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Original Research

NEOPLASTIC DISEASES

Prognosis of Lung Cancer Patients With Life-Threatening Complications*

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Background: **The management of patients with lung cancer has improved recently, and many of them will require admission to the ICU. The aims of this study were to determine hospital mortality and to identify risk factors for death in a large cohort of critically ill patients.**
Methods: **Cohort study in two ICUs specialized in the management of patients with cancer, in France and Brazil.**
Results: **Of the 143 patients (mean age, 61.6 ± 9.9 years [± SD]), 25 patients (17%) had small cell lung cancer and 118 patients (83%) had non-small cell lung cancer. The main reasons for ICU admission were sepsis (44%) and acute respiratory failure (31%). Mechanical ventilation (MV) was used in 100 patients (70%), including 38 patients in whom lung cancer was considered a reason for MV. Hospital mortality was 59% overall and 69% in patients receiving MV. By multivariate logistic regression, airway infiltration or obstruction by cancer, number of organ failures, cancer recurrence or progression, and severity of comorbidities were associated with increased mortality.**
Conclusions: **The improved survival previously reported in patients with cancer admitted to the ICU seems to extend to patients with lung cancer, including those who need MV. Mortality increased with the number of organ failures, severity of comorbidities, and presence of respiratory failure due to cancer progression. The type of the cancer *per se* was not associated with mortality and, therefore, should not be factored into ICU triage decisions.**
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Key words: acute respiratory failure; intensive care; lung cancer; mechanical ventilation; outcome

Abbreviations: ACE-27 = Adult Comorbidity Evaluation 27; ARF = acute respiratory failure; CI = confidence interval; DFLST = decisions to forego life-sustaining treatment; INCA = Instituto Nacional de Câncer; LOD = Logistic Organ Dysfunction; MV = mechanical ventilation; NSCLC = non-small cell lung cancer; OR = odds ratio; SAPS = Simplified Acute Physiology Score; SCLC = small cell lung cancer

Lung cancer is the leading cause of cancer-related mortality worldwide. The cure rate remains < 15% despite improvements in surgery, radiotherapy, and chemotherapy.[1] Nevertheless, the management of patients with lung cancer has improved recently. A complete recovery or prolonged survival is now achieved in some patients with non-small cell lung cancer (NSCLC).[2–5] Moreover, many new anticancer medications are currently under clinical evaluation, especially in patients with advanced disease.[6,7] Survival rates in critically ill patients with cancer have improved over the last decade.[8–10] However, ICU admission is widely believed to be of little avail in patients with lung cancer with acute life-threatening events, most notably those with acute respiratory failure (ARF) requiring mechanical ventilation (MV).[11,12] In addition, these patients usually exhibit cardiac and pulmonary comorbidities related to smoking.[13] Nevertheless, survival data are scant.[11,12,14–16] Data on current survival rates and factors that influence survival would help to make appropriate management decisions. The objective of this study was to measure survival and to identify risk factors for hospital mortality in a large cohort of patients with lung cancer admitted to two ICUs.

Materials and Methods

Design and Setting

This cohort study was performed at the ICUs of the Instituto Nacional de Câncer (INCA), Rio de Janeiro, Brazil, and of the

Hôpital Saint-Louis, Université Paris 7, Assistance Publique, Hôpitaux de Paris, France. The INCA is a 200-bed teaching hospital for patients with cancer. Its ICU is a 10-bed medical-surgical unit. The Hôpital Saint-Louis is a 650-bed hospital with 330 beds in hematology and oncology wards and a 12-bed medical ICU. The organization and admission policies of both ICUs have been described elsewhere.[17,18] As a rule, only patients for whom potentially lifespan-extending treatment is available are considered for ICU admission. Decisions to forego life-sustaining treatment (DFLSTs) are made in the ICU when acute illness persists or worsens despite full-code management. The study was supported by institutional funds. The institutional review boards of both institutions approved the study and waived the need for informed consent. The study did not interfere with patient management decisions.

Selection of Participants, Data Collection, and Definitions

Patients from the INCA were included between May 2000 and April 2006. TNM classification, histopathologic classification, and previous treatments were retrieved from patient charts and institution database. All other data were collected prospectively. Patients from the Hôpital Saint-Louis were admitted to the ICU between January 2000 and June 2005. Their charts were reviewed retrospectively.

All adults (age $\geq$ 18 years) who had a definite diagnosis of lung cancer and were admitted to the ICU during the study period were potentially eligible. Cancer remission for $>$ 5 years, ICU stay $<$ 24 h, and ICU admission for routine postoperative care were exclusion criteria. In patients with multiple ICU admissions, only the first admission was considered.

The following variables were collected on the first ICU day: age, gender, Simplified Acute Physiology Score (SAPS) II,[19] Logistic Organ Dysfunction (LOD) score,[20] main reason for ICU admission, weight loss $>$ 10% of usual body weight in the last 3 months, and comorbidities. We used the Adult Comorbidity Evaluation-27 (ACE-27) to determine the overall comorbidity score based on the severity of organ decompensation (none, mild, moderate, or severe) and on the prognostic impact of a wide range of comorbid diseases and conditions.[21] The type of cancer, cancer status (controlled/remission, newly diagnosed, or progression/recurrence) and extent, anticancer treatments, and performance status (Eastern Cooperative Oncology Group scale)[22] during the week before hospital admission were also assessed. Disease extent was evaluated by the TNM classification,[23] with limited disease being defined as stage I-IIIa and extensive disease as stage IIIb-IV. During the ICU stay, the need for vasopressors (any dose of norepinephrine or epinephrine, $\geq$ 5 μg/kg/min of dopamine or dobutamine), conventional or noninvasive MV for $>$ 24 h, reasons for MV, development of acute organ failures, and anticancer treatments were recorded. Cancer was considered to be a reason for MV in patients with bilateral involvement, carcinomatous lymphangitis, or tumor masses resulting in airway obstruction or atelectasis. Sepsis was diagnosed using the criteria developed at the American College of Chest Physicians/Society of Critical Care Medicine consensus conferences[24] and infection using criteria from the Centers for Diseases Control and Prevention.[25] Community-acquired pneumonia was defined according to criteria of the American Thoracic Society established in 2001.[26] ARDS was defined according to the American-European consensus conference.[27] Individual organ failure was defined as a LOD score $\geq$ 1 point for each system.[20] Patients were followed up until hospital death or discharge. The primary evaluation criterion was in-hospital death from any cause.

Data Presentation and Statistical Analysis

Standard descriptive statistics were computed. Continuous variables were reported as mean $\pm$ SD or median (25 to 75% interquartile range). Univariate and multivariate logistic regression were used to identify factors associated with hospital mortality. Linearity between each continuous variable (age, SAPS II score, and number of organ failures) and the dependent variable was demonstrated using locally weighted scatterplot smoothing (lowess).[28] Variables yielding p values $<$ 0.2 by univariate analysis were entered in a forward multivariate logistic regression analysis, as well as variables considered clinically relevant. Two analyses were performed, one in the entire study population, and other in the subpopulation of patients who received MV. In both multivariate analyses, a base model including cancer status and number of organ failures was created. These variables were chosen because they had been previously shown to strongly influence mortality in ICU patients with cancer.[29–31] The other covariates were entered into the model with critical entry and removal p values of 0.05 and 0.1, respectively. Effects on covariate coefficients were also considered. Odds ratios (ORs) with their 95% confidence intervals (CIs) were computed. Colinearity and interactions were tested. The SAPS II score was not initially entered in multivariate analyses because it encompassed other study variables such as age and variables used to define organ failures.[19] The area under the receiver operating characteristic curve was used to evaluate the ability of the model to discriminate between patients who survived and those who died.[32] The Hosmer-Lemeshow goodness-of-fit test was used to evaluate agreement between the observed and expected numbers of survivors and decedents across all strata of probabilities of death (calibration).[28] With this test, p $>$ 0.05 indicates a good fit for the model. Two-tailed p values $<$ 0.05 were considered statistically significant.

Results

Patient Characteristics

The study included 152 patients: 98 patients (64%) from INCA and 54 patients (36%) from Hôpital Saint-

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Louis. Nine patients from Hôpital Saint-Louis were excluded due to missing data, leaving 143 patients for the study. Baseline patient characteristics were similar in the two institutions (Table 1). The main reasons for ICU admission are depicted in Table 2. Infection was present at ICU admission in 86 patients (60%), with the main categories being community-acquired pneumonia (n = 46, 53%), nosocomial pneumonia (n = 21, 24%), abdominal infection (n = 4, 5%), and urinary tract infection (n = 3, 3%). During the ICU stay, the following organ failures were diagnosed: respiratory (n = 102, 71%), cardiovascular (n = 82, 57%), renal (n = 34, 24%), neurologic (n = 23, 16%), hematologic (n = 22, 15%), and hepatic (n = 5, 3%). Only five patients (3%) had neutropenia. Eighteen patients (13%) received emergency anticancer treatment while in the ICU (chemotherapy alone [n = 12], radiation therapy alone [n = 3], or combined therapy [n = 3]). Ten patients had small cell lung cancer (SCLC) and 8 had NSCLC. Indications for emergency anticancer treatment were airway infiltration/obstruction (n = 13), spinal cord compression (n = 2), superior vena cava syndrome (n = 1), paraneoplastic vasculitis (n = 1), and carcinoid syndrome (n = 1).

Table 1—*Characteristics of the 143 Study Patients

Variables	Data
Factors at ICU admission	
Age, yr	61.6 ± 9.9
Hospital days prior to ICU admission	2 (0–5)
Male gender	105 (73)
SAPS II score, points	47.4 ± 21.0
LOD score, points	5 (2–7)
Type of cancer	
Squamous-cell carcinoma	56 (39)
Adenocarcinoma	49 (34)
SCLC	25 (17)
Large cell	8 (6)
Other	5 (3)
Extensive disease (TNM classification)	
No (I-IIIa)	59 (41)
Yes (IIIb-IV)	84 (59)
Distant metastasis	44 (31)
Airway obstruction	36 (25)
Cancer status	
Controlled	55 (38)
Uncontrolled, newly diagnosed	55 (38)
Uncontrolled, recurrence/progression	33 (23)
Performance status	
0–2	111 (78)
3–4	32 (22)
Previous anticancer treatments	
Combined therapy	51 (36)
Surgery to cure the cancer only	20 (14)
Radiation therapy only	16 (11)
Chemotherapy only	13 (9)
No previous anticancer treatments	43 (30)
Weight loss ≥ 10%	13 (9)
Comorbidity score (ACE-27)	
None	53 (37)
Mild	54 (38)
Moderate	19 (13)
Severe	17 (12)
Most frequent comorbidities	
COPD	48 (34)
Systemic arterial hypertension	33 (23)
Diabetes mellitus	10 (7)
Chronic heart failure	7 (5)
Factors during the ICU stay	
MV	100 (70)
Vasopressors	82 (57)
Dialysis	12 (8)
Acute organ failures	2 (1–3)
Outcome data	
Length of ICU stay, d	6 (3–13)
Length of hospital stay, d	15 (8–32)
DFLST	41 (29)
ICU mortality	60 (42)
Hospital mortality	84 (59)

*Data are presented as mean ± SD, median (interquartile range), or No. (%).

Table 2—*Main Reasons for ICU Admission (n = 143)*

Variables	No. (%)
Severe sepsis/septic shock	63 (44)
ARF (excluding sepsis)	45 (31)
Cardiovascular complications	18 (13)
Shock (excluding sepsis)	9 (6)
Neurologic complications	4 (3)
Miscellaneous	10 (7)

Outcome Analysis

In the 152 included patients, ICU and hospital mortality rates were 44% and 60%, respectively. ICU mortality was similar in the two institutions (47% [46 of 98 patients] vs 39% [21 of 54 patients], p = 0.432), whereas hospital mortality was slightly higher at the INCA (65% [64 of 98 patients]) than at the Hôpital St. Louis (50%, 27 of 54 patients; p = 0.095). Of the nine excluded patients, seven died in the ICU and two were discharged alive from the hospital. DFLSTs were made in 42 patients (28%) after a median of 4 days (range, 2 to 10 days) in the ICU, and 4 days (range, 2 to 10 days) prior to hospital death or discharge. The rates of DFLSTs were similar in the two institutions (29% [28 of 98 patients] vs 26% [14 of 54 patients], p = 0.873).

Outcome data of the 143 study patients are reported in Table 1. Overall ICU and hospital mortality rates were 42% and 59%, respectively. Age was similar in survivors and decedents (62.6 ± 10.0 years vs 60.3 ± 9.7 years, p = 0.181), as was the number of hospital days prior to ICU admission (2 days [range, 1 to 5 days] vs 1 day [range, 0 to 7 days], p = 0.388). As expected, patients who died had higher SAPS II score (53.7 ± 21.8 vs 38.4 ± 17.2, p < 0.001) and

LOD score (median, 6 [range, 4 to 8]; vs median, 3 [range, 1 to 7], $p < 0.001$) compared to the survivors.

The results of univariate analysis are reported in Table 3. Age, cancer extent, performance status, cancer status, airway obstruction by cancer, moderate or severe comorbidity score, infection at ICU admission, need for MV or vasopressors, and number of organ failures during the ICU stay were entered in the multivariate analysis. A moderate or severe comorbidity score, cancer recurrence or progression, a larger number of organ failures, and airway obstruction due to cancer invasion or compression independently predicted increased hospital mortality (Table 3). The final model showed good discrimination and calibration. The SAPS II score, DFLSTs, and type of cancer (NSCLC = 0; SCLC = 1) were then forced into the final model. As expected DFLSTs were selected ($p = 0.001$) but the SAPS II score ($p = 0.455$) and type of cancer ($p = 0.338$) were not selected. In general, the effects of the other covariates on the dependent variable remained unchanged.

Of the 59 patients who were discharged home, 48 patients (81%) were alive and 11 patients (19%) were dead at last follow-up. Median follow-up duration was 79 days (range, 15 to 182 days).

Patients Requiring MV

MV was required in 100 patients, either within 24 h of ICU admission (n = 94) or later on during

Table 3—*Univariate and Multivariate Analyses of Factors Associated With Hospital Mortality (143 Patients)*

Variables	Hospital Mortality, %	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yr		1.02 (0.99–1.06)	0.182		
Gender					
Female	68	1.00	0.222		
Male	55	0.57 (0.26–1.25)			
Type of cancer					
NSCLC	56	1.00	0.208		
SCLC	72	2.03 (0.79–5.22)			
Extensive disease (TNM classification)					
No (I-IIIa)	44	1.00	0.005		
Yes (IIIb-IV)	69	2.83 (1.42–5.65)			
Cancer status					
Controlled	47	1.00	0.014	1.00	
Uncontrolled, newly diagnosed	60	1.71 (0.80–3.67)		0.79 (0.31–2.03)	0.619
Uncontrolled, recurrence/progression	79	4.25 (1.60–11.27)		3.20 (1.07–9.51)	0.037
Performance status					
0–2	51	1.00	0.002		
3–4	84	5.12 (1.84–14.25)			
Airway obstruction by cancer					
No	51	1.00	0.001	1.00	
Yes	83	4.91 (1.89–12.75)		4.59 (1.52–13.91)	0.007
Weight loss > 10% of usual body weight					
No	58	1.00	0.610		
Yes	69	1.65 (0.48–5.63)			
Moderate/severe comorbidity (ACE-27)					
No	53	1.00	0.036	1.00	
Yes	75	2.63 (1.13–6.12)		3.11 (1.18–8.21)	0.022
COPD					
No	60	1.00	0.802		
Yes	56	0.86 (0.43–1.73)			
Infection					
No	46	1.00	0.015		
Yes	67	2.47 (1.24–4.92)			
MV					
No	35	1.00	< 0.001		
Yes	69	4.16 (1.95–8.86)			
Vasopressors					
No	38	1.00	< 0.001		
Yes	74	4.80 (2.34–9.83)			
No. of organ failures		2.23 (1.59–3.13)	< 0.001	1.96 (1.38–2.79)	< 0.001

*Area under receiver operating characteristic curve = 0.81 (95% CI, 0.74–0.88); Hosmer-Lemeshow goodness of fit ($\chi^2 = 3.33$; $p = 0.912$).

the ICU stay (n = 6). Conventional MV was used initially in 87 patients, and noninvasive MV was used in 13 patients, of whom 7 patients subsequently required conversion to conventional MV. The reasons for MV were pulmonary sepsis (n = 60), acute decompensation of COPD (n = 14), coma (n = 12), extrapulmonary sepsis (n = 8), pulmonary embolism (n = 5), cardiac pulmonary edema (n = 3), cardiopulmonary arrest (n = 3), and miscellaneous (n = 12); some patients had more than one reason for MV. Lung cancer was considered a reason for MV in 38 patients. Diagnostic criteria for ARDS were met by 59 patients. Median MV duration was 7 days (range, 3 to 13 days). Patients who received MV were slightly younger (60.7 ± 10.1 years vs 63.8 ± 9.4 years, p = 0.085) and had higher scores on SAPS II (52.7 ± 19.5 vs 35.2 ± 19.4, p ≤ 0.001) and LOD (median, 6 [range, 4 to 8]; vs median, 2 [range, 1 to 4], p < 0.001).

ICU and hospital mortality rates in the subgroup treated with MV were 56% and 69%, respectively. Table 4 reports the results of univariate analysis in

Table 4—*Univariate and Multivariate Analyses of Factors Associated With Hospital Mortality in the 100 Patients Treated With MV**

Variables	Hospital Mortality, %	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	p Value	OR (95% CI)	p Value
Age, yr		1.05 (1.01–1.10)	0.015	1.08 (1.02–1.15)	0.015
Gender					
Female	73	1.00	0.706		
Male	67	0.74 (0.29–1.92)			
Type of cancer					
NSCLC	67	1.00	0.466		
SCLC	75	1.47 (0.52–4.16)			
Extensive disease (TNM classification)					
No (I-IIIa)	62	1.00	0.371		
Yes (IIIb-IV)	73	1.65 (0.69–3.97)			
Cancer status					
Controlled	60	1.00	0.084	1.00	
Uncontrolled, newly diagnosed	67	1.36 (0.54–3.47)		1.53 (0.45–5.28)	0.499
Uncontrolled, recurrence/progression	88	4.77 (1.20–18.87)		8.81 (1.56–49.67)	0.014
Performance status					
0–2	62	1.00	0.018		
3–4	89	4.98 (1.37–18.08)			
Airway obstruction by cancer					
No	62	1.00	0.049	1.00	
Yes	83	3.02 (1.10–8.30)		3.55 (1.02–12.32)	0.046
Weight loss > 10% of usual body weight					
No	69	1.00	0.943		
Yes	70	1.05 (0.25–4.38)			
Moderate/severe comorbidity (ACE-27)					
No	65	1.00	0.235		
Yes	79	2.08 (0.75–5.79)			
COPD					
No	69	1.00	0.999		
Yes	69	0.97 (040–1.80)			
Sepsis					
No	63	1.00	0.234		
Extrapulmonary source	50	0.60 (0.13–2.86)			
Pulmonary source	75	1.80 (0.72–4.54)			
ARDS					
No	59	1.00	0.096		
Yes	76	2.28 (0.96–5.40)			
Noninvasive ventilation					
No	72	1.00	0.112		
Yes	46	0.33 (0.10–1.07)			
Vasopressors					
No	44	1.00	0.003		
Yes	78	4.45 (1.74–11.40)			
No. of organ failures		1.88 (1.16–3.04)	0.011	1.95 (1.16–3.28)	0.012

*Area under the receiver operating characteristic curve = 0.79 (95% CI, 0.71 to 0.86); Hosmer-Lemeshow goodness of fit (χ^2 = 1.88; p = 0.984).

this subgroup. In the multivariate analysis, older age, cancer recurrence or progression, airway obstruction by cancer, and a larger number of organ failures were associated with increased mortality. Model fit and discrimination were good. In particular, among 24 patients with SCLC, cancer was considered a reason for MV in 19 patients; of these patients, only 1 survived. This patient received chemotherapy and radiation therapy in the ICU, was discharged on day 62, and died 82 days after ICU admission.

Discussion

Many patients with lung cancer require admission to the ICU during the course of the disease. That ICU admission is beneficial in the postoperative period after pulmonary resection for lung cancer is well established. However, when acute life-threatening complications develop, most notably ARF, oncologists and intensivists are often doubtful about the wisdom of ICU admission. ARF in these patients is usually considered a consequence of advanced disease that is not responsive to supportive care. To the best of our knowledge, the present study is the largest cohort of critically ill patients with lung cancer investigated to date. The study population consisted of patients from two large centers whose ICU triage policies are based on extensive experience with cancer patients.

In previous studies[11,12,14,15] of critically ill patients with lung cancer, mortality rates ranged from 75 to 91%. Very recently, Reichner et al[16] reported a 60% mortality rate in a study with 47 patients. Similarly, we found somewhat lower mortality rates, 59% overall and 69% in patients who needed MV. Over the last decade, advances in both oncology and intensive care have translated into better survival rates in ICU patients with cancer. In addition, improved selection of patients likely to benefit from ICU management may have contributed to the higher survival rates in our patients. Finally, few patients had treatment-related complications; notably, only five patients had neutropenia.

Together with the number of organ failures and the presence of cancer recurrence or progression, the severity of comorbidities was a major determinant of increased mortality in our study. Piccirillo and colleagues[13] reported that 69% of patients with lung cancer had comorbidities, and the highest levels of comorbidity were found in these patients.[33] Moreover, severe comorbidities as evaluated by ACE-27 score were associated with higher 6-month mortality rates in critically ill patients with cancer.[34]

Not surprisingly, ARF due to cancer invasion or compression was the strongest predictor of increased mortality, in keeping with a recent study.[29] In particular, all patients with SCLC (generally highly responsive to chemotherapy or radiation therapy) in whom cancer was considered a reason for MV died within 3 months after ICU admission, despite receiving anticancer treatment in the ICU. In a study by Jennens et al[15] of five patients with SCLC who required MV and received chemotherapy in the ICU, three patients had extensive disease, failed to respond to chemotherapy, and died shortly after ICU admission. Moreover, cancer involvement is associated with failure of noninvasive MV.[35] All these factors may explain the infrequent use of noninvasive ventilation in our patients. In a retrospective study[12] of 81 patients receiving MV, airway obstruction was not associated with a lower rate of weaning from MV. However, hospital mortality was 85.2%, and factors that predicted death were not evaluated.[12]

The present study has several limitations. Although standard definitions were used, biases related to differences in data collection between the centers cannot be ruled out. In many patients, long-term follow-up was not available. Although we focused on predictors of short-term mortality, we acknowledge this aspect as an important shortcoming of our study that deserves further evaluation. In addition, health-related quality of life was not assessed. Ideally, outcome evaluations should include parameters other than mortality. In a previous study of long-term survivors of NSCLC, high rates were found for comorbidities, distressed mood, and respiratory distress; nevertheless, health-related quality of life was good in 70% of patients.[36]

In conclusion, recent improvements in survival rates in patients with cancer who are admitted to the ICU seem to extend to patients with lung cancer, including those requiring MV, and ICU support can be of benefit for selected patients. Mortality increased with the number of organ failures and severity of comorbidities; however, the strongest predictor of mortality was respiratory failure due to cancer progression. Of special note, the type of the cancer *per se* was not associated with mortality and for that reason should not substantially influence ICU triage decisions in patients with lung cancer.

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