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Incidence, management, and outcome of lung cancer in patients with long-term oxygen therapy

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Abstract

Background: Here, we aimed to assess the specific features of lung cancer in patients with long-term oxygen therapy (LTOT), and compare their outcomes with patients suffering from lung cancer without LTOT.

Methods: This retrospective, case-controlled study included patients with LTOT and an incident diagnosis of lung cancer treated at Rouen University Hospital.

Results: Out of 2201 patients with LTOT, 31 were diagnosed with lung cancer. Among 24 patients with proven lung cancer, the most frequent histological type was squamous cell carcinoma ($n = 12/24$, 50%). Active treatment of any type was given in 19/31 (61%) and 41/62 (66%) of patients in the LTOT and control groups, respectively ($p = 0.83$). In the LTOT group, median survival was 38 days with best supportive care and 462 days with active treatment ($p = 0.003$). However, when adjusting on performance status and disease stage, LTOT was not significantly associated with a worse outcome. Hazard ratio (HR): 1.56 (95% confidence interval [CI]: 0.87 to 2.81) ($p = 0.137$). Administration of any treatment was associated with a better prognostic: HR: 0.35 (95% CI: 0.19 to 0.66). Both groups had a similar treatment safety profile.

Conclusion: Incidence of lung cancer in patients with LTOT was comparable to the general population. The proportion of LTOT patients who received active treatment was similar to controls, and overall survival did not differ from controls in a multivariate analysis. Although reaching a histological diagnosis may be challenging in LTOT patients, the efficacy and safety of the management strategies of lung cancer seem preserved.

KEYWORDS
best supportive care, long-term oxygen therapy, lung cancer, stereotactic radiotherapy

INTRODUCTION

Chronic respiratory failure (CRF) and lung cancer are associated with high mortality.[1–3] Both are favored by tobacco exposure. CRF may also favor the development of lung cancer by various physiopathological mechanisms such as inflammation, parenchymal destruction or nocturnal hypoxemia.[4–7] Histological diagnosis of lung cancer in patients with CRF treated

by long-term oxygen therapy (LTOT) is more challenging. For instance, bronchoscopies are at higher risk of complication in patients with CRF,[8] and CT-guided percutaneous core needle biopsies are associated with a higher risk of pneumothorax.[9] These risks matter given the ongoing development of lung cancer screening programs, for which peripheral lung nodules are the most common finding.[10] Therefore, to date, no specific recommendation has been made regarding lung cancer screening in patients with LTOT.[11] Management of lung cancer in patients with LTOT is also more difficult. First, patients with LTOT and early-stage cancer are less likely to have surgical resection given a higher postoperative risk.[12–14] Chemotherapy is also less likely to be administered owing to a poorer functional status.[15] Also, patients with LTOT caused by interstitial lung disease are at a higher risk of severe radiation pneumonitis.[16] Finally, given their tobacco exposure, patients with LTOT are less likely to harbor actionable oncogenic driver alterations such as *EGFR* mutation and ALK/ROS1 translocations.[17]

Despite these particularities, there is very few data available regarding lung cancer in patients with LTOT.[18] Our study aimed to address this gap in the current literature. Our primary objective was to assess the incidence of lung cancer in a cohort of patients with LTOT. Our secondary objectives were to report the clinical presentation and the management of lung cancer in patients with LTOT and to compare their outcomes to a control cohort of patients with lung cancer but without LTOT.

METHODS

We conducted a retrospective case-controlled study. Approval for the study was obtained from the local Ethical Board (CERNI – n° E2019-20).

Cases

Cases were identified by cross-referencing two databases: (1) Administrative data from the local home healthcare provider database (Asten Santé, Isneauville, France) allowing us to identify all patients established on long-term oxygen therapy (LTOT) and/or noninvasive ventilation (NIV) between 2009 and 2019; (2) lung cancer diagnoss during the same time period, extracted from the electronic medical system of Rouen University Hospital using the International Classification of Diseases (ICD-10) coding system (C34.0, C34.1, C34.2, C34.3, C34.8, C34.9). For each case, we verified that the onset of LTOT was anterior to lung cancer diagnosis.

Controls

We matched two controls to each case. Controls were lung cancer patients diagnosed within the same interval, without LTOT, identified from thoracic oncology multidisciplinary team meeting (MDTM) reports at Rouen University Hospital.

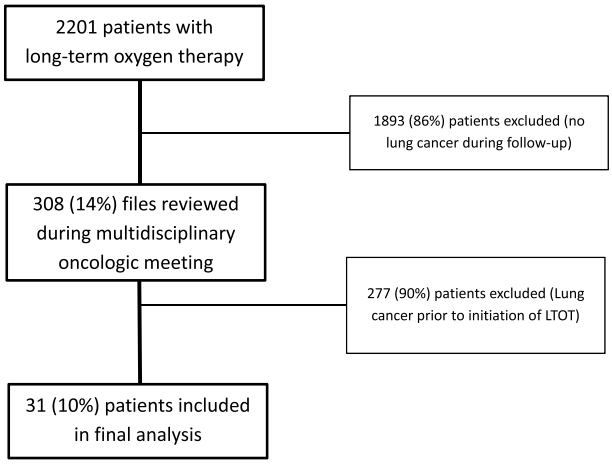

FIGURE 1 Flow chart of the study population.

Controls were matched on cases according to the first-line of treatment. First-line treatment was decided during lung cancer MDTM: radiotherapy, chemotherapy, and so forth. When multiple patients matched the control case, optional matching was performed based on extent of disease, histological type, age and performance status.

Data collection

For all patients, medical data were collected from the electronic medical record system. Staging of lung cancer was performed during lung cancer MDTM using 2017 Tumor Node Metastasis (TNM) classification system.[19] First- and second-line treatments were collected. Treatment tolerance and complications were retrieved from systematic clinical evaluations performed routinely for each patient. Toxicity induced by treatment were recorded using Common Terminology Criteria for Adverse Events (CTCAE).[20] Survival was defined as the time beween diagnosis of lung cancer and death.

Statistical analysis

Normality of distributions was assessed using Shapiro–Wilk tests. Results were expressed as number and percentages, mean and SD when nonsignificantly non-normal, or medians and interquartile range [IQR] when significantly non-normal. Comparisons were performed using Student's unpaired *t*-test for normally distributed continuous variable and a Mann–Whitney test for non-normally distributed continuous variable. Fisher's exact test was used for categorical values. Survival data were analyzed using the Kaplan–Meier method and log-rank tests. A Cox regression model was used to analyze factors associated to survival. Multivariate analysis was performed on variables with a *p*-value for the likelihood ratio test lower than 0.2 in univariate analysis. Hazard ratios (HRs) for Cox model regression were provided with their 95% confidence interval (CI). All tests were

TABLE 1 Characteristics of patients with long-term oxygen therapy who received an active treatment

Case	Age years	Sex	CRF etiology	FEV (L)	Smoking (PY)	PS	BMI kg/m^2	Albumin (g/l)	Histology	Stage	First-line	Second-line	Toxicity grade	Survival (days)
1	77	M	ILD	1.49	40	NA	NA	40	ADK	IV	TKI	BSC	2	217
2	69	M	COPD	NA	25	NA	NA	NA	SqCC	IV	RC	Chem	0	443
3	74	M	ILD	2.44	60	1	24.6	19.7	SqCC	III	Chem	Chem	3	122
4	77	M	COPD	1.16	45	0	31.8	NA	Other NSCLC	III	SBRT	BSC	0	727
5	70	M	COPD	1.35	NA	0	24.2	NA	UK	III	RC	Radio	3	765
6	62	F	COPD	0.94	NA	1	30.1	NA	BAC	III	Chem	Chem	4	1441
7	55	M	COPD	1.84	46	NA	27.1	31	ADK	IV	Chem	BSC	3	241
8	69	M	PAH	1.09	30	1	17.8	25.9	UK	IV	Chem	Immuno	4	335
9	55	M	COPD	NA	NA	0	NA	NA	ADK	III	RC	Immuno	NA	345
10	48	M	COPD	2.06	35	2	26.2	42.8	ADK	IV	Chem	Chem	0	182
11	74	F	COPD	0.97	45	2	20.5	NA	LCC	IV	RC	Chem	1	273
12	64	M	COPD	0.84	NA	1	25.6	34.3	SqCC	II	Chem	Chem	0	566
13	68	M	COPD	1.44	50	1	24.6	42.1	SqCC	I	Surg	BSC	0	462
14	64	M	COPD	1.91	40	3	35.5	24.5	ADK	I	TKI	BSC	1	285
15	66	F	COPD	0.61	45	4	23.5	29	SCC	IV	Chem	BSC	0	6
16	68	M	COPD	1.66	60	NA	35.1	27.5	UK	I	SBRT	BSC	0	663
17	67	M	COPD	0.65	50	1	25	NA	SqCC	II	SBRT	Chem	3	766
18	83	M	COPD	0.43	30	NA	21.9	NA	UK	I	SBRT	BSC	0	722
19	63	M	COPD	0.87	90	0	28.7	39.7	SqCC	I	SBRT	NA	0	344
20	67	M	COPD	0.93	50	1	29.4	43.9	UK	I	SBRT	NA	0	174

Abbreviations: ADK, adenocarcinoma; BAC, bronchioloalveolar carcinoma; BMI, body mass index; BSC, best supportive care; Chem, chemotherapy; COPD, chronic obstructive pulmonary disease; CRF, chronic respiratory failure; F, female; FEV, forced expiratory volume; Immuno, immunotherapy; ILD, interstitial lung disease; LCC, large cell neuroendocrine carcinoma; M, male, NA, not available; NSCL, non-small cell lung carcinoma; PAH, pulmonary arterial hypertension; PS, performance status; PY, pack-year; RC, radiochemiotherapy; Radio, radiotherapy; surg, surgery; SBRT, stereotactic body radiation therapy; SqCC, squamous cell carcinoma; SCC, small cell carcinoma; TKI, tyrosine kinase inhibitor; UK, unknown.

two-sided with type I error rate set at 0.05. The analyses were performed using GraphPad Prism 6 for Mac OS X (GraphPad Software, Inc.) or IBM SPSS Statistics version 20.0 (IBM Corporation).

RESULTS

Incidence of lung cancer among patients with long-term oxygen therapy

Out of 2201 patients established on LTOT over the study period, 31 (1.4%) developed lung cancer (Figure 1). In the 31 patients who developed cancer, 24 were treated by LTOT alone and seven were treated with LTOT and NIV. None of the 31 patients were treated by NIV without LTOT. The annual incidence rate of lung cancer in patients with LTOT was 0.33% per year.

In patients with lung cancer, the underlying chronic respiratory disease was COPD ($n = 27$, 87%), interstitial lung disease ($n = 3$, 10%) and pulmonary hypertension ($n = 1$; 3%). At the time of lung cancer diagnosis, patients were established on LTOT for 2.2 (1.1 to 4.0) years.

Management of lung cancer in patients with long-term oxygen therapy

In seven (23%) patients, lung cancer was not histologically proven, but diagnosis was deemed certain by multidisciplinary team meeting (MDTM). For those with a histological diagnosis, the findings were squamous cell ($n = 12$, 50%), adenocarcinoma ($n = 8$, 32%), small-cell lung cancer ($n = 2$, 8%), large cell neuroendocrine carcinoma ($n = 1$, 4%), and carcinoma ($n = 1$, 4%). Staging at diagnosis was: IV ($n = 15$, 49%), III ($n = 5$, 16%), II ($n = 2$, 6%), I ($n = 7$, 23%) and could not be assessed in two patients (6%).

After MDTD, the first-line treatment was best supportive care ($n = 11$, 36%), chemotherapy ($n = 7$, 23%), stereotactic body radiation therapy (SBRT) ($n = 6$, 19%), radiochemotherapy ($n = 4$, 13%), tyrosine kinase inhibitors ($n = 2$, 6%) and surgery ($n = 1$, 3%). PD-L1 status was available for five patients and three were positive, but all below 50%. Oncogenic driver mutation screening was performed for nine patients, but none was positive. Among the seven patients without histologically proven lung cancer, an active treatment was given in five: SBRT ($n = 3$) and chemotherapy ($n = 2$). Management of patients with LTOT is summarized in Table 1. For those who received active treatment, grade 3 toxicity was seen in six patients (30%) and grade 4 toxicity in two patients (10%).

Survival was significantly longer in patients on long-term oxygen therapy that received any treatment when compared to those who received best supportive care with a median survival of 462 days versus, 38 days ($p = 0.003$). Survival of patients with metastatic disease was significantly shorter than those with localized disease: 0.49 years versus, 1.99 years ($p < 0.001$). Median survival was 241 days in patients treated with chemotherapy, 443 days for those treated with radiochemotherapy and 747 days for those treated with radiotherapy ($p = 0.043$) (Figure 2). Death was mainly due to respiratory failure (13/23, 57%) and never to treatment toxicity.

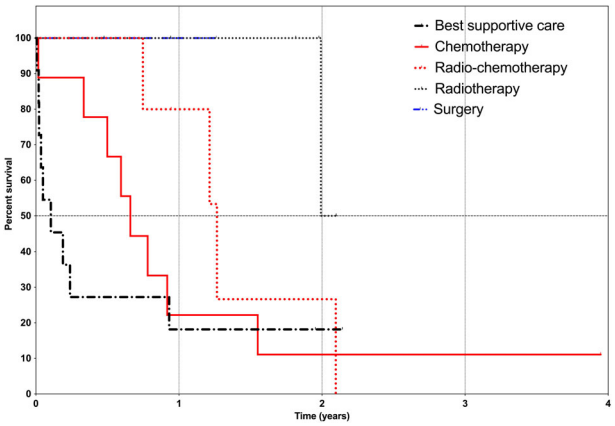

FIGURE 2 Survival of patients with long-term oxygen therapy with lung cancer according to first-line treatment (p: 0.048, log-rank)

Comparison to control lung cancer cases without long-term oxygen therapy

Baseline characteristics of cases with LTOT were not significantly different from controls except for pulmonary function tests and for performance statuses that were lower for patients with LTOT (Table 2).

Treatment safety profile did not differ between cases and controls (Table 3).

Median survival in those who received any active treatment was 462 days in patients with long-term oxygen therapy and 924 days in patients without long-term oxygen therapy ($p = 0.027$) (Figure 3). However, in multivariate analysis, LTOT was not significantly associated with a worse outcome. Hazard ratio (HR): 1.56 (95% confidence interval [CI]: 0.87 to 2.81) ($p = 0.137$) whereas stage IV disease and performance status were: HR: 1.34 (95% CI: 1.14 to 1.59) ($p < 0.001$) and 1.52 (95% CI: 1.20 to 1.93) ($p = 0.001$) respectively. Administration of any treatment was associated with a better prognosis: HR: 0.35 (95% CI: 0.19 to 0.66).

DISCUSSION

In this retrospective cohort study, we found an annual incidence rate of lung cancer in patients with LTOT of 0.33% per year. Particularities of lung cancer in long-term oxygen therapy patients are: (1) A high rate of not histologically proven malignancies, (2) a high proportion of squamous cell lung cancer, and (3) a high rate of therapeutic abstention despite the acceptable tolerance and effectiveness of radiotherapy in this population.

TABLE 2 Demographic, clinical and functional characteristics of lung cancer patients with long-term oxygen therapy compared to those without long-term oxygen therapy

	Patients with LTOT ($n = 31$)	Patients without LTOT ($n = 62$)	*p*-value
Gender (male)	25 (81%)	51 (82%)	1.000
Age at diagnosis (years)	70.6 (± 9.2)	70.2 (± 10.2)	0.874
BMI (kg/m^2)	25.3 (± 5.4)	26.1 (± 5.7)	0.959
Current smoker	9 (29%)	24 (38.7%)	0.491
Tobacco exposure (PY)	45 [33.5–50.0]	40 [30.0–55.0]	0.411
COPD	27 (87%)	19 (30%)	0.004
Admission for severe exacerbation following lung cancer diagnosis	20 (64%)	39 (63%)	0.999
Comorbidities			
Arterial hypertension	14 (45%)	28 (45%)	1.000
Ischemic heart disease	12 (39%)	15 (24%)	0.158
PAOD/AAA	9 (29%)	14 (23%)	0.611
Chronic renal failure	2 (6%)	4 (6%)	1.000
Diabetes	9 (29%)	15 (24%)	0.624
History of cancer	9 (29%)	25 (40%)	0.363
Autoimmune disease	2 (6%)	1 (2%)	0.256
Performance status	1.0 [1.0–3.7]	1.0 [0.0–1.0]	0.043
Albumin	31.4 (± 6.9)	31.7 (±6.0)	0.752
Pulmonary function tests			
FEV (L)	1.0 [0.8–1.6]	1.7 [1.3–2.7]	<0.001
FEV (%)	45.8 [31.0–60.5]	64 [51–98.5]	<0.001
FVC (L)	2.3 [1.6–3.0]	2.9 [2.4–3.9]	0.011
FEV/FVC (%)	50.6 [41.0–60.0]	65.7 [53.6–78.2]	0.001
DLCO (%)	36 [21–61], $n = 16$	60 [47–71], $n = 30$	0.0122
Histology			
Squamous cell carcinoma	12 (39%)	26 (42%)	0.913
Adenocarcinoma	8 (26%)	21 (34%)	
Large cell carcinoma	1 (3%)	1 (2%)	
Carcinoma NOS	1 (3%)	1 (2%)	
Small cell carcinoma	2 (6%)	6 (9%)	
Unknown	7 (23%)	7 (11%)	
Lung cancer stage at diagnosis			
I	7 (23%)	9 (14%)	0.711
II	2 (6%)	3 (5%)	
III	5 (16%)	11 (18%)	
IV	15 (49%)	37 (60%)	
Unknown	2 (6%)	2 (3%)	
First-line treatment			
Best supportive care	11 (36%)	21 (34%)	0.782
Chemotherapy	7 (23%)	12 (19%)	
TKI	2 (6%)	1 (2%)	
SBRT	6 (19%)	12 (19%)	
Radiochemotherapy	4 (13%)	14 (23%)	
Surgery	1 (3%)	2 (3%)	

Abbreviations: AAA, abdominal arterial aneurysm; BMI, body mass index; LTOT, long-term oxygen therapy; FEV, forced expiratory volume; FVC, forced vital capacity; NSCL, non-small cell lung carcinoma; NOS, not otherwise specified; PAOD, peripheral arterial occlusion disease; PY, pack-year; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor.

TABLE 3 Comparison of treatment-related toxicity in patients with long-term oxygen therapy compared to those without

	Grade	Case: treated patients with LTOT ($n = 20$)	Control: treated patients without LTOT ($n = 41$)
Chemotherapy		$n = 7$	$n = 12$
Maximum grade of toxicity following chemotherapy	None	3 (42%)	3 (25%)
	I	0 (0%)	2 (17%)
	II	0 (0%)	3 (25%)
	III	2 (29%)	1 (8%)
	IV	2 (29%)	3 (25%)
Radiotherapy		$n = 6$	$n = 12$
Maximum grade of toxicity following radiotherapy	None	6 (100%)	9 (75%)
	I	0 (0%)	1 (8%)
	II	0 (0%)	1 (8%)
	III	0 (0%)	0 (0%)
Radiochemotherapy		$n = 4$	$n = 14$
Maximum grade of toxicity following radiochemotherapy	None	1 (25%)	1 (7%)
	I	1 (25%)	4 (29%)
	II	0 (0%)	4 (29%)
	III	1 (25%)	4 (29%)
	IV	0 (0%)	1 (7%)
TKI		$n = 2$	$n = 1$
Maximum grade of toxicity following TKI	None	0 (0%)	1 (100%)
	I	1 (50%)	0 (0%)
	II	1 (50%)	0 (0%)
	III	0 (0%)	0 (0%)
	IV	0 (0%)	0 (0%)
Surgery		$n = 1$	$n = 2$
Maximum grade of toxicity following surgery	None	1 (100%)	2 (100%)
	I	0 (0%)	0 (0%)
	II	0 (0%)	0 (0%)
	III	0 (0%)	0 (0%)
	IV	0 (0%)	0 (0%)

Abbreviations: LTOT, long-term oxygen therapy; TKI, tyrosine kinase inhibitor.

An important finding of our study was that, in LTOT patients, treatment of lung cancer appeared to be well tolerated. As our analysis might have failed to show a significant association due to the sample size, we can only suggest that this treatment might be associated with acceptable outcomes in this specific population and need further confirmation with a larger sample size. These results highlights the importance of an active monitoring screening strategy in patients with long-term oxygen therapy, and support the inclusion of these patients in a systematic lung screening strategy.[21] Indeed, according to data from the FRANCIM French cancer registries, the incidence rate of lung cancer in patients aged 70–74 is 0.36 and 0.09% among males and females, respectively.[22] In our cohort, the annual incidence rate of lung cancer in patients with LTOT was similar. These results could be explained by the poor survival of patients with LTOT[2,23] acting as a competing risk of lung cancer development. Our results may also be explained by an attrition bias as only patients with a diagnosis of cancer performed in Rouen University Hospital were included; patients may have had initial LTOT prescription in Rouen University Hospital but were moved to another hospital, city, or region before developing lung cancer. Moreover, given the frailty of patients with long-term oxygen therapy, physicians may have decided not to explore further peripheral nodules or other CT abnormalities because of higher risk of respiratory complications during bronchoscopy or CT-guided biopsy.[24] The fact that 23% of our patients had nonhistologically proven lung cancer supports that hypothesis. Patients with LTOT should benefit from lung cancer screening programs, and, conversely, the generalization of the usage of low-dose CT scanner for the screening of lung cancer in smokers may help identify early signs of chronic respiratory disease in this population, before its progression to the LTOT stage.[25] Following a positive screening test in patients with LTOT, the involvement of an expert multidisciplinary team in the

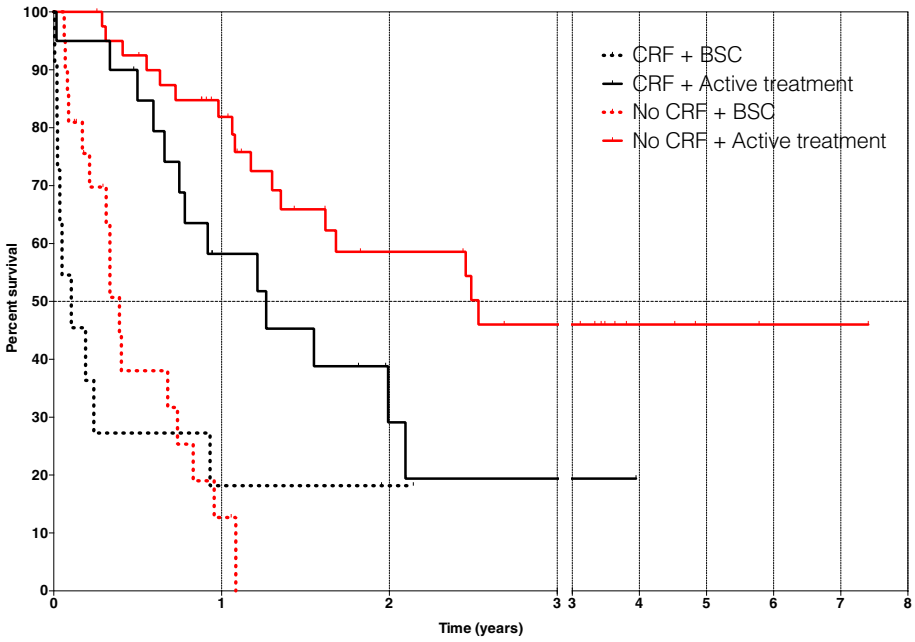

FIGURE 3 Survival of patients according to long-term oxygen therapy status and first-line treatment ($p < 0.001$, log-rank).

diagnostic management following a positive screening test appears critical. For instance, referral to an expert center with proficiency in performing bronchoscopy in severely ill patients as well as adjunctive treatment during the bronchoscopy such as noninvasive ventilation or high-flow oxygen therapy may alleviate the risk of complications.[8,26,27] The development of noninvasive diagnostic techniques such as liquid biopsy may also be of particular relevance in this cohort of patients.[28]

Our results showed a better survival in patients with active treatments that may be explained by a better prognostic of treated patients (indication bias) as well as the treatment effect. The treatment associated with the best outcome in our cohort was SBRT (Figure 2, $p < 0.041$) with 747 days median survival. This outcome, which is similar to that observed in patients on LTOT without cancer in a historical cohort,[29] suggests that radiotherapy may be an efficient, well-tolerated treatment option for this population. As peripheral nodules are more challenging to diagnose, stereotactic radiotherapy may have a favorable risk–benefit ratio in this population in nondiagnosed nodules. Indeed, we have shown that LTOT patients with an early-stage lung cancer treated with SBRT had acceptable survival outcomes, despite bearing two life-threatening diseases. However, treatment decisions depend on individual risk assessment and should be discussed by an expert multidisciplinary team.

Unfortunately, we were unable to collect complete and detailed data on driver mutations harbored by patient tumors, neither were we able to fully assess tumor PD-L1 expression. This lack of data is explained by the retrospective nature of our study, the high percentage of nonhistologically proven tumor, and the fact that systematic PD-L1 assessment was only implemented in 2017 in our center. Nevertheless, oncogenic driver mutations were probably rare in our cohort, as they are less frequently evidenced in squamous cell carcinoma and in heavy smokers.[17] On the contrary, PD-L1 expression could be higher than evidenced, as PD-L1 is usually expressed in heavy smokers and in squamous cell carcinoma.[30] Indeed, in our cohort, unlike that seen in the general population,[31] squamous cell carcinoma was the most common histological type.

Considering the study period, none of our patients received first-line immunotherapy. However, given the favorable safety profile of this treatment modality compared to standard chemotherapy regimens, it is possible that, in the near future, the outcome of patients with LTOT and lung cancer may be even better as more patients become eligible to active systemic treatment. This is especially relevant as more than a third of patients with LTOT in our study did not receive active oncological first-line treatment, suggesting that the relative frailty of these patients may limit their access to potentially indicated treatments, for fear of complications.

Our study has obvious limitations given its retrospective, monocentric design. However, these results stress the relevance of a proactive strategy regarding lung cancer in patients with LTOT.

In conclusion, our study suggests that patients with LTOT should benefit from the development of lung cancer screening programs, as the incidence of lung cancer is similar in this population and treatments are associated with an acceptable outcome as well as acceptable toxicity. The development of multidisciplinary expert centers appears necessary to optimize the uniquely challenging management of this group of patients.

CONFLICT OF INTEREST

Timothée Lambert, Kinan El Husseini, André Gillibert, Edouard Dantoing, Luca Campedel report no conflict of Interest. Maeva Zysman reports personal fees from CSL Behring, GSK, AstraZeneca, AVAD, Fondation pour la

recherché médicale, Boehringer Ingelheim, Novartis, Chiesi, unrelated to the work submitted. Boris Duchemann reports personal fees from Roche, Pfizer, Astra Zeneca, Chiesi, Amgen, Lilly, Oxyvie, unrelated to the work submitted. Dr Camille Rolland-Debord reports personal fees from Sanofi and Astra-Zeneca, unrelated to the work submitted. Maxime Patout reports personal fees from Philips Respironics, Chiesi, Resmed Isis Médical, Fisher & Paykel, Lowenstein, SOS Oxygène, Asten Santé, Air Liquide Médical, Antadir, unrelated to the work submitted.

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