

No compensatory lung growth after resection in a one-year follow-up cohort of patients with lung cancer

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Background: As compensatory lung growth after lung resection has been studied in animals of various ages and in one case report in a young adult, it has not been studied in a cohort of adults operated for lung cancer.

Methods: A prospective study including patients with lung cancer was conducted over two years. Parenchymal mass was calculated using computed tomography before (M0) and at 3 and 12 months (M3 and M12) after surgery. Respiratory function was estimated by plethysmography and CO/NO lung transfer (D_{LCO} and D_{LNO}). Pulmonary capillary blood volume (V_c) and membrane conductance for CO (Dm_{CO}) were calculated. Insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) plasma concentrations were measured simultaneously.

Results: Forty-nine patients underwent a pneumonectomy (N=12) or a lobectomy (N=37) thirty two completed the protocol. Among all patients, from M3 to M12 the masses of the operated lungs (239 ± 58 to 238 ± 72 g in the lobectomy group) and of the non-operated lungs (393 ± 84 to 377 ± 68 g) did not change. Adjusted by the alveolar volume (V_A), D_{LNO}/V_A decreased transiently by 7% at M3, returning towards the M0 value at M12. Both V_c and Dm_{CO} increased slightly between M3 and M12. IGF-1 and IGFBP-3 concentrations did not change at M3, IGF-1 decreased significantly from M3 to M12.

Conclusions: Compensatory lung growth did not occur over one year after lung surgery. The lung function data could suggest a slight recruitment or distension of capillaries owing to the likely hemodynamic alterations. An angiogenesis process is unlikely.

Keywords: Lung resection; cancer; lung growth; lung mass (m_L); pulmonary diffusion

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Introduction

Various effects of pulmonary resection on lung growth have been reported in mammals. Compensatory lung growth has been well documented after pneumonectomy in various young and adult animals (1-5). Both parenchymal and nonparenchymal cells participate in this lung growth (1,6). In humans, the vital capacity and transfer factor for carbon monoxide (D_{LCO}) are still slightly decreased 1 year after surgery, suggesting a long recovery after resection; however, these alterations are not direct signs of growth (7,8). Circulating growth factors seem to have a predominant impact on this compensatory effect. Insulin-like growth factor-1 (IGF-1) is a potential source of the mitogenic activity observed in the lung (9,10); however, the impact of growth factor concentrations on lung mass (m_L) after lung resection has been poorly investigated. Lung growth following resection induces a secretion of growth factors stimulating tumor growth (11). A specific increase in the lung capillary blood volume (V_c) could be interpreted either as a hemodynamic adaptation of the lung after resection or as an abnormal stimulation of angiogenesis due to growth factors. Only one article has reported an increase in m_L following right pneumonectomy in a young woman (12); however, no measurement of m_L after lung resection has been reported in a cohort of patients.

The purpose of this study was to investigate compensatory lung growth after lung resection by measurements of m_L , pulmonary capacity, pulmonary diffusion and circulating growth factors and to assess the putative role of the angiogenic process.

Methods

Patients

Patients were recruited consecutively when admitted for lung resection of known or suspected lung cancer. They were prospectively assessed over a two-year period. Inclusion factors were: non-small-cell lung cancer staged T1, T2 or T3A of TNM classification with or without cerebral or adrenal metastasis. Exclusion factors were: small-cell lung cancer, non-small-cell lung cancer staged 3B and 4, multiple metastasis, benign tumor, atypical resections, inoperable patient and neo-adjuvant treatment before surgery. This study was performed according to the declaration of Helsinki. All patients provided informed written consent for the study, which was approved by the Hospital Ethical Committee of Bordeaux (CCPRB A n 2005/58).

Protocol

Each patient had a routine full clinical assessment prior inclusion. Several measurements were performed at inclusion (M0), 3 months (M3) and 12 months (M12) after lung resection: IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) plasma concentrations; m_L of operated and non-operated lung via computerized tomography (CT); lung volumes; and CO and NO diffusion capacity (DL_{CO} and DL_{NO}), from which capillary lung volume V_c and Dm_{CO} the membrane conductance for CO were derived.

Pulmonary function

Pulmonary function tests included the measurements of total lung capacity (TLC), vital capacity (VC) by whole body plethysmography and D_{LCO} and D_{LNO} (Hypercompact +, Dinant Be). The single breath technique for the measurement of D_{LCO} and D_{LNO} has been described elsewhere (13). Dm_{CO} and V_c were calculated as described in previous studies (14,15). Diffusion tests were repeated twice at 5-min intervals. If a difference greater than 10% appeared, a third test was performed. The mean of two validated tests was calculated.

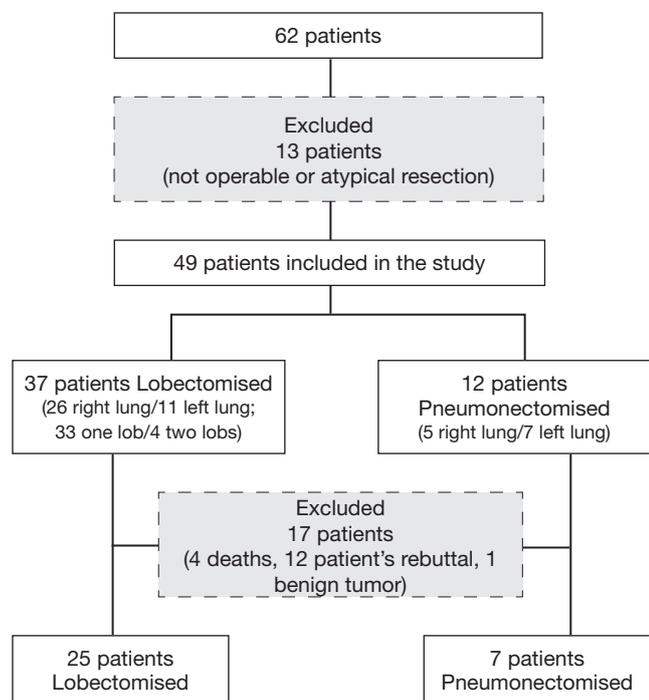
CT

The CT examinations were performed using a Siemens Somatom 16-slice scanner (Siemens medical system, Erlangen, Germany) with a volumetric acquisition covering both lungs and a collimation of 0.75 mm. Next, 1-mm-thick sections were reconstructed without gaps. Subjects were scanned in the supine position without an injection of IV contrast. The following parameters were employed: 100–120 KV and 60–80 mAs leading to a product dose-length varying between 100–150 mGy·cm depending on BMI. Attenuation values were expressed in HU. These units are related to density (d), $d = 1 + (HU/1,000)$. Conventionally, water has a HU value of 0, and air has a value of -1,000. An average of 350 slices was required to cover the totality of both lungs. Images were photographed on hard copies with a 200, -1,000 HU window. The pulmoCT software (Siemens medical system, Erlangen, Germany) allowed the calculation of lung density and volume. The program is based on an algorithm that accurately delineates lung contour along the parietal and pleural surface from the clear-cut difference between lung density (-1,000 HU) and pleural/mediastinal wall density

Table 1 Morphometric and pulmonary function of 49 patients

Variables	Gender/Mean \pm SD
Sex	44 males, 5 females
Age, years	62 \pm 10
Height, cm	170 \pm 7
Weight, kg	73 \pm 12
VC, L (% ref)	3.74 \pm 0.8, (96 \pm 18)
FEV ₁ , L (% ref)	2.48 \pm 0.6, (84 \pm 20)
D _{LCO} , (mL·min ⁻¹ ·mmHg ⁻¹) (% ref)	24.7 \pm 5.9, (92 \pm 24)
D _{LNO} , (mL·min ⁻¹ ·mmHg ⁻¹) (% ref)	120 \pm 32, (82 \pm 21)
Vc, mL (% ref)	73 \pm 17, (100 \pm 33)

Data are presented as the mean \pm SD. VC, slow vital capacity; FEV₁, forced expiratory volume in one second; D_{LCO}, lung transfer capacity for CO; D_{LNO}, lung transfer capacity for NO; Vc, pulmonary capillary blood volume; % ref, percentage of reference values.

**Figure 1** Screening and inclusion in the protocol.

(60 HU). The volume, density and m_L of each lung were calculated separately. Tumor volume and density were defined by contouring the tumor by eye.

The slices were all selected at 5-mm, beginning at the top of the apex. The volume and mean HU of each slice in each

lung were calculated separately. The mass of each slice was obtained by multiplying the mean density and the volume. The methodology used was similar to that described by Manier *et al.* (16). The entire lung was reconstructed from 30 to 40 contiguous slices. The m_L was calculated as the sum of the mass of the slices. The weight of the tumor was excluded from the calculation of the lung weight. The hilar and perihilar lung regions were excluded from the region of interest and the central great vessels using the software.

Immunoradiometric assay of IGF-1 and IGFBP-3

All the samples were assayed by trained staff at the hospital laboratory. The serum concentrations of IGF-1 and IGFBP-3 were measured by immuno-radiometric assay using commercially available kits (Immunotech). The mean intra-assay coefficient of variation for the quality control serum samples was 5.6% for IGF-1 and <4.4% for IGFBP-3. The range of reliable measurement was 0–160 ng/mL for IGF-1 and 0.3–100 ng/mL for IGFBP-3.

Statistical analysis

Data are expressed as the mean values \pm SD or as the median (25th; 75th percentiles) after assessing the normality of the distributions. Statistical analyses were performed using SAS/STAT Software v8.2. (SAS Institute Inc., Cary, NC, USA). Analysis of variance (ANOVA) was performed for comparisons of repeated measurement or between groups. Paired *t*-tests or Wilcoxon tests were applied whenever appropriate. Linear regressions were calculated using the least squares method. A *P* value <0.05 was considered significant.

Results

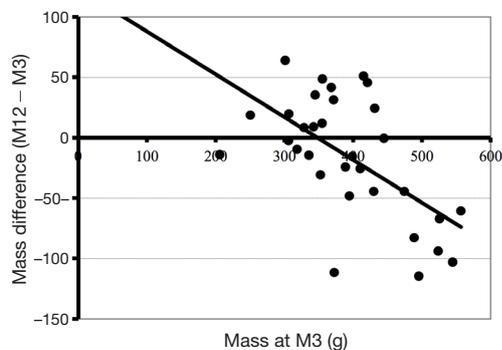
Patients (Table 1)

In total, 62 patients were recruited, and 13 were excluded from the study (Figure 1). The morphometric characteristics of the 49 patients are presented in Table 1. Among them, 12 patients underwent a pneumonectomy, and 37 patients had a lobectomy. Seventeen patients did not complete the protocol, 4 died, 12 gave up and 1 was excluded as having a benign tumor. Pre-operative treatment was performed in 5 patients. The postoperative TNM classification of the lungs was as follows: 18 stage 1; 13 stage 2; 17 stage 3; and 1 stage 4. The types of cancer cells included were as

Table 2 Mass (g) of the non-operated and operated lungs at M0, before lung resection, and 3 and 12 months after lung resection (M3 and M12 respectively)

	Non operated lung				Operated lung			
	M0	M3	M12	M12-M3	M0	M3	M12	M12-M3
Mean	394	393	377	-16	377	239*	238*	-1
SD	67	84	68	50	75	58	72	32
n	32	32	32	32	25	25	25	25

Changes in lung mass (M12-M3) are not significant. *, P<0.001 vs. M0.

**Figure 2** Mass difference of the non-operated lung between M3 and M12 as a function of the initial reading at M3. Masses are reported in grams. The linear regression equation is: $y = -0.354x + 123$, $r^2=0.35$ (n=32).**Table 3** Lung function variables before surgery (M0) and 3 and 12 months after (M3 and M12) in 32 patients

	Time measurements		
	M0	M3 (vs. M0)	M12 (vs. M3)
TLC (L)	6.33±1.03	5.02±1.04***	5.18±0.95*
VC (L)	3.65±0.75	3.03±0.73***	3.08±0.68
D _{LCO}	24.9±6.6	19.3±4.8***	21.3±6.1**
D _{LNO}	123±35	89±21***	98±29*
Dm _{CO}	156±84	98±54***	107±51
Vc (mL)	51.9±13	42.3±13***	45.6±13*
DL _{NO} /V _A	19.3±3.5	17.4±2.6***	18.6±3.5**

DL in mL·min⁻¹·mmHg⁻¹; DL_{NO}/V_A in mL·min⁻¹·mmHg⁻¹·L⁻¹. *, P≤0.05; **, P<0.01; ***, P<0.001. Data are mean ± SD. TLC, total lung capacity; VC, vital capacity; D_{LCO}, lung diffusion capacity for CO; D_{LNO}, lung diffusion capacity for NO; Dm_{CO}, membrane conductance for CO; Vc, pulmonary capillary blood volume.

follows: 26 adenocarcinomas, 21 squamous cell carcinomas, and 1 neuroendocrine cancer. After surgery, adjuvant treatment was performed in 17 patients, among which 13 completed the study. The median mass (25th; 75th percentiles) of the tumor was lower in the group of lobectomies [24 g (4.3; 49)] compared with the pneumonectomies [171 g (7.6; 335)]. In total, 34% of the patients experienced lung cancer recurrence during the time of the study.

Lung masses

At inclusion, left and right m_L did not differ regardless of the site of the tumor. Lobectomy induced an m_L average decrease of 138 g of the lung (P<0.001); this mass was maintained between M3 and M12 (Table 2). The average mass of the non-operated lung did not change significantly between M0 and M12; however, the change of mass between M3 and M12 was inversely proportional to the mass at M3, this relationship was significant (P=0.0004) (Figure 2). In other words, the lightest lungs at M3 gained mass from M3 to M12 while conversely the heaviest lung could loss mass.

Of 32 patients, 13 received chemotherapy and radiotherapy after surgery. This group had a lower non-operated m_L than the group without treatment at M3 (352.5 vs. 415 g, P=0.0017). This difference fade out at M12 as the m_L increased in the group with chemotherapy (+20 g) as it decreased (-31 g) in the group without chemotherapy.

Lung function (Table 3)

The pulmonary functions of the patients at M0 were within the normal reference values (Table 1). Lung resection induced a significant decrease in TLC by 1.31±0.9 L. From

Table 4 Plasmatic concentrations of IGF-1 and IGFBP-3 before (M0), 3 (M3) and 12 (M12) months after lung resection in 32 patients

	IGF-1			IGFBP-3		
	M0	M3	M12	M0	M3	M12
Mean	135	146	116***	2.38	2.38	2.25
SD	48	57	48	0.80	0.78	0.70

***, $P < 0.001$ vs. M0 and M3. IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3.

M3 to M12, TLC increased by 0.17 ± 0.4 L ($P = 0.03$) while the change in VC was not significant. D_{LCO} and D_{LNO} values were greater at M12 compared with M3 ($P \leq 0.01$). The ratio of D_{LNO}/VA decreased after resection and returned towards its initial value at M12. Both Vc and Dm_{CO} were slightly increased between M3 and M12. The increase was significant for Vc ($P = 0.05$). The decrease in Vc from 51.9 ± 13 to 42.3 ± 13 mL after resection was partially restored 12 months after lung surgery to 45.6 ± 13 mL.

IGF-1 and IGFBP-3 (Table 4)

At inclusion, IGF-1 and IGFBP-3 concentrations were 135 ± 48 and 2.38 ± 0.8 ng/L respectively. Both concentrations remained steady at M3. Then, from M3 to M12, IGF-1 concentration decreased from 146 ± 57 to 116 ± 48 ng/L ($P < 0.0001$), and IGFBP-3 decreased from 2.38 ± 0.8 to 2.25 ± 0.7 ng/L ($P = 0.08$).

Discussion

Lung mass and lung function were assessed during the one-year period after pulmonary resection in a cohort of patients receiving lung cancer operations. The main finding is that the non-operated and operated lungs had not grown 1 year after lung resection.

Compensatory lung growth after lung resection

Age dependency of lung growth

Immature dogs responded robustly to major lung resection (5). The adult/puppy comparison demonstrates an enhanced regenerative alveolar-capillary growth in the immature dog after pneumonectomy (17). Hsia *et al.* concluded that in adult dogs after left pneumonectomy, compensation by tissue growth is quite limited, and only adjustments occur in existing structures of the remaining lung (18). In the present study, patients were, on average, in the last fourth of the predicted life span for man. It is worth noting that the

only increase in m_L after pulmonary resection was observed in a 33-year-old woman (12).

Time dependency of lung growth

Three months after surgery m_L changes were minimally detected because of the acute remodeling processes and the effects of post-surgical therapies. Inflammation, which increases m_L and blood flow, can persist only a few months after lung resection (19,20). In the present cohort, the m_L of the non-operated lung did not change significantly at M3, but individual values were scattered, suggesting that some patients exhibit a transient increase in their m_L that is subsequently lost, as demonstrated by the negative correlation between the changes in m_L between M3 and M12 and mass at M3.

The case reported by Butler *et al.* suggested that compensatory lung growth requires years (12), which is consistent with the fact that no increase in lung weight was observed in the present cohort during a one-year follow-up.

Surgery location dependency of lung growth

Some authors suggested that the compensatory lung growth depends on the volume of lung resected and the location of resection (21). The present data suggest that a relatively heavy non-operated lung loses mass between M3 and M12, whereas light lungs gained mass. These changes may not be due to growth but to water content associated with acute post-surgery processes.

Other factors altering lung growth

Compensatory lung growth hypothesized includes passive structural changes by an adjustment of existing structures in the remaining lung (3,5,6,17). These changes may include enlargement of alveolar spaces, thinning of the alveolo-capillary membrane, increase in capillary blood volume etc. Otherwise, lung growth response may be induced by growth factors. Several growth factors may be involved in this compensatory response among which IGF-1 that acts on development of various tissues by linking with IGFBP-3 in blood (9-11).

Lung function after lung resection

As changes in m_L after months are likely related to lung growth, immediate changes in lung function are related to the mechanical adaptation of the lung to the resection without growth. Such was the case in this study in which the average mass of both non-operated and operated lungs did not change, whereas the function of the lungs was progressively altered. The increase in TLC is consistent with the results reported by Nagamatsu (8). As the mass of the lung did not increase concomitantly, these changes in lung volumes strengthen the hypothesis of a stretching effect of the chest through the remaining parenchyma.

The D_{LCO}/D_{LNO} method was used to calculate V_c and Dm_{CO} . It has been recently suggested that D_{LCO} mainly depends on V_c , making this measurement a good marker of microcirculation (14) given that D_{LNO} depends equally on V_c and Dm . Bolliger *et al.* observed that D_{LCO} at rest was decreased 3 months after lobectomy or pneumonectomy, whereas D_{LCO}/VA did not change (7). In the present study, Dm and V_c decreased from M0 to M3 by 33% and 20%, respectively. The predominance of the decrease in Dm and D_{LNO}/VA suggest the induction of a slight interstitial edema. These alterations could also be due to early changes in pulmonary hemodynamics after resection. Tayama *et al.* reported a positive correlation between total pulmonary vascular resistance (PVR) and BNP plasma concentration a few days after lung resection (22).

Between M3 and M12, the diffusion variables increased, suggesting an adaptation of the capillary network of the lung to the conditions of lung resection. Just after the resection the increase in PVR would induce at constant cardiac blood flow a raise in vascular pressure and an increase in volume of the most compliant part of the circuit, i.e., in capillary blood volume. The increase in shear stress might also induce arterial vasodilation and a concomitant decrease in PVR (23). In the long term lung growth could be induced as suggested by experimental findings, morphometric analyses highlighting the compensatory growth of capillary volume and surface area one year after pneumonectomy in dogs (5). Capillary growth alone would have no measurable effect on the lung weight of an adult human, as the mass of blood in capillaries compared with the total m_L is small; a 10% change in V_c would represent approximately 6 g in the present cohort. If no bronchial growth occurred, the increase in weight would remain non-significant. In the case study by Butler *et al.*, a gain in lung weight was observed after several years; the alveolar and bronchiolar proliferation

probably took more time than capillary proliferation (12).

Growth factor concentrations following lung resection

Changes in blood growth factor concentrations in human after lung resection has not been extensively studied. In the present study, IGF-1 and IGFBP-3 concentrations were altered 3 months after surgery with a marked decrease in IGF-1 (~20%) observed between M3 and M12. These results were unexpected as IGF-1 and IGFBP-3 are known to induce epithelial proliferation and angiogenesis (24). Studies evaluating the changes in IGF-1 following lung surgery in animals provided differing results; however, most studies suggest an increase in IGF-1 (25,26). The IGF-1 decrease from M3 to M12 could be explained by several parameters, including aging and poor nutritional status (27). This status was not precisely evaluated in this study, and the duration of the follow-up was only 1 year. This decrease was more likely due to the lack of IGF-1 secretion after the removal of cancer cells (28).

Limitations and power of the study

A limitation of the study is the sample size. The lack of statistical power may explain the absence of significant differences in m_L between M3 and M12. m_L measurement implies many parameters that cause unavoidable variation. However biological markers have higher statistical power due to reduced measurement error. The absence of alteration of IGF-1 and IGFBP-3 concentrations between M0 and M3, followed by their decreases at M12 gives an argument against the stimulation of lung growth.

Another limitation is the duration of the follow-up. A longer duration would have increased the likelihood to observe a lung growth. However owing to the death rate of this population a longer duration would have need more patients which was out of our means.

Finally, among patients included in this study, some received post-operative treatment that could be suspected to slow down lung growth. However, in this sub-group, m_L in contrast to the other, increased slightly from M3 to M12.

Conclusions

In conclusion, no compensatory lung growth was observed in a human cohort after lung resection during a one-year follow-up. No increase in the concentrations of IGF-1 and IGFBP-3 were observed. The slight capillary lung volume

increase between M3 and M12 was likely due to minimal hemodynamic adaptation after resection. As the biological markers were not increased an angiogenic effect does not appear to be involved.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Hospital Ethical Committee of Bordeaux (CCPRB A n 2005/58) and written informed consent was obtained from all patients.

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