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Lung clearance index: a new measure of late lung complications of cancer therapy in children

Giuseppe Fabio Parisi[1], Emanuela Cannata[1], Sara Manti[1], Maria Papale[1], Mariaclaudia Meli[1], Giovanna Russo[1], Andrea Di Cataldo[1], and Salvatore Leonardi[1]

[1]University of Catania

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Abstract

Introduction Childhood cancer survivors (CSs) might face an increased lifelong risk of lung function impairment. The Lung Clearance Index (LCI) has been described as being more sensitive than spirometry in the early stages of some lung diseases. The aim of this study was to evaluate this index in a cohort of patients with a history of childhood cancer for the first time. Materials and Methods We evaluated 57 off-treatment CSs aged 0–18 years old and 50 healthy controls (HCs). We used the multiple breath washout (MBW) method to study LCI and spirometry. Results CSs did not show any differences from the controls in ventilation homogeneity (LCI 6.78 ± 1.35 vs. 6.32 ± 0.44, P: ns) or lung function (FEV1 99.9 ± 11.3% vs. 103.0 ± 5.9% of predicted, P: ns; FVC 98.2 ± 10.3% vs. 101.1 ± 3.3% of predicted). LCI significantly correlated with the number of years since the last chemotherapy ($r = 0.35$, $P < 0.05$). Conclusions Our study describes the trend of LCI in a cohort of CSs and compares it with the results obtained from healthy controls. The results show that patients maintain both good values of respiratory function and good homogeneity of ventilation during childhood. Moreover, the LCI identifies the tendency toward pulmonary fibrosis, which is typical of adult CSs, at an earlier time than spirometry.

Lung clearance index: a new measure of late lung complications of cancer therapy in children

Authors:

Giuseppe Fabio Parisi[1*] MD, Emanuela Cannata[2] MD, PhD, Sara Manti[1] MD, PhD, Maria Papale[1] MD, Mariaclaudia Meli[2] MD, Giovanna Russo[2] MD, PhD, Andrea Di Cataldo[2] MD, PhD, Salvatore Leonardi[1] MD, PhD.

Affiliations:

[1] Pediatric Pulmonology Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy.

[2] Pediatric Hemato-Oncology Unit, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

***Corresponding author:**

Dr. Giuseppe Fabio Parisi MD

Department of Clinical and Experimental Medicine,

University of Catania, Catania, Italy

Via Santa Sofia, 78 – 95123 Catania (Italy)

Tel: +390954794181. Fax +390954794176

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Email: *gf.parisi@policlinico.unict.it*

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Short title: LCI in childhood cancer survivors

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ASTRACT

Introduction

Childhood cancer survivors (CSs) might face an increased lifelong risk of lung function impairment. The Lung Clearance Index (LCI) has been described as being more sensitive than spirometry in the early stages of some lung diseases. The aim of this study was to evaluate this index in a cohort of patients with a history of childhood cancer for the first time.

Materials and Methods

We evaluated 57 off-treatment CSs aged 0–18 years old and 50 healthy controls (HCs). We used the multiple breath washout (MBW) method to study LCI and spirometry.

Results

CSs did not show any differences from the controls in ventilation homogeneity (LCI 6.78 $\pm$ 1.35 vs. 6.32 $\pm$ 0.44, P: ns) or lung function (FEV1 99.9 $\pm$ 11.3% vs. 103.0 $\pm$ 5.9% of predicted, P: ns; FVC 98.2 $\pm$ 10.3% vs. 101.1 $\pm$ 3.3% of predicted). LCI significantly correlated with the number of years since the last chemotherapy ($r = 0.35$, $P < 0.05$).

Conclusions

Our study describes the trend of LCI in a cohort of CSs and compares it with the results obtained from healthy controls. The results show that patients maintain both good values of respiratory function and good homogeneity of ventilation during childhood. Moreover, the LCI identifies the tendency toward pulmonary fibrosis, which is typical of adult CSs, at an earlier time than spirometry.

Introduction

In recent years, the improvement of diagnostic techniques and therapeutic strategies has led to an increase in the number of pediatric cancer survivors (CSs). The latest data show that more than three-quarters of children diagnosed with malignancy survive 5 years after diagnosis, and 1 in 600 young adults are estimated to be pediatric CSs in Western countries. In the face of improved survival, a downside is the complications that childhood CSs might experience as a result of the same life-saving treatments. In fact, the treatment-related complications represent one of the main causes of morbidity, they have a strong impact on the quality of life, and they predispose CSs to higher mortality in adulthood [1].

Pulmonary complications in children with malignant neoplasms can be distinguished as acute (if they occur during treatment) or as late. Different causes related to both the neoplasm itself and the treatment are recognized. Regarding acute complications, infections are the most common cause of lung damage. The use of cytotoxic and immunosuppressive drugs alters the body's innate and adaptive physiological defense mechanisms, and it frequently causes neutropenia, a type of cell-mediated and humoral immunity deficiency [2].

Long-term complications are the result of lung surgery, mediastinal radiation therapy, the immune phenomena following the transplantation of hematopoietic cells (HCT), and chemotherapy drugs (where provided) [3]. For these reasons, the Children's Oncology Group (COG) developed the COG Long-Term Follow-Up

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(COG-LTFU) Guidelines to identify risk categories for patients who have undergone cancer treatment and thus establish the stages of follow-up. Regarding respiratory complications, follow-up is recommended for patients who have been treated with bleomycin, busulfan, nitrosoureas, chest irradiation, or allogenic HCT with chronic graft versus host disease, if associated with chest X-ray abnormalities (scarring of pulmonary parenchyma or pleura) or impairment in lung function (Forced Expiratory Volume in 1 second, FEV1, $<$ 80% of predicted, Forced Vital Capacity, FVC, $<$ 80% of predicted, Total Lung Capacity $<$ 80% of predicted, or Diffusing Capacity of the Lungs for Carbon Monoxide, DLCO, $<$ 80% of predicted).

As for the other categories of patients, no specific recommendations are given [4]. However, more recently, cyclophosphamide has also been reported as toxic to the lungs. This drug is widely used in the treatment of Acute Lymphoblastic Leukemia (ALL), the most common type of pediatric tumor [5]. Conventional spirometry is considered the main examination method for respiratory function to evaluate the degree of any obstructive or restrictive deficit. However, there is growing evidence that conventional spirometry is insensitive when detecting early damage to the small airways and assessing the distribution of ventilation. This response has also been described in many other pathologies, such as cystic fibrosis. In this context, there is growing interest in gas dilution techniques, especially multiple breath-washout (MBW), for the evaluation of peripheral airway function and to evaluate the possible inhomogeneity of ventilation [6, 7].

The MBW technique was used for the first time more than half a century ago but was set aside for many decades until recently. It has returned to the fore in the field of pediatric pulmonology as an essential exam to obtain the Lung Clearance Index (LCI). High LCI values are an expression of ventilatory inhomogeneity reflecting damage to the small airways. Furthermore, since tidal breathing is sufficient for the examination, it can be performed on uncooperative children [8, 9]. Several studies have evaluated respiratory complications in childhood CSs with conventional spirometry, but to our knowledge, there are no studies on LCI in this cohort of patients. The aim of our study was to evaluate this index in a cohort of patients with a history of childhood cancer who do not belong to only the categories defined as at risk. We also compared them to a group of healthy controls of the same age. The findings could indicate whether this approach offers any information beyond that obtained by conventional spirometry.

1. **Materials and Methods**
2. *Study design and participants*

We designed a case-control study in which child CSs were compared with healthy controls (HCs). This study is part of a departmental project of the University of Catania, Department of Clinical and Experimental Medicine, with the aim of studying the long-term complications of chemotherapy and radiotherapy in patients who have recovered from cancers diagnosed in the pediatric age range. CSs (0–18 years old) were recruited from the Pediatric Hemato-Oncology Unit at the Polyclinic University Hospital of Catania, Italy. All children had a history of pediatric cancer, undergoing chemotherapy, or radiotherapy treatment.

The eligibility criteria included an interval time of at least 1 year from the end of the cancer treatment. The exclusion criteria included prematurity, congenital heart disease, other chronic lung diseases, and smoking. All these patients usually undergo one spirometry session per year at our Pediatric Bronchopneumology Unit of the hospital. To carry out this study, we also performed the MBW test in addition to conventional spirometry. Frequency-matched HCs for sex and age with no history of cancer were recruited from the general population. The study has been approved by the local committee for clinical investigations, and informed consent was obtained from all parents of participants.

2.2 Clinical and pulmonary function evaluation

A physician collected the medical history and performed a detailed physical examination of the study participants. The medical history included the type of cancer, date of diagnosis, type of treatment, date of suspension of treatment, and any respiratory symptoms. Subsequently, MBW and then the conventional spirometry were performed (always in that order).

MBW testing was performed during relaxed and stable tidal breathing using the Exhalyzer D (EcoMedics

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AG, Duernten, Switzerland) and an inert intrinsic gas (nitrogen). All subjects underwent the test until the test gas reached $1/40^{th}$ of the initial gas concentration to obtain the LCI value. Testing was performed in triplicate, and the mean LCI is reported from a minimum of two (but aiming for three) technically acceptable tests [10-12]. LCI was analyzed as both raw scales and z-scores calculated based on published reference equations [13]. Spirometry was performed in the laboratory according to ERS/ATS guidelines [14, 15]. The best spirometric measure of at least three attempts was recorded for the analysis. FEV1 and FVC were expressed as a percentage of predicted values and z-scores using the GLI equations [16].

Statistical analysis

Statistical analyses were performed with the software Graph Pad Prism version 8.3.0. CSs and HCs were matched by sex, age, and height. Subjects' characteristics are presented as the median (interquartile range) for continuous variables or a frequency for categorical variables. Comparisons between groups were calculated using the student t-test or Mann-Whitney U test for continuous variables, while Fisher's exact test was used for categorical variables. The degree of association was determined by applying a linear regression model and calculating the Pearson correlation coefficient (r). P-values < 0.05 were considered to be significant.

Results

The baseline clinical characteristics of the study subjects are summarized in **Table 1** . We enrolled 57 off-treatment CSs and 50 HCs matched for sex, age, and height. Three CSs and two HCs were also asthmatic. Among the patients with a history of cancer, those with a history of ALL were the most common (n = 38, 67%), followed by four (7%) patients with a history of Acute Myeloid Leukemia (AML). 15 (26%) patients had solid tumors (**Figure 1**). The median age at diagnosis was 3.2 years, and the median number of years since the last treatment was 6.2 years. Cyclophosphamide was the most frequently used chemotherapeutic agent (**Table 2**).

Compared with HCs, CSs' mean LCI values were 0.46 units higher (95% confidence interval (CI): 0.06–0.85), and their z-scores were 0.003774 units higher (95% CI: 0.000160–0.007388). However, these differences were not statistically significant. For conventional spirometry, we observed that CSs maintained good levels of respiratory function indices in comparison with HCs (**Table 3**).

Next, we assessed whether there was a correlation between the respiratory function indices and the years since the last chemotherapy session. To make the sample homogeneous, we only considered patients with ALL as having undergone similar treatment. In these patients, we observed that the LCI z-scores were closely related to the years that had passed since the end of chemotherapy treatment ($r = 0.35$, $P < 0.05$, **Figure 2**). This correlation was not shown for conventional respiratory function indices, such as FEV1 ($r = 0.16$, P = not significant (ns)) and FVC ($r = 0.20$, $P = 0.23$, **Figure 3**).

Discussion

The results of our study show that off-treatment CSs maintain good respiratory function values during childhood according to conventional spirometry and the LCI, which is a sensitive index of damage to the small airways. The respiratory function values obtained in both methods (MBW and spirometry) were comparable to those of healthy subjects. With regard to drug-induced respiratory complications, the most frequent clinical conditions described in CSs in the literature are hypersensitivity pneumonia, pulmonary edema, pulmonary hypertension, pleural effusions, pulmonary veno-occlusive disease (VOD), restrictive diseases, and obstructive pulmonary diseases [17, 18].

Among these complications, the most frequent clinical presentation is Drug-induced Interstitial Lung Disease (DILD) [17]. Although this pathological condition occurs in a minority of subjects treated with anticancer drugs, it can evolve towards severe respiratory insufficiency and acute respiratory distress syndrome. From a histopathological [19] and radiographic [20, 21] profile, DILD can present in various ways, such as diffuse alveolar damage, chronic interstitial pneumonia, eosinophilic pneumonia, hypersensitivity pneumonia, and granulomatous pulmonary disease. The two main etiopathogenetic factors responsible for lung damage from

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drugs are direct lung toxicity mechanisms (production of reactive oxygen species, reduction of inactivation of metabolites in the lungs, and the same drugs) and immune-mediated mechanisms [17, 22].

Several chemotherapeutic agents have toxic effects on the lungs. These include bleomycin, a drug used in therapy for Hodgkin lymphomas and germ cell tumors. This drug accumulates in the lungs due to the reduced presence of the enzyme that performs detoxification in these organs. Pneumonia induced by this drug is a serious and often fatal complication. Pulmonary fibrosis is actually rare in children, whose bleomycin dosages are lower than in adults. Obstructive airway diseases and pulmonary hyperinflation are more frequently observed but are symptomatic in only a minority of patients [23, 24].

Another drug that is believed to be toxic to the lungs is cyclophosphamide, one of the most common alkylating agents in the treatment of pediatric tumors. It is also frequently used in preparatory regimens for hematopoietic cell transplantation. Cyclophosphamide is responsible for interstitial pneumonia (early onset), which can evolve into pulmonary fibrosis (late complication) [5]. Also, for busulfan and nitrosoureas (carmustine and lomustine), there is a possibility of conditions similar to those previously described [1].

Most of the follow-up studies of such patients have assessed the onset of respiratory complications in only categories of at-risk patients defined by the COG-LTFU guidelines (i.e., patients who have undergone treatment with thoracic radiation therapy, thoracic surgery, HCT, busulfan, bleomycin, and nitrosoureas) [4]. In such patients, studies have shown a percentage of lung complications varying between 45% and 85% [25-29]. Mulder et al. identified restrictive lung disease in patients treated with radiation only, bleomycin and radiation, and radiation with surgery and compared them to those treated with bleomycin only [25]. Landier et al. studied 370 childhood CSs and applied the COG-LTFU guidelines to identify patients at risk for pulmonary complications, of which 84% experienced lung complications over the years [26].

A report from the St. Jude Lifetime Cohort Study on 1713 adult survivors of childhood cancer showed that 65.2% have abnormalities in pulmonary function among survivors exposed to pulmonary-toxic cancer treatments. The highest prevalence occurred among those treated with lung radiation (74.4%), followed by those treated with bleomycin (73.3%) and thoracotomy (53.2%) [27]. In a study by Armenian et al., the percentage of patients in the risk category for lung complications experienced restrictive dysfunctions in 45% of cases [28]. The Childhood Cancer Survivor Study (CCSS) published in 2016 reported a cumulative incidence of pulmonary symptoms (chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia) of 29.6% among a population of 14,316 CSs at 45 years of age (vs. 26.5% in siblings) [29].

In our patient series, few belonged to the risk categories since few patients had undergone treatments known to be associated with pulmonary complications. There is an exception with cyclophosphamide, however, which instead represents one of the main treatments of ALL and was associated with neoplasm occurring more frequently in our case history. In this regard, studies that have assessed respiratory complications in patients with a history of ALL are mainly dated and thus involve patients undergoing chemotherapy regimens with different drugs than those used today.

In 1998, Nysom et al. studied 94 survivors of ALL and showed that several of their participants had a subclinical, restrictive ventilatory insufficiency or restrictive flow-volume curve patterns [30]. Previously, in a study by Miller et al. on 15 patients with a history of ALL, 48% had lung function abnormalities [31]. Jenney et al. demonstrated that at a median of 6 years after diagnosis among 70 survivors of childhood ALL, more than 50% had lower lung volumes and impaired maximal exercise capacity [32].

The strength of our study is that it evaluated not only patients at risk but all patients with a history of cancer for the first time. Furthermore, a more sophisticated method, MBW, was used and allowed for the study of the LCI. These data suggest that the chemotherapeutic agents used in the treatment of tumors previously analyzed have less toxicity than expected, at least in childhood. Furthermore, this study allowed for validation of the MBW method in this category of patients since it can also be carried out on preschool children who have difficulties performing the forced expiratory maneuvers, unlike traditional spirometry.

Also, the LCI study showed that this index increases and worsens as the years pass after the end of the

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treatment. This correlation is not evident with conventional spirometry and probably expresses a greater sensitivity than MBW in identifying lung damage, albeit minimal, for small airways 5-6 years after the end of treatment. In this age range, the degeneration to pulmonary fibrosis becomes more evident.

Conclusions

Our study described the trend of LCI in a variegated cohort of off-treatment cancer survivors and compared it with the results obtained from HCs. The results showed that patients maintain good values of respiratory function and good homogeneity of ventilation during childhood. However, the LCI identifies the tendency towards pulmonary fibrosis, which is typical of adult CSs, at an earlier time than spirometry.

Our study also assessed not only classically defined at-risk patients but all cancer patients, including those with previous ALL treated with cyclophosphamide, a drug for which toxic effects of the lungs have been were described but not included in the list of COG-LTFU guidelines. Finally, the study allowed for the validation of MBW for the calculation of the LCI in these patients since it can also be performed on preschool patients who are unable to perform forced expiratory maneuvers, unlike conventional spirometry.

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Authors' contributions: GFP, ADC, and SL conceived the study. GFP, EC, SM, MP, MM, GR, ADC, and SL designed the study. GFP, EC, and MP collected data. GFP, EC, and SM analyzed the data. All authors contributed to data interpretation, drafting, critical review, and final approval of the manuscript and are accountable for the accuracy and integrity of the results.

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