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**Short-term and long-term outcomes of patients with lung cancer
and life-threatening complications**

Short title: outcomes of lung cancer patients in the ICU

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Abbreviations: ICU (intensive care unit); SOFA (Sepsis-related Organ Failure Assessment); CSH (Cause Specific Hazard); PS (Performance Status)

To the Editor,

Lung cancer accounts for the second most frequent solid tumour and for about one in four deaths by cancer. Survival to lung cancer has improved since the 1990s owing to early tumor detection, therapeutic advances through improvements in surgical techniques and the development of immunotherapy and targeted therapy ¹. However new treatments resulted in new life-threatening side effects likely to require intensive care unit (ICU) admission ^{2,3}.

Patients with lung cancer may be considered as a particular group of interest in the ICU for the following reasons: i) lung cancer accounts for the leading malignancy among patients with solid tumors and unplanned ICU admission ⁴; ii) The majority of patients requiring unplanned ICU admissions have newly diagnosed cancer, and the acute episode is often related to a specific complication of cancer ^{5,6}; iii) short-term survival of critically ill lung cancer patients remains poor ^{4,5}; iv) data about their long-term outcomes are scarce.

The aim of our study was to analyse the admission patterns and the eventual short-term and long-term prognosis of critically ill lung cancer patients requiring unplanned ICU admission.

Methods

We enrolled adult patients with a diagnosis of lung cancer (before or during the ICU stay) hospitalized in a medical ICU located inside a tertiary care hospital with oncology and thoracic surgery departments, over a 12-year period (2007-2018). Post-operative management of patients with elective thoracic surgery is provided in surgical ICU. Exclusion criteria were the following: cancer cured for more than 5 years, planned admissions following elective surgery and admissions for securing a procedure. Continuous variables were expressed as median (interquartile range) and categorical variables as counts (percentages), and were compared over time by using Cuzik test and chi-square test for trend, respectively.

Determinants of vital status were analysed through a multivariate time-dependent Cox cause-specific proportional hazard model. The study was approved by the ethics committee of the French Intensive Care Society (#CE-SRLF-17-03)

Results

The study included 379 patients. Non-small cell lung cancer accounted for the large majority (75%) of cancer subsets (Table 1). The oncologic characteristics dramatically changed over the study period. Proportions of patients with new-onset disease decreased while patients presented with more advanced stages of cancer in the recent years, as revealed by extended time between diagnosis and ICU admission and increasing proportions of metastatic diseases. Patients from the recent period were more likely to be under immunotherapy or targeted therapy. ICU admissions linked to drug-related and procedure-related adverse events increased over time from 4.0% in 2007-2008 to 11.6% in 2017-2018 ($p=0.02$). The severity of illness at ICU admission, as assessed by the Sequential Organ Failure Assessment (SOFA) score, as well as requirements of ventilatory and circulatory supports did not change over time. Decisions to forgo life-sustaining therapies were taken in 38.5% of patients. ICU, hospital and one-year mortality rates were 32.2%, 53.3% and 68.9% and did not change over the study period. Independent factors associated with ICU mortality were a Performance Status (PS) ≥ 3 prior to the acute complication (cause specific hazard (CSH) 2.04 [1.32-3.15], $p=0.001$), and the requirements for invasive mechanical ventilation (CSH 8.28 [1.78-38.5], $p=0.007$) and non-invasive ventilation (CSH 16.4 [3.87-69.1], $p<0.001$).

When adjusted with admission SOFA score, one-year mortality in ICU survivors was independently associated with advanced metastatic stage (CSH 2.10 [1.38-3.18], $p<0.001$), prior PS 3-4 (CSH 2.60 [1.75-3.87], $p<0.001$), ICU admission for specific complications

(CSH 1.53 [1.07-2.19], $p=0.020$), cancer treatment < 3 months (CSH 1.36 [1.02-1.93], $p=0.045$), decisions to forgo life-sustaining therapies (CSH 2.63 [1.74-3.95], $p<0.001$), and inability to receive oncologic treatment at ICU discharge (treated as reference for ability to receive oncologic treatment (CSH 0.23 [0.13-0.42], $p=0.001$) and for absence of indication (CSH 0.15 [0.05-0.48], $p=0.002$) (Figure 1).

Discussion

We observed a remarkable raise in ICU admissions over the 12-year study period, albeit linked in part to the development of a thoracic oncology center in our hospital in the early 2010s. In addition, we have long been promoting a broad ICU admission policy for onco-hematology patients, with indications driven by the emergence of new therapeutic strategies. Some patients with metastatic diseases, considered without realistic therapeutic options a few years ago, became eligible to advanced ICU management with new strategies based on immunotherapy or targeted therapy³. This is highlighted by an overall increase in stages of malignancy during the study period, probably explaining why we did not observe any continuous improvements in outcomes^{7,8}.

Specific complications accounted for one quarter of ICU admissions. Procedural interventions such as pleurocentesis, laser airway desobstruction, tracheobronchial or intravascular prosthesis insertion aim at rapidly restoring organ functionalities, pending histologic documentation and prompt initiation of antitumoral treatment whenever possible. Only cytostatic chemotherapy, and to a lesser extent targeted therapies such as kinase inhibitors in patients with adenocarcinoma and actionable oncogenic mutations, are likely to result in fast tumor reduction required in the setting of life-threatening acute respiratory failure. In contrast,

the effect of immunotherapy on tumor volume is delayed and may occasionally result in paradoxical transient flare-up.

With respect to short-term mortality rates ranging from 22% to 31% and long-term 6-month and one-year mortality rates ranging from 32% to 55% in previous studies performed elsewhere^{5,7,9}, differences in underlying oncologic characteristics make them hardly comparable with those observed in our own cohort. Besides common and largely described determinants of ICU mortality, identification of prognostic factors for one-year survival is a hallmark of this study. Impaired functional status prior to the acute complication, decisions to forgo life-sustaining therapies and the ability to receive optimal oncologic treatment thereafter are intertwined determinants of long-term prognosis. The decision-making process for ICU admission should be able to take into account the eventual realistic therapeutic options in ICU survivors.

Conclusions

ICU admissions in lung cancer patients shifted to more advanced malignancy stages over the study period, albeit without impairing both short-term and long-term survival rates. Performance status prior to the acute complication and the continuation of oncologic treatment after ICU discharge are major prognostic factors of one-year survival.

Acknowledgments

Guarantor statement

FP takes responsibility for the content of the manuscript, including the data and analysis

Author contributions

CV and FP designed the study and drafted the manuscript.

CV and JC collected the data.

MJ performed the statistical analysis.

JC, MJ, MW, JPM, AL, LF contributed to data interpretation and analysis, and revised the manuscript for important intellectual content.

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Characteristics	2007-2008 (n=50)	2009-2010 (n=55)	2011-2012 (n=50)	2013-2014 (n=60)	2015-2016 (n=69)	2017-2018 (n=95)	p
Age (years)	66 [56-73]	68 [59-75]	69 [59-72]	64 [56-73]	66 [61-72]	68 [62-74]	0.23
Male gender	35 (70.0)	36 (65.5)	39 (78.0)	41 (68.3)	46 (66.7)	65 (68.4)	0.76
Type of cancer							0.003
Small cell lung cancer	6 (12.0)	10 (18.2)	4 (8.0)	6 (10.0)	12 (17.4)	7 (7.4)	
Non-small cell lung cancer	36 (72.0)	31 (56.4)	40 (80.0)	46 (76.7)	51 (73.9)	83 (87.4)	
Unknown	8 (16.0)	14 (25.5)	6 (12.0)	8 (13.3)	6 (8.7)	5 (5.3)	
Delay diagnosis-ICU admission (days)	67 [10-302]	101 [0-302]	122 [30-334]	148 [15-303]	136 [43-461]	183 [53-388]	0.01
Stage							0.03
Localized	10 (20.0)	8 (14.5)	6 (12.0)	9 (15.0)	13 (18.8)	11 (11.6)	
Advanced	13 (26.0)	19 (34.5)	10 (20.0)	14 (23.3)	13 (18.8)	16 (16.8)	
Metastatic	25 (50.0)	25 (45.5)	34 (68.0)	37 (61.7)	43 (62.3)	68 (71.6)	
Status							0.01
Newly diagnosed	27 (54.0)	29 (52.7)	20 (40.0)	22 (36.7)	28 (40.6)	33 (34.7)	
Partial remission	3 (6.0)	1 (1.8)	7 (14.0)	9 (15.0)	11 (15.9)	19 (20.0)	
Complete remission	6 (12.0)	8 (14.5)	2 (4.0)	9 (15.0)	5 (7.2)	9 (9.5)	
Progressive	14 (28.0)	17 (30.9)	21 (42.0)	20 (33.3)	25 (36.2)	34 (35.8)	
Treatment within last 3 months							
Antitumoral drugs	17 (34.0)	20 (36.4)	26 (52.0)	29 (48.3)	41 (59.4)	51 (53.7)	0.009
Immuno- and targeted therapy	5 (10.0)	1 (1.8)	5 (10.0)	9 (15.0)	10 (14.5)	21 (22.1)	0.001
First-line treatment	11 (22.0)	13 (23.6)	14 (28.0)	22 (36.7)	27 (39.1)	27 (28.4)	0.15
Radiotherapy	2 (4.0)	4 (7.3)	5 (10.0)	6 (10.0)	6 (8.7)	7 (7.4)	0.58
Surgery	6 (12.0)	3 (5.5)	3 (6.0)	7 (11.7)	3 (4.3)	5 (5.3)	0.24
Performance status 3-4	0/7(0)	10/32 (31.2)	16/44 (36.3)	14/57 (24.5)	24/64 (37.5)	28/93 (30.1)	0.57
Main causes of ICU-admissions							
Specific complications	19 (38.0)	24 (43.6)	13 (26.0)	30 (50.0)	19 (27.5)	37 (38.9)	0.79
Airway obstruction	5 (10.0)	4 (7.3)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	
Pleural effusion	1 (2.0)	3 (5.5)	3 (6.0)	6 (10.0)	1 (1.4)	5 (5.3)	
Metabolic disorders	1 (2.0)	3 (5.5)	0 (0.0)	1 (3.3)	3 (4.3)	1 (1.1)	
Other	12 (24.0)	15 (27.3)	10 (20.0)	21 (35.0)	16 (23.2)	23 (24.2)	0.16
Non-specific complications	29 (58.0)	30 (54.5)	34 (68.0)	28 (46.7)	45 (65.2)	55 (57.9)	
Infection	19 (38.0)	12 (21.8)	17 (34.0)	15 (25.0)	25 (36.2)	25 (26.3)	
Venous thromboembolism	2 (4.0)	4 (7.3)	4 (8.0)	2 (3.3)	3 (4.3)	3 (3.2)	
Miscellaneous	8 (16.0)	14 (25.5)	13 (26.0)	11 (18.3)	17 (24.6)	19 (20.0)	
Adverse event complications	2 (4.0)	1 (1.8)	3 (6.0)	2 (3.3)	5 (7.2)	11 (11.6)	0.02
Drug-related	0 (0.0)	1 (1.8)	2 (4.0)	1 (1.7)	3 (4.3)	3 (3.2)	
Procedure-related	2 (4.0)	0 (0.0)	1 (2.0)	1 (1.7)	2 (2.9)	8 (8.4)	
SOFA	7 [4-12]	5 [4-9]	5 [4-8]	4 [3-6]	6 [4-8]	5 [4-8]	0.35
Organ support requirements							
Invasive mechanical ventilation	27 (54.0)	29 (52.7)	25 (50.0)	21 (35.0)	30 (43.5)	40 (42.1)	0.07
Non-invasive mechanical ventilation	6 (12.0)	7 (12.7)	6 (12.0)	13 (21.7)	9 (13.0)	21 (22.1)	0.09
Vasopressors/inotropes	27 (54.0)	19 (34.5)	13 (26.0)	13 (21.7)	27 (39.1)	32 (33.7)	0.15
Renal replacement therapy	11 (22.0)	9 (16.4)	7 (14.0)	5 (8.3)	6 (8.7)	7 (7.4)	0.006
Outcome							
ICU mortality	22 (44.0)	17 (30.9)	10 (20.0)	19 (31.6)	23 (33.3)	31 (32.6)	0.59
Hospital mortality	29 (58.0)	29 (52.7)	26 (52.0)	31 (51.7)	38 (55.1)	49 (51.6)	> 0.9
One-year mortality	35 (70.0)	35 (63.6)	37 (74.0)	40 (66.7)	50 (72.5)	64 (67.4)	0.63

Table 1. Characteristics of patients

Figure legend

Figure 1. One year-mortality in ICU survivors (landmark set at one month post-ICU discharge).

One year-mortality in ICU survivors depending on the ability to receive chemotherapy after ICU-discharge (landmark set at one month post-ICU discharge): withdrawal chemotherapy (red line), continuation of chemotherapy (black line) and chemotherapy non indicate (green line)

Figure 1. One year-mortality in ICU survivors (landmark set at one month post-ICU discharge)

