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Cumulative radiation dose after lung transplantation in patients with cystic fibrosis

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KEYWORDS
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Effective dose

Abstract
Purpose: The purpose of this study was first to evaluate the imaging-related cumulative post-transplantation radiation dose in cystic fibrosis (CF) lung transplantation (LT) recipients and second, to identify the occurrence and type of malignancies observed after LT.
Materials and methods: A total of 52 patients with CF who underwent LT at our institution between January 2001 and December 2006 with at least 3 years of survival were retrospectively included. There were 27 men and 25 women with a mean age of 24.4 ± 9.2 (SD) years (range: 7.6—52.9 years) at the time of LT. Calculation of cumulative effective and organ doses after LT were based on dosimetry information and acquisition parameters of each examination. Cumulative radiation doses were calculated until June 2016, but stopped at the time of *de novo* malignancy diagnosis, for patients developing the condition.
Results: Patients received a mean cumulative effective dose of 110.0 ± 51.6 (SD) mSv (range: 13—261.3 mSv) over a mean follow-up of 8.1 ± 3.6 (SD) years (range: 0.5—13.5 years), with more than 100mSv in 5 years in 19/52 patients (37%). Chest CT accounted for 73% of the cumulative effective dose. Mean doses to the lung, breast and thyroid were 152.8 ± 61.1 (SD) mGy

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(range: 21.2—331.6 mGy), 106.5 ± 43.2 (SD) mGy (range: 11.9—221.4 mGy) and 72.7 ± 31.8 (SD) mGy (range: 9.5—165.0 mGy), respectively. Nine out of 52 patients (17%) developed a total of 10 *de novo* malignancies, all but one attributable to immunosuppression after a mean post-transplantation follow-up period of 11.1 ± 3.5 (SD) years (range: 3.7—16.3 years). Six-month cumulative effective dose was not greater in patients with *de novo*malignancies than in those without *de novo*malignancies (28.9 ± 14.5 (SD) mGy (range: 13.0—53.4) vs 25.6 ± 15.3 (range: 5.0—69.7), respectively, $P > 0.05$).

Conclusion: The cumulative effective dose exceeded 100 mSv in 5 years in 37% of LT recipients, the reason why continuous efforts should be made to optimize chest CT acquisitions accounting for 73% of the radiation dose.

Lung transplantation (LT) improves survival in patients with diseases that cause terminal respiratory insufficiency, such as cystic fibrosis (CF). Since the first LT in human, LT recipients survival has significantly improved [1,2]. The long-term outcome in these patients is related to complications including infections, chronic allograft rejection, and a high proportion of de novo malignancies [2]. According to the International Society for Heart and Lung Transplantation (ISHLT) registry including a total of 55,795 adults who underwent LT, the incidence of malignancy among survivors was 23% and 42% at 5- and 10-years post-transplantation, respectively [2]. The increased risk of malignancy in transplant recipients is mainly due to immunosuppression and oncogenic viral infections [3]. LT recipients are exposed to high postoperative radiation doses because repeated imaging procedures with ionizing radiations are required to detect both short- and long-term complications. Although radiation exposure potentially increases the risk of malignancy, only one published study has evaluated its influence on the occurrence of malignancy in LT recipients and did not find any significant association, possibly because of a lack of power [4].

Worldwide, CF represents 16% of primary indications for single or bilateral LT in the ISHLT database [2]. In France, the proportion is around 25%, thus not representing the majority of LT [5]. However, evaluating CF LT recipients seems appropriate in view of their younger age, making them more sensitive to the effects of radiation, and usually lack of smoking history, which could be a confounding factor. Indeed, there was an increased risk of solid cancer associated with decreasing age in Hiroshima and Nagasaki atomic bomb survivors [6]. When studying radiation exposure due to computed tomography (CT) examinations in childhood or adolescence, Pearce et al. found a positive association between radiation from CT and leukemia and brain tumors in 178,604 patients [7]. Similarly, Matthews et al. found an overall excess incidence rate of malignancy following exposure to CT radiation in childhood or adolescence in 680,211 patients [8].

The purpose of this study was first to evaluate the imaging-related cumulative post-transplantation radiation dose in CF LT recipients and second, to identify the occurrence and type of malignancies observed after LT.

Materials and methods

Patients

The Institutional Review Board of the French Society for Respiratory Medicine (*Société de pneumologie de langue française*) approved the study (CEPRO 2017-030). The need for individual consent was waived due to the retrospective design. All patients with CF who had undergone LT, alone or in combination with other organ transplants at the Hôpital Européen Georges-Pompidou, between January 2001 and December 2006, were eligible. Fifty-two patients who survived for at least 3 years were included. Patient charts were analyzed for age at transplantation to distinguish between adult and younger (<18 years) patients, type of transplantation, smoking history, and the occurrence of de novo malignancies. Follow-up for the development of malignancies was continued until June 2016. There were 27 men and 25 women with a mean age of 24.4 ± 9.2 (SD) years (range: 7.6—52.9 years) at the time of LT. Eleven patients were < 18 year-old at the time of LT. All 52 patients had a double-LT and 5 of them had a concomitant liver transplantation. All patients except one were lifetime non-smokers. Three patients underwent a second LT and 16 patients died during the follow-up period, all more than 3 years after initial LT according to our inclusion criteria. None of the patients were lost to follow-up.

Imaging procedures

The standard imaging follow-up protocol after LT included a daily postoperative chest X-ray (CXR) and at each visit after discharge. Chest CT was systematically performed within 48 hours after LT, then depending upon the clinical progress. CT examinations were performed on a 4-slice CT unit (SOMATOM® Plus, Siemens Healthineers) without dose modulation before August 2005, and then on 64-detector units (LightSpeed™VCT, General-Electric Healthcare) using automated mA with a noise index of 42 for thoracic CT. Abdominal CT protocols were more heterogeneous in terms of acquisition parameters. Other examinations with ionizing radiation such as ventilation/perfusion lung scan (V/Q scan)

to evaluate the functional status of the lung and positron emission tomography (PET)-CT or mammograms were performed when needed.

Cumulative radiation dose calculation

All diagnostic imaging procedures with ionizing radiation performed at our institution between the day of LT until June 2016 were retrieved for each patient from our picture archiving and communicating system. Dosimetry information and acquisition protocols were retrieved for each examination as described below.

For CXR and mammograms, X-ray beam size, peak tube voltage, X-ray source filtration, X-ray tube anode angle, projection angle and source to image receptor distance as input beam parameters were analyzed for dose calculation. The two-dimensional mammography equipment (Senographe DMR Mammography Unit, General-Electric Healthcare) included a molybdenum anode filtered with molybdenum or rhodium. Effective and organ doses were estimated using PCXMC 1.5 software (STUK), which is a Monte Carlo-based program. This program calculates effective and organ doses based on tissue weighting factors of the International Commission on Radiological Protection (ICRP) Publication 103 [9]. The anatomical data are based on the mathematical hermaphrodite phantom models of Cristy and Eckerman, which describe patients of six different ages: newborn, 1, 5, 10, 15 years old and adult patients. In our study, the phantom sizes were adjusted to mimic patients according to their age, gender, weight and height. Bedside CXR were distinguished from upright CXR to separate antero-posterior acquisitions from postero-anterior with lateral acquisitions.

For CT, tube voltage and current, rotation time, pitch factor, image slice thickness, scan length, number of scan series, spiral mode and dose-length-product. These parameters and ICRP-defined tissue weighting were used to calculate individual effective and organ doses with CT-expo (version1.7.1; Medizinische Hochschule). This Microsoft Excel application is dedicated to patient CT dose calculation based on standard anthropomorphic phantoms, including male (ADAM) and female (EVA) adults based on the ICRP 103 [9]. Dose calculations were performed for all age groups and according to the gender.

For ventilation/perfusion (V/Q) scans and positron emission tomography (PET): effective and organ doses were calculated using dose coefficients of per unit administered radionuclide activity from the ICRP [10—12]. These calculations were based on biokinetic data and mathematical medical internal radiation dose phantoms proposed by Cristy and Eckerman [13].

Cumulative effective dose (CED) and organ doses were calculated by summing the doses of all procedures for each patient, from the day of transplantation. The medical physicist of the radiology department performed all dosimetry calculations. Dose calculations stopped when the first de novo malignancy was diagnosed. Six-month and 3-year doses were also calculated, and 6-month doses were compared for patients with and without de novo malignancy.

CED was also estimated according to the method proposed by Rosengarten et al. [4]. Briefly, the number of ionizing procedures was multiplied by the corresponding published reference effective dose: 0.1mSv for CXR, 7mSv for chest CT, 8mSV for abdominal CT, 2.5mSv for V/Q scans, 14.1mSv for PET and 0.4mSv for mammogram [4,14]. Thus, calculated and estimated CED were available for each patient.

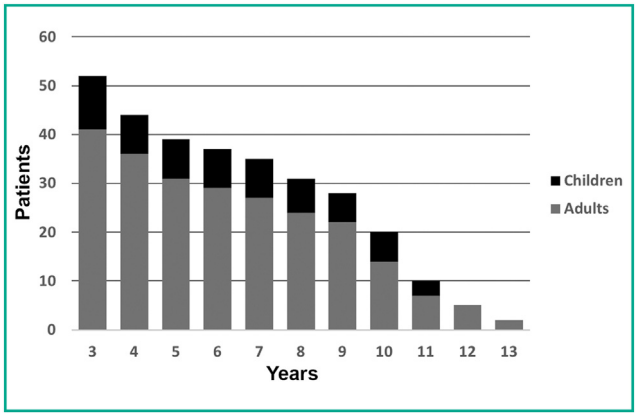

Figure 1. Diagram shows follow-up time for dose calculation in adult and young patients. CT: computed tomography; CXR: chest X-ray; PET: positron emission tomography; V/Q scan: ventilation/perfusion scan.

Statistical analysis

Statistical analysis was performed using 'R' software (version 3.3.3, R Foundation, Vienna, Austria). Calculated CED and CED estimated by the Rosengarten et al. method were compared using a paired *t*-test. Patient characteristics, 6-month CED and organ doses were compared in patients with and without de novo malignancy using the Student's *t*-test. A P value < 0.05 was considered to indicate statistically significant difference. Quantitative data were expressed as mean $\pm$ standard deviation (SD) and range. Qualitative data were expressed as raw numbers, proportions and percentages.

Results

Cumulative effective and organ doses

Mean follow-up duration for the calculation of cumulative radiation dose was 8.1 ± 3.6 (SD) years (range: 0.5—13.5 years) in the whole population. This duration was not statistically different between adult (7.6 ± 4.6 (SD) years; range: 0.5—11.8 years) and young patients (8.2 ± 3.3 (SD) years; range: 0.8—13.5 years) ($P = 0.72$) (Fig. 1). During this period, each patient underwent a mean number of 56.5 ± 50.3 (SD) bedside CXR (range: 15—305 examinations), 37.8 ± 21.9 (SD) upright CXR (range: 8—93 examinations) and 24.4 ± 10.6 (SD) chest CT examinations (range: 5—56 examinations) (Table 1). Of the 52 included patients, 49/52 (94%) also underwent a V/Q scan and 29/52 (56%) underwent abdominal CT examination and 9/52 (17%) and 1/52 (2%) 18F-f.luorodeoxyglucose PET-CT and mammogram, respectively.

At the end of dose follow-up, the mean calculated CED was 110.0 ± 51.6 (SD) mSv (range: 13—261.3 mSv) for the

Table 1 Ionizing radiation procedures, effective and organ doses after lung transplantation in 52 patients with cystic fibrosis.

Examination	Number of patients (%)	Mean number of examinations	Mean estimated CED* (mSv)	Mean calculated CED (mSv)	Mean dose to the lung (mGy)	Mean dose to the breast (mGy)	Mean dose to the thyroid (mGy)
Bedside CXR	52 (100)	56.5 ± 50.3 [15—305]	5.6 ± 5.0 [1.5—30.5]	1.5 ± 1.3 [0.2—7.9]	2.3 ± 2.0 [0.4—12.2]	5.0 ± 4.5 [1.4—27.5]	2.8 ± 2.5 [0.5—15.3]
Upright CXR	52 (100)	37.8 ± 21.9 [8—93]	3.8 ± 2.2 [0.8—9.3]	1.9 ± 1.1 [0.6—4.7]	1.5 ± 0.9 [0.3—3.7]	0.4 ± 0.2 [0.1—0.9]	0.4 ± 0.2 [0.1—0.9]
Chest CT	52 (100)	24.4 ± 10.6 [5—56]	170.8 ± 74.2 [35—392]	80.5 ± 47.6 [6.3—227.3]	77.1 ± 34.5 [16.0—179.2]	78.1 ± 34.9 [16.2—181.4]	66.3 ± 29.6 [13.8—154.0]
V/Q scan	49 (94)	3.8 ± 2.3 [0—9]	9.5 ± 5.75 [0—22.5]	8.5 ± 5.3 [0—21.9]	54.4 ± 33.5 [0—129.3]	21.8 ± 13.4 [0—51.8]	2.5 ± 1.5 [0—5.9]
Abdominal CT	29 (56)	1.6 ± 2.0 [0—7]	12.8 ± 16 [0—56.0]	16.3 ± 21.6 [0—73.0]	16.1.0 ± 20.0 [0—71.4]	0 [0—0]	0 [0—0]
PET-CT	9 (17)	0.2 ± 0.5 [0—2]	2.8 ± 7.0 [0—28.2]	1.1 ± 3.5 [0—22.2]	1.1 ± 3.2 [0—14.4]	0.7 ± 1.9 [0—10.1]	0.6 ± 1.8 [0—11.7]
Mammogram	1 (2)	0.1 ± 0.6 [0—4]	0.0 ± 0.2 [0—1.6]	0.1 ± 0.7 [0—5.0]	0 [0—0]	0.2 ± 1.4 [0—10.4]	0 [0—0]
Total	52 (100)	123.2 ± 72.1 [45—409]	205.4 ± 86.0 [37.3—540.1]	110.0 ± 51.6 [13—261.3]	152.8 ± 61.1 [21.2—331.6]	106.5 ± 43.2 [11.9—221.4]	72.7 ± 31.8 [9.5—165.0]

CED: cumulative effective dose; CT: computed tomography; CXR: chest X-ray; PET: positron emission tomography; V/Q scan: ventilation/perfusion scan. Data are presented as mean ± standard deviation and range between brackets, or number of patients with percentages in parentheses.

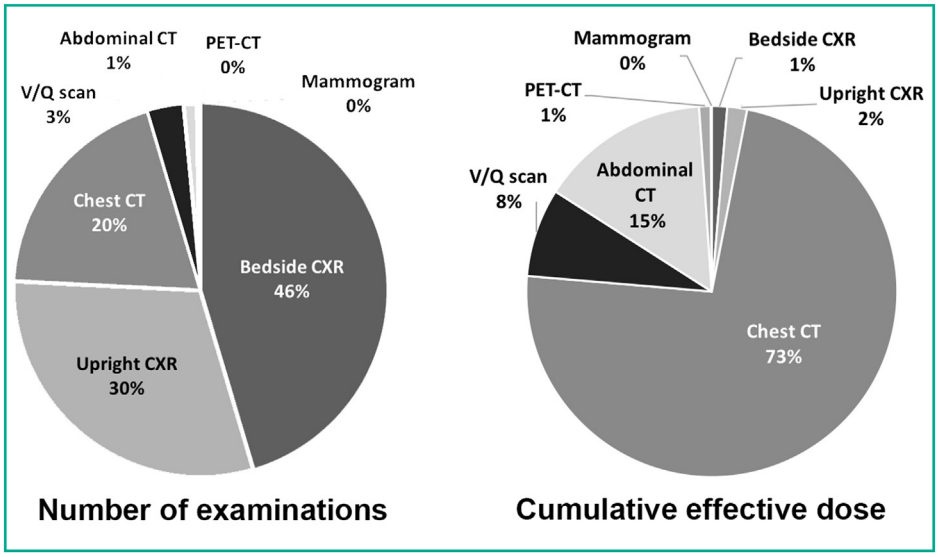

Figure 2. Pie charts show the respective proportions of each imaging modality in the total number of examinations and in the cumulative effective dose. CT: computed tomography; CXR: chest X-ray; PET: positron emission tomography; V/Q scan: ventilation/perfusion scan.

whole study population. Mean doses to the lung, breast and thyroid are given in Table 1. No differences in mean calculated CED were found between young (109.6 ± 69.8 (SD) mSv [range: 13—261.3 mSv]) and adult (110.1 ± 46.6 (SD) mSv [range: 31.4—241.7 mSv] patients ($P = 0.98$). No differences in mean doses to the lung, breast and thyroid were found between young patients (158.8 ± 76 (SD) mGy [range: 21.1—270.7 mGy]; 110.5 ± 56.8 (SD) mGy [range: 11.9—190.3 mGy]; 76.5 ± 41.4 (SD) mGy [range: 9.5—134.5 mGy], respectively) and adult patients (151.1 ± 57.4 (SD) mGy [range: 35.2—331.6 mGy]; 105.4 ± 39.7 (SD) mGy [range: 26.6—221.4 mGy]; 71.7 ± 29.3 (SD) mGy [range: 21.5—165.0 mGy)], respectively) ($P = 0.76$; 0.78 and 0.72, respectively).

CED exceeded 100mSv in 19/52 patients (37%) after less than 5 years, including one child. While most imaging procedures were bedside (57/123; 46%) or upright (24/123; 30%) CXR, chest CT accounted for 73% of the CED (80.5/110 mSv) (Fig. 2). V/Q scan, bedside and upright CXR accounted for 8% (8.5/110mSv), 1% (1.5/110 mSv) and 2% (1.9/110 mSv) of the CED, respectively. Most radiation exposure occurred within the first six months after LT resulting in a mean CED of 26.5 ± 15.1 (SD) mSv (range: 5.0—69.7 mSv) compared to only 6.0 ± 2.5 (SD) mSv (range: 0—23.5 mSv) for each of the next 6-month periods (Fig. 3). Mean 6-month and 3-year CED were 26.5 ± 15.1 (SD) mSv (range: 5.0—69.7 mSv) and 65.8 ± 26.3 (SD) mSv (range: 9.9—123.6 mSv), respectively.

Mean CED at the end of dose follow-up would have been significantly higher, by nearly two times, if estimated according to methodology used by Rosengarten et al. [4]: 205.4 ± 86.0 (SD) mSv (range: 47—489.1 mSv) vs 110.0 ± 51.6 (SD) mSv (range: 13—261.3 mSv); $P < 0.001$)) (Table 1).

De novo malignancies

The median follow-up for de novo malignancies occurrence was 11.1 ± 3.5 (SD) years (range: 3.7—16.3 years). Nine patients ($n = 9/52$; 17%) developed a total of 10 de novo malignancies (Table 2). None of the patients developed breast or thyroid cancer. There were 2 skin cancers, 3 non-skin carcinomas (1 lung and 2 colon cancers) and 5 lymphoproliferative disorders (3 observed in children), including 3 Epstein-Barr Virus (EBV)-related lymphomas. The mean interval between LT and the diagnosis of cancer was 4.1 ± 3.8 (SD) years. All lymphomas developed within the first 2 years after LT, while other malignancies developed later.

No significant differences in patient characteristics, or 6-month CED and organ doses were found between patients with de novo malignancies and those without de novo malignancies (Table 3). The dose to the lung in the patient who developed a lung adenocarcinoma was 87.1 mGy at 3 years, compared to a mean dose of 89.7 ± 28.4 (SD) mGy (range: 21.1—186.2 mGy) in the remaining cohort. Neither the patient nor the donor in our study had a history of smoking. A pT3 TTF1+ wild-type lung adenocarcinoma was diagnosed after wedge resection, invading the parietal pleura.

Discussion

In this study we have reported the calculated radiation exposure per organ following LT in patients with CF. We found that the mean post-transplantation CED was 110 mSv and that chest CT accounted for 73% of the dose for all patients. Seventeen percent of the patients developed de novo malignancies, with no significant difference in characteristics or radiation dose as compared with malignancy-free patients.

Rosengarten et al. estimated the radiation exposure in LT recipients by multiplying the number of ionizing procedures by their corresponding published reference effective dose [4,9]. In our cohort, this method would have overestimated the mean CED by nearly two times. Limiting radiation dose exposure is essential in young patients who undergo repeated procedures [7,8], especially for CT examinations, which are pivotal imaging examinations to detect postoperative complications. Although up to 305 bedside CXR were

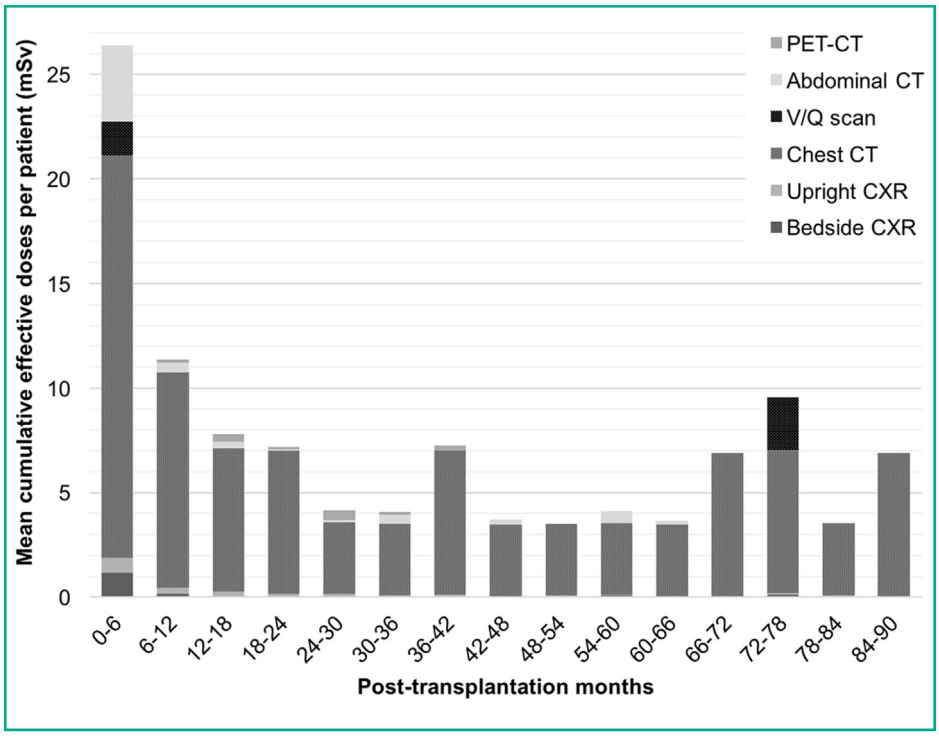

Figure 3. Diagram shows mean cumulative effective dose per patient per 6-month periods during follow-up after lung transplantation. CT: computed tomography; CXR: chest X-ray; PET: positron emission tomography; V/Q scan: ventilation/perfusion scan.

Table 2 De novo malignancies after lung transplantation in 9 out of 52 patients with cystic fibrosis.

Patients	Age at time of malignancy diagnosis (years)	Time between lung transplantation and malignancy (years)	Type of malignancy
1	7.9	0.5	LPD (EBV positive B lymphoma)
2	15.7	0.8	LPD (EBV positive B lymphoma)
3	21.2	0.8	LPD (B lymphoma)
4	17.0	1.0	LPD (MALT lymphoma)
5	21.9	1.7	LPD (EBV positive T lymphoma)
6	52.3	9.4	Bowen's disease
7	31.9	6.3	Basal-cell carcinoma
7	34.6	9.1	Lung adenocarcinoma
8	43.6	7.8	Adenocarcinoma of the colon
9	53.4	8.5	Adenocarcinoma of the colon

LPD: lymphoproliferative disorder; EBV: Epstein-Barr virus; MALT: mucosa-associated lymphoid tissue.

performed per patient, bedside CXR only accounted for 1% of the CED in our study.

Iterative reconstruction results in important dose savings for CT and was used to improve dose optimization when it became available at our institution. Debray et al. used iterative reconstruction for follow-up after LT, which resulted in a six-fold dose reduction [10].

Despite dose optimization, CED reached or exceeded the 100mSv limit at 5 years, the current occupational dose limit according to European Union recommendations, in 37% of our patients [11]. Even though these recommendations do not apply for patients, the Life Span Study (LSS) performed in atomic bomb survivors showed an increased relative risk of solid cancer for radiation doses above 100 mSv [6]. An increased incidence of solid cancer was found for most organs, but higher excess relative risks were observed for bladder, breast and lung cancers [6,12]. Radiation-associated hematopoietic malignancies mainly include leukemia as well as a significant increase in non-Hodgkin lymphoma in men [13]. However, the exposure time is not the same for atomic bomb survivors and for patients, thus the 100 mSv radiation dose might not induce the same cancer risks. The 17% malignancy rate in our population was slightly higher than the 12.5% reported by Moreno et al. in CF LT recipients [14], possibly because our population did not include patients who died early after LT, having less time to

Table 3 Risk factors for de novo malignancy.

Variable	Malignancy ($n=9$)	No malignancy ($n=43$)	*P* value
Age at time of LT	25.4 ± 13.1 [7.6–44.9]	24.2 ± 8.4 [8.1–43.9]	0.79
Male gender	3 (33)	24 (56)	0.28
Smoking history	1 (9)	0	0.17
Concomitant liver transplantation	1(9)	4 (9)	1
Overall dose follow-up duration (years)	4.1 ± 3.8 [0.9–9.4]	8.9 ± 3.0 [3.0–13.5]	0.004
6-month CED (mSv)	28.9 ± 14.5 [13.0–53.4]	25.6 ± 15.3 [5.0–69.7]	0.59
6-month dose to the lung (mGy)	43.3 ± 22.6 [21.2–96.3]	33.2 ± 13.5 [11.7–73.8]	0.23
6-month dose to the breast (mGy)	28.9 ± 12.1 [11.9–53.9]	26.3 ± 9.3 [14.5–54.3]	0.57
6-month dose to the thyroid (mGy)	19.4 ± 6.9 [9.5–30.1]	18.3 ± 6.7 [7.0–42.5]	0.65

CED: cumulative effective dose; LT: lung transplantation. Data are presented as mean ± standard deviation and range between brackets, or number of patients with percentages in parentheses.

develop malignancy. Moreover, the malignancies observed in our study were mainly attributable to immunosuppression. Fifty-six percent of malignancies were EBV-related lymphomas and skin cancers, both known to be favored by immunosuppression [3]. Due to the higher immunogenicity of the lung compared to other organs and a higher risk of rejection, lung transplant recipients tend to receive more aggressive immunosuppression than other solid organ transplant recipients [15]. Thus the reported incidence of cancer in LT recipients is higher than that in solid organ transplant recipients [16].

In our study, lung adenocarcinoma occurred in the donor lung in 1/52 patients (2%) 9 years after LT. Neither the patient nor the donor had a history of smoking. Lung cancer in LT patients usually occurs in the native lung of patients who undergo single LT [17,18]. Magruder et al. only identified 57 lung cancers (0.6%) in 10,297 patients who underwent bilateral LT, including at least 23 that were donor-attributed [19]. Extended lung donors and immunosuppression have been suggested as the main causes of lung cancer in the transplanted lung [17,20,21]. The average dose to the lung in this patient was similar to the values in the entire cohort, excluding radiation exposure, which is a reported risk factor for lung cancer, as the cause [6].

The remaining malignancies in our series, in particular the 2 cases of colorectal cancer, occurred outside the chest area, making radiation exposure an unlikely cause. An increased risk of colorectal cancer in CF lung recipients has been reported by Safaeian et al, who hypothesized that several factors may be involved, including epithelial changes related to the cystic fibrosis transmembrane conductance regulator gene mutation and the immunosuppressive regimen [22].

There are several limitations to our study. One relates to the small sample size. A cohort of 670 LT recipients would have been necessary to show a significant difference in 6-month CED between LT recipients who developed de novo malignancies and those who did not (expected difference = 3.3mSv, expected standard deviation = 15mSv, significance level = 0.05, statistical power = 0.90). The power of the study by Preston et al. was insufficient to detect a significantly increase risk for dose exposures below 100 mSv, even though more than 69,000 individuals were included [6]. Another limitation is that certain examinations may have been performed outside our institution and thus, not have been included in the dose calculation. However, like Rosengarten et al. [4], we found that most radiation exposure occurred during the immediate postoperative LT period, when patients are evaluated at the LT institution. Also we could not evaluate radiation dose before LT. Dose monitoring should become easier with recent specific dose-monitoring software tools [23]. The use of dedicated low dose protocols should reduce the dose given to patients with CF in the future [24]. Finally, we did not evaluate the influence of the immunosuppressive regimen on the development of malignancies, because it was outside the scope of this study.

In conclusion, CED exceeded the limit of 100mSv within 5 years in nearly 40% of our CF patients, with chest CT accounting for 73% of the cumulative dose. Thus, continuous efforts should be carried out to further reduce chest CT dose. This will be made possible by the development and validation of ultralow dose protocols, close to the dose of chest radiography [24].

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Disclosure of interest

The authors declare that they have no competing interest.

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