a maximum dose for the spinal cord of 36 Gy. Gross tumor volume was the same as clinical target volume plus target volume, and the planning volume was the clinical target volume plus surrounding 1.5-cm margin. The elective nodal irradiation was never administered. The prescription dose was 50.4 Gy, given in daily single 1.8-Gy fractions or in a 1.2-Gy dose twice daily on week days. A CT-based planning was performed in each case. Heterogeneity correction was routinely applied.

A photon beam (linear accelerator) with a 6- to 10-MV energy source was used in all cases.

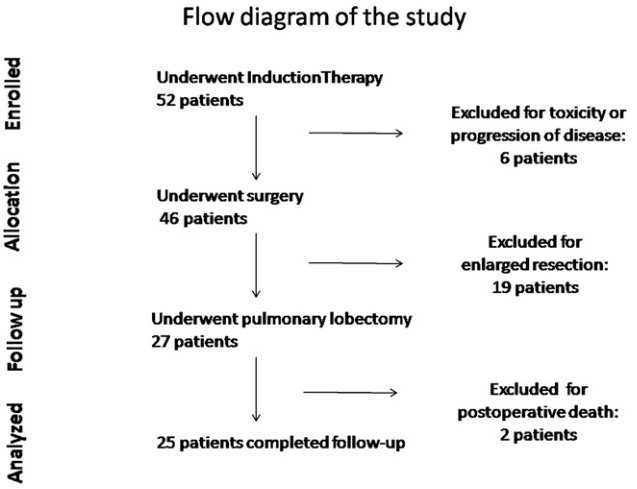

FIGURE 1. Consort diagram.

Pulmonary Function Evaluation

Pulmonary function tests were performed using the Spirometer System (Biomedin, Padua, Italy). The DLCO was measured by the single breath method and corrected with hemoglobin value. Blood gas analysis was performed by sampling of radial artery blood.

The parameters we finally considered for this analysis are the absolute value of vital capacity (VC), forced vital capacity (FVC), forced expiratory volume at first second (FEV_1), total lung capacity (TLC), residual volume (RV), peak expiratory flow (PEF), forced expiratory flow 25%–75% ($FEF_{25–75}$), DLCO, arterial blood pressure of oxygen (Pao_2), arterial blood pressure of carbon dioxide ($Paco_2$), and pH.

All of the aforelisted parameters were measured before IT (time 0, T0), 4 weeks after IT and before surgery (time 1, T1), 1 month after surgery (time 2, T2), 3 months after surgery (time 3, T3), 6 months after surgery (time 4, T4), and 1 year after surgery (time 5, T5).

Further on, we stratified the cohort of patients according to age as ''young'' (<65 years old) and ''elderly'' (>65 years old) and according to surgical intervention (all lobectomies) as ''upper lobectomy'' and ''lower lobectomy.'' A cross comparison matching these criteria has then been realized.

Surgery

The criteria for surgery indication followed in our center are extensively reported elsewhere.[11] Put briefly, in locally advanced stage IIIA (N2) NSCLC cases where an IT has been administered, we indicate surgery in the so-called ''responder'' cases where a downstaging is obtained and in all those cases where a progression of disease was not confirmed and where a radical operation is reasonably foreseeable.

Surgery consisted of anatomic resection (lobectomies only were considered in this series) plus hilar and mediastinal systematic lymph node dissection,[12] and it was performed 2 weeks (10–17 days) after clinical restaging (thus, on an average, 6 weeks after the beginning of the IT) through a lateral muscle-sparing thoracotomy. The resection was considered complete if

TABLE 1. Main population characteristics

	Patients	
	No.	%
Smoking habits		
Yes	6	22.2
No	19	70.4
Ex	2	7.4
Gender		
Male	20	74.1
Female	7	25.9
Comorbidity		
No	19	70.4
Yes	8	29.6
COPD		
No	18	66.7
Yes	9	33.3
Histology		
Squamous	12	44.4
ADK	14	51.9
Adenosquamous	1	3.7
Surgery		
RLL	4	14.8
LLL	4	14.8
ML	1	3.7
RUL	7	25.9
LUL	11	40.7

COPD, Chronic obstructive pulmonary disease; *ADK,* adenosine kinase; *RLL,* right lower lobectomy; *LLL,* left lower lobectomy; *ML,* middle lobectomy; *RUL,* right upper lobectomy; *LUL,* left upper lobectomy.

proximal resection margins were free of tumor on frozen section examination and if the highest mediastinal resected node was free of tumor.

Follow-up

Patients were to be followed up at the first, third, sixth, and twelfth postoperative months. Investigations included interim history, physical examination, laboratory tests, functional respiratory test, chest radiograph, and oncologic follow-up.

Statistical Analysis

To compare the respiratory parameter means at different moments of the follow-up time considering the nonindependence in the outcome, we applied a log-normal *random effect* model,[13] inasmuch as each individual represented a *cluster* of allegedly correlated outcomes. This model takes into account the within-subject correlation and provides accordingly suitable estimates of the standard errors of the regression coefficients. The *fixed effects* estimated from this model correspond—for each respiratory parameter—to the relative difference between the mean at different steps of the follow-up and the baseline. Gender, age, smoking habits, histology, comorbidity, and surgery have been considered as possible confounders and were included in the models when they influenced the regression coefficients estimate. χ^2 Statistic was applied to test the linear relationship between the respiratory parameters and time. The analysis was performed with Stata statistical software (Stata Corporation, College Station, Tex).[14]

RESULTS

Surgery

The 30-day mortality was 2 (7.4%) of 27: 1 case of myocardial infarction and 1 case of pulmonary embolism. The morbidity was 5 (18.5%) of 27. In 4 cases a respiratory cause underlay the complication: 1 case of late bronchopleural fistula that caused the death of the patient 55 days after surgery, 1 case of persistent air leak (8 days, spontaneous closure), and 2 cases of acute respiratory failure (one 3 days after surgery, owing to lobar atelectasis in the residual lung treated with bronchial aspiration, and one 2 days after surgery, owing to lobar pneumonia that required 48 hours of mechanical ventilation and prolonged [> 7 days] antibiotic therapy). The remaining nonrespiratory complication was a case of atrial fibrillation, medically treated. Age, gender, IT response, and lung functionality were homogeneous among the patients in whom a postoperative morbidity of any type developed.

Three patients discontinued the planned follow-up owing to the appearance of distant metastases (1 at the level of the bone, 2 at the level of the brain) and started palliative treatment. The remaining patients completed the planned follow-up and thus the records included complete respiratory data for the present analysis. All of the patients who reached the twelfth month alive were free of evident disease.

Respiratory Function

Table 2 and Figure 2 show the observed respiratory parameter means at each follow-up time.

To measure the short-term effects of IT treatment and surgery, we performed a multivariate regression analysis for each functional parameter, comparing post-IT (T1) and postoperative (T2) performances with baseline data (T0). The results of this analysis are described in Table 3.

At time T1, only DLCO decline (–22.80%; $P < .001$) was significant and no particular worsening in each of the other parameters at this time check point was observed.

At time T2, a significant decrease of VC (–20.50%; $P < .001$), FVC (–22.50%; $P < .001$), FEV_1 (–23,00%; $P < .001$), PEF (–29,0; $P < .001$), $FEF_{25–75}$ (–13,7%; $P < .005$), and DLCO (–43.6%; $P < .001$) was present with respect to T0.

The comparison of T1 to T2, which represents the effect of acute perioperative changes, showed the same significant differences as between T0 and T2 with the addition of TLC (–22.0%; $P < .032$).

The relationship between the respiratory parameters and time after surgery (T2–T5) was explored by testing whether the slope of the linear trend, estimated by the *random effect* model, was significantly different from zero. Only DLCO presented a significant increase from T2 to T5 (+25.8%; $P = .007$).

We found that in younger subjects (aged $\leq$ 65 years), the time trends after surgery for VC, FEV_1, TLC, and RV were significantly different from those of the elderly subjects (aged > 65 years) by testing the statistical interaction between age and time of follow-up. In the younger group, VC

TABLE 2. Respiratory parameter means at each time of the follow-up

	Time of follow-up: mean (SE)					
	T0	T1	T2	T3	T4	T5
VC (L)	3.39 (0.16)	3.38 (0.15)	2.62 (0.16)	2.69 (0.16)	2.74 (0.15)	2.69 (0.16)
FVC (L)	3.29 (0.15)	3.26 (0.16)	2.49 (0.14)	2.55 (0.16)	2.60 (0.15)	2.55 (0.16)
FEV_1 (L)	2.28 (0.14)	2.23 (0.15)	1.67 (0.13)	1.69 (0.12)	1.74 (0.14)	1.78 (0.15)
TLC (L)	5.25 (0.37)	5.49 (0.24)	4.26 (0.23)	4.34 (0.18)	4.39 (0.19)	4.28 (0.17)
RV (L)	2.17 (0.24)	2.15 (0.19)	1.62 (0.15)	1.56 (0.11)	1.60 (0.12)	1.54 (0.11)
PEF (L/s)	6.06 (0.48)	5.97 (0.46)	4.12 (0.39)	4.44 (0.30)	4.49 (0.40)	4.56 (0.43)
FEF 25-75 (L/s)	1.52 (0.19)	1.50 (0.18)	1.30 (0.23)	1.23 (0.22)	1.33 (0.26)	1.33 (0.22)
DLCO ($mL \cdot mm\,Hg^{-1} \cdot mm^{-1}$)	15.42 (1.13)	13.58 (0.91)	8.94 (0.95)	9.29 (0.65)	11.91 (1.39)	12.05 (1.37)
Pao_2 (mm Hg)	80.72 (2.07)	83.16 (1.85)	81.57 (2.52)	82.77 (2.33)	83.37 (3.36)	84.45 (2.81)
$Paco_2$ (mm Hg)	39.05 (0.87)	38.21 (1.02)	39.17 (1.01)	38.56 (0.42)	39.02 (0.74)	38.51 (0.86)
pH	7.45 (0.02)	7.46 (0.02)	7.44 (0.01)	7.43 (0.01)	7.43 (0.01)	7.43 (0.01)

VC, Vital capacity; *FVC*, forced vital capacity; FEV_1, forced expiratory volume in 1 second; *TLC*, total lung capacity; *RV*, residual volume; *PEF*, peak expiratory flow; *FEF 25–75*, forced expiratory $flow_{25\%-75\%}$; *DLCO*, diffusing capacity of the lung for carbon monoxide; Pao_2, arterial blood pressure of oxygen; $Paco_2$, arterial blood pressure of carbon dioxide.

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($P < .001$), FEV_1 ($P < 0.001$), TLC ($P < .045$), and RV ($P < .031$) showed a progressive increment. Instead, in the elderly patients, all the just-mentioned parameters did not show significant variations (P = not significant). The multivariate models fitted for all parameters are reported in Table 3.

DISCUSSION

It has been clearly demonstrated that IT (different paradigms) can increase morbidity and mortality after surgery, mainly related to acute respiratory events.[7–10] The DLCO was found to be significantly and constantly decreased in the IT (CT only, cisplatin plus gemcitabine regimens) experiences recently reported by Leo,[15] Maas,[16] and their associates. An increase in perioperative morbidity rate was reported as well. No reasoning was made with respect to the understanding of such an event under these specific conditions, where the need of a comprehensive analysis of prospectively gathered data remains unmet.

Where an association of CT and RT is considered within an IT setting, the general idea is that a higher morbidity rate is expected when a lung resection is performed owing to the inclusion of the RT component. It is worth mentioning, to allow the reader a careful and conservative interpretation of this message, that this common belief is supported by data that are at least heterogeneous. As well, we would like to underline that the absence of a control group in this observational analysis is due to the fact that we have explored the pulmonary function of patients who undergone CT-RT and surgery for locally advanced NSCLC. The only possible comparison group would have been a surgical population without prior IT. This is not possible for two reasons: first, because stage III NSCLC standard treatment is CT-RT; second, because a surgical population (all lobectomies) would be constituted by earlier stage cases and would lack the main element under investigation, that is, the RT component of the IT.

At the moment of this writing, very few substantial data are in fact available to cross match and discuss the effect of induction RT-CT and surgery on pulmonary function. To the best of our knowledge, none of those available is similar to ours for number of serial time-trend checkpoints (1 pre-IT, 1 post-IT, and 3 postoperative), homogeneity (as regards staging and surgical indication criteria and pulmonary function assessment), and completeness.

Abratt and Wilcox,[17] in 1995, reported the effects of RT on respiratory function and proved that the DLCO is constantly decreased after irradiation (6 and 12 months after treatment). Similarly, Borst and associates,[18] in 2004, reported that pulmonary function is significantly decreased after RT. However, in both of these studies, the level of complexity and heterogeneity is enhanced by the fact that the patients, all with inoperable NSCLC, were treated with high-dose exclusive RT (70 Gy) and never underwent surgery.

The recently published experience from Takeda and associates[10] reported the results regarding the analysis of the lung function before and after surgery in a cohort of cases closer to ours (pulmonary resection after IT). It was demonstrated that the DLCO is a clear and valid predictor of morbidity (pulmonary) in the perioperative period. The authors did not investigate pulmonary function beyond the surgical step. Moreover, a certain degree of heterogeneity in the population characteristics diminishes the value of the conclusive figures. This was particularly true for the type (extent) of resection and the type of IT (both cases where CT alone and cases where RT-CT schemes were used had been considered for the analysis; furthermore, in the CT group, different chemotherapeutic regimens had been adopted, these being known to have, among themselves, a different impact on pulmonary function).

Still, in 2002, as additional information of side but useful importance for this discussion, we have supported the

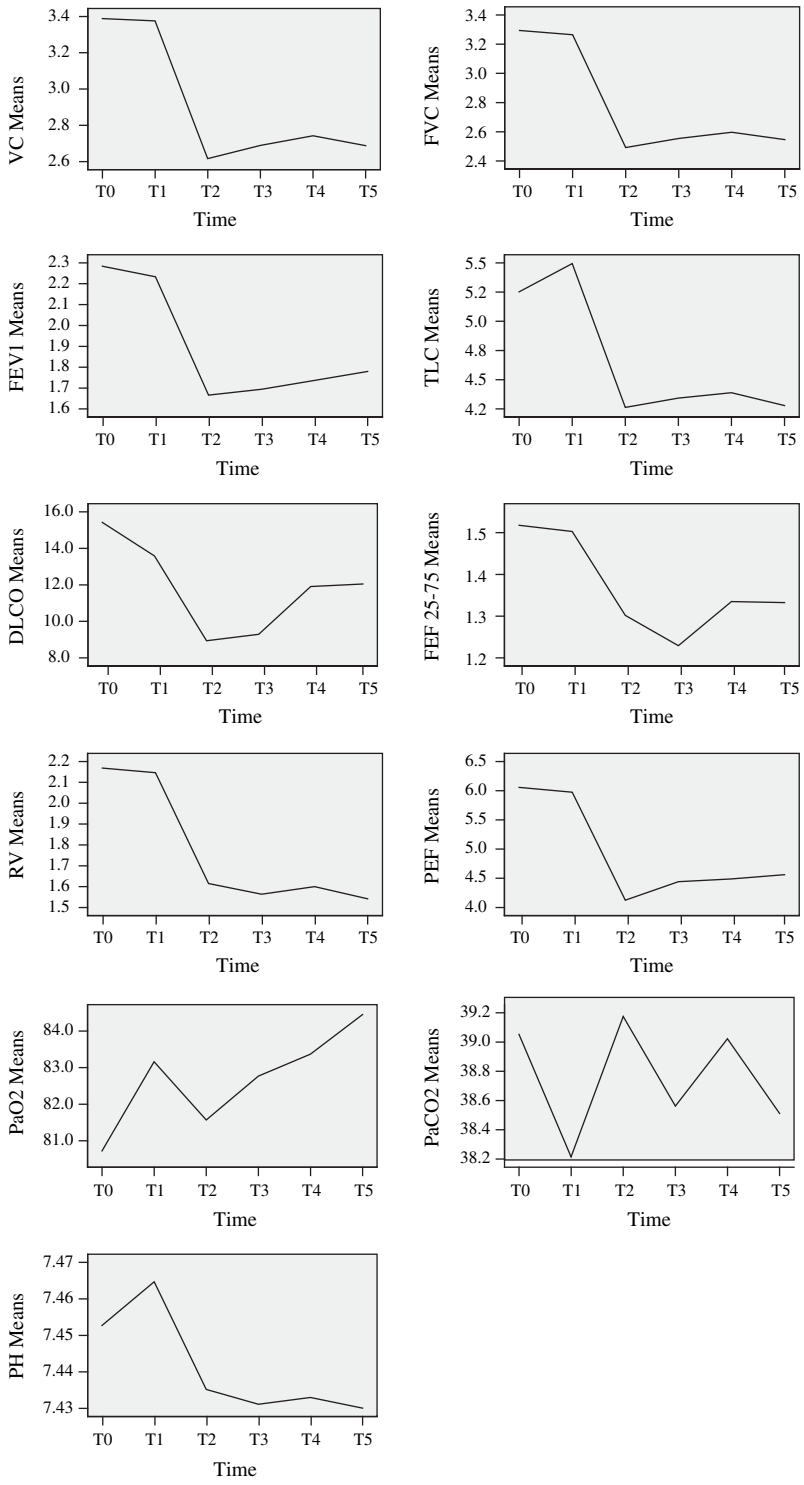

FIGURE 2. Respiratory parameter means at each time of the follow-up. *VC,* Vital capacity; F*VC,* forced vital capacity; FEV_1, forced expiratory volume in 1second; *TLC,* total lung capacity; *DLCO,* diffusing capacity of the lung for carbon monoxide; $FEF_{25\%-75\%}$, forced expiratory flow25%–75%; *RV,* residual volume; *PEF,* peak expiratory flow.

hypothesis that the functional postoperative lung damage is correlated with the extent of pulmonary resection to a greater extent than to the IT treatment.[6]

As well, it is to be considered that the evidence of the decrease in pulmonary function is related to the dose and the volume of irradiated parenchyma and, not less

TABLE 3. Multivariate regression analysis

Respiratory parameters	Time	N	Mean difference (%)	95% CI	*P* value
VC	T0	22	0.0		
	T1	27	–1.2	–6.0/3.8	.621
	T2	16	–20.5	–25.2/–15.6	<.001
FVC	T0	22	0.0		
	T1	27	–2.4	–7.1/2.6	.340
	T2	16	–22.5	–27.0/–17.7	<.001
FEV1	T0	22	0.0		
	T1	27	–3.5	–7.4/0.5	.086
	T2	16	–23.0	–26.7/–19.0	<.001
TLC	T0	19	0.0		
	T1	26	11.2	–8.9/35.8	.296
	T2	14	–10.2	–28.9/13.5	.368
RV	T0	19	0.0		
	T1	26	–1.5	–15.5/14.8	.846
	T2	14	–15.2	–29.4/1.7	.075
PEF	T0	22	0.0		
	T1	27	–3.0	–11.5/6.2	.507
	T2	16	–29.0	–36.5/–20.7	<.001
$FEF_{25–75}$	T0	22	0.0		
	T1	27	–2.2	–10.1/6.5	.612
	T2	16	–13.7	–22.1/–4.3	.005
DLCO	T0	10	0.0		
	T1	15	–22.8	–32.3/–12.0	<.001
	T2	9	–43.6	–50.9/–35.3	<.001
Pao_2	T0	21	0.0		
	T1	27	3.2	–0.8/7.3	.122
	T2	16	2.2	–2.6/7.2	.373
$Paco_2$	T0	21	0.0		
	T1	27	–2.7	–7.4/2.3	.285
	T2	16	–1.8	–7.5/4.3	.562
pH	T0	19	0.0		
	T1	27	–0.1	–0.5/0.3	.627
	T2	15	–0.2	–0.7/0.2	.334

CI, Confidence interval; *VC*, vital capacity; *FVC*, forced vital capacity; *FEV_1*, forced expiratory volume in 1 second; *TLC*, total lung capacity; *RV*, residual volume; *PEF*, peak expiratory flow; *$FEF_{25–75}$*, forced expiratory flow 25%–75%; *DLCO*, diffusing capacity of the lung for carbon monoxide; *Pao_2*, arterial blood pressure of oxygen; *$Paco_2$*, arterial blood pressure of carbon dioxide.

importantly, to the quota of nonpathologically damaged lung.[19,21]

Worth addressing herein is the relative effect the use of conformational RT may have had on the reported outcome. In fact, it appears intuitively clear that an irradiation of the lung to a lesser (still accurate) extent and, therefore, the resection of part of the lung damaged by irradiation could indeed reduce the functional lung decrease. Over the immediate postoperative period, this is more true in the long term (when the residual healthy lung parenchyma is recruited more and more extensively). This belief is supported by the fact that, in our experience, the functional decrease is more evident immediately after surgery instead of soon after RT-CT. In this phase, in fact, the DCLO (mainly) deterioration derives from subclinical damage to the alveolocapillary membrane.[10,15,22–24] The degree of this injury may be proportional to the extent of the DLCO decline. It has been hypothesized to predict the overall risk of respiratory postoperative morbidity.[10,15] We could not confirm this double correlation (small population and low morbidity rate).

Another issue that deserves some additional lines of reasoning is the progressive improvement of lung function with particular increase of the DLCO in all patients. When the time gap from T2 and T5 is considered, the younger subjects showed a significantly different pattern (VC, FEV_1, TLC, and RV) than the elderly ones, this being clearly increased in the former group. The behavior of DLCO may be correlated with a reduction of edema in the interstitial space and with the degree of damage to the alveolocapillary membrane. Despite the fact that we could not hypothesize other pathophysiologic mechanisms, our data did not confirm those (DLCO and FEV_1 parameters' behavior) reported in previously published studies where these were constantly and significantly decreased in the long term after RT-CT.[17–20]

Higher overall doses and different RT-CT schedules and planning, along with the absence of the surgical step, could easily justify this discrepancy (the irradiated parenchyma stayed on site thus providing its ''*minus*'' to the global pulmonary function).

The partial irreversibility of the obstructive damage in the elderly population can support the evident difference (''none'' versus ''significant increase'' of FEV_1) with the younger group. This is maintained despite the common overarching improvement of flows induced by the parenchymal resection in the midterm to long-term period. Moreover, the increase of all pulmonary volumes (VC, TLC, RV) in the younger patients could be related to a progressive easier recovery of respiratory mechanics and muscular power (with respect to the elderly) after surgery.

Finally, our data support the widely established evidence that the predictive value of FEV_1 and FVC assessed after IT as indicators of the likelihood of respiratory postoperative morbidity is inferior to that of DLCO, which is commonly believed to be the most sensitive risk indicator in this setting.[15] As a matter of reference, a low preoperative DLCO (<45%) is associated with an increase in postoperative morbidity and mortality and predicts a poor quality of life[25]; furthermore, a decrease of more than 20% in DLCO suggests that a relevant, but of limited clinical value, degree of toxic damage to the pulmonary parenchyma may have occurred.[23] The moderate decline in DLCO preoperative levels (baseline to T1, –22.80%; $P < .001$) was in fact correlated with a very low rate of pulmonary related postoperative complications.

Limitations and Recommendations

Functional evaluation before lung resection in patients receiving neoadjuvant treatment remains controversial. However, as similarly demonstrated in CT-only based regimens, particular attention must be put on the DLCO levels.

We support the hypothesis that a decrease in DLCO (a marker of alveolar–interstitial injury) could negatively affect the risk of respiratory complications after surgery following CT-RT.

We also believe that the FEV_1 after IT is not a sensible marker of postoperative complication (as demonstrated in the T0–T1 period analysis of our study). Within the scopes (and limits) of the reported setting, DLCO and FEV_1 need further investigation to gather sufficient proof and strength to enter the clinical decision-making process as independent parameters; in particular, for example, DLCO levels could be possibly considered as cutoff criteria to stratify the preoperative risk in patients operated on after concurrent CT-RT delivered at full therapeutic doses.

On the basis of these premises, we are currently evaluating, during the postoperative period (in the short and long term), the value of DLCO levels as a reliable indicator of lung function worsening or recovery. Furthermore, we are investigating the relationship among the low DLCO levels in the long-term post-RT complications and novel therapeutic strategies including preoperative and postoperative pulmonary rehabilitation.[26,27]

Finally, since they showed a slower recovery after surgery, we recommend for elderly patients an intensive postoperative respiratory rehabilitation program and follow-up with particular attention to caloric support.

CONCLUSION

The IT damages lung functionality (DLCO, flows, and volumes) demonstrated by a significant decline of these parameters. If directly matched within the setting of a homogenous population, the degree of postoperative damage is greater than that of post-IT damage.

In our series, the DLCO was constantly increased in the entire population in the postoperative (up to 1 year) period. The volumes and flows (FEV_1, VC, TLC, and RV) demonstrated a positive trend in the younger patients only. Our data support the evidence that when the irradiated lung is then excised, lung function injury is dependent on pulmonary resection to a greater extent than on the IT, provided this is administered along modern paradigms. Further investigation on the possible role of other treatment opportunities, such as pulmonary rehabilitation scheduled along with the IT plus surgery, is currently underway in our group, and preliminary data will be available soon.

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