Intensive Care in Patients with Lung Cancer: A Multinational Study

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Keywords:	Lung Cancer, Intensive care, Cancer-related complications, Multicenter study, Outcome

Abstract:	Background: Detailed information about lung cancer patients requiring admission to intensive care units (ICU) is mostly restricted to single center studies. Our aim was to evaluate the clinical characteristics and outcomes of lung cancer patients admitted to ICUs. Patients and Methods: Prospective multicenter study in 449 patients with lung cancer (small-cell, n=55; non-small-cell, n=394) admitted to 22 ICUs in six countries in Europe and South America during 2011. Multivariate Cox proportional hazards frailty models were built to identify characteristics associated with 30-day and 6-month mortality. Results: Most of the patients (71%) had newly diagnosed cancer. Cancer-related complications occurred in 56% of patients; the most common was tumoral airway involvement (26%). Ventilatory support was required in 53% of patients. Overall hospital, 30-day and 6-month mortality rates were 39%, 41% and 55%, respectively. After adjustment for type of admission and early treatment-limitation decisions, determinants of mortality were organ dysfunction severity, poor performance status (PS), recurrent/progressive cancer, and cancer-related complications. Mortality rates were far lower in the patient subset with non-recurrent/progressive cancer and a good PS, even those with sepsis, multiple organ dysfunctions, and need for ventilatory support. Mortality was also lower in high-volume centers. Poor PS predicted failure to receive the initially planned cancer treatment after hospital discharge. Conclusions: ICU admission was associated with meaningful survival in lung cancer patients with good PS and non-recurrent/progressive disease. Conversely, mortality rates were very high in patients with intractable disease and poor PS. In this subgroup, palliative care may be the best option.

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Intensive Care in Patients with Lung Cancer: A Multinational Study

Running-head: Lung Cancer in Critical Care (LUCCA) Study

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ABSTRACT (248 words)

Background: Detailed information about lung cancer patients requiring admission to intensive care units (ICU) is mostly restricted to single center studies. Our aim was to evaluate the clinical characteristics and outcomes of lung cancer patients admitted to ICUs.

Patients and Methods: Prospective multicenter study in 449 patients with lung cancer (small-cell, n=55; non-small-cell, n=394) admitted to 22 ICUs in six countries in Europe and South America during 2011. Multivariate Cox proportional hazards frailty models were built to identify characteristics associated with 30-day and 6-month mortality.

Results: Most of the patients (71%) had newly diagnosed cancer. Cancer-related complications occurred in 56% of patients; the most common was tumoral airway involvement (26%). Ventilatory support was required in 53% of patients. Overall hospital, 30-day and 6-month mortality rates were 39%, 41% and 55%, respectively. After adjustment for type of admission and early treatment-limitation decisions, determinants of mortality were organ dysfunction severity, poor performance status (PS), recurrent/progressive cancer, and cancer-related complications. Mortality rates were far lower in the patient subset with non-recurrent/progressive cancer and a good PS, even those with sepsis, multiple organ dysfunctions, and need for ventilatory support. Mortality was also lower in high-volume centers. Poor PS predicted failure to receive the initially planned cancer treatment after hospital discharge.

Conclusions: ICU admission was associated with meaningful survival in lung cancer patients with good PS and non-recurrent/progressive disease. Conversely, mortality

rates were very high in patients with intractable disease and poor PS. In this subgroup, palliative care may be the best option.

Key words: Lung Cancer, intensive care, cancer-related complications, multicenter study, outcome.

Abbreviation List

Confidence interval - CI

Electronic Supplementary Material - ESM

Eastern Cooperative Oncology Group - ECOG

Intensive care unit - ICU

Interquartile range – IQR

Length of stay - LOS

Non-small-cell lung cancer - NSCLC

Organ failure - OF

Performance status – PS

Renal replacement therapy - RRT

Small-cell lung cancer - SCLC

Sequential Organ Failure Assessment – SOFA

Simplified Acute Physiology Score - SAPS

Surveillance, Epidemiology, and End Results - SEER

Treatment limitation decisions – TLD

Word Count: 2,732 (Text: 2,159 words; References: 573 words)

INTRODUCTION

Lung cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality worldwide.[1] Despite advances in the management, overall long-term survival remains poor particularly in patients with non-resectable or metastatic tumors.[2] Nevertheless, complete recovery or prolonged survival can be achieved in some patients with non-small-cell lung cancer (NSCLC).[3-5]

Lung cancer patients account for approximately 8% of all ICU admissions of patients with malignancies and 27% of those with solid cancer.[6,7] Over the last decade, improvements in ICU outcomes of these patients were documented in studies performed worldwide.[8-13] However, lung cancer patients are usually perceived as having substantially worse ICU outcomes compared to other cancer patients. Therefore, ICU admission for life-threatening events is still widely viewed as unlikely to benefit these patients, particularly when ventilatory support is needed.[14,15]

The available information about lung cancer patients requiring ICU admission comes chiefly from single-center studies reporting ICU or hospital mortality rates in small groups of patients.[8-15] Recently, however, two studies used administrative databases to evaluate the outcomes of lung cancer patients admitted to the ICU.[16,17] Nevertheless, both were conducted in a single country (the USA) and did not provide detailed information about the reasons for ICU admission, characteristics of the lung malignancies, or anticancer treatments. Moreover, data on the clinical course and anticancer treatment continuation rates in ICU survivors are very limited.[10]

Here, our objective was to study a large population of critically ill patients with lung cancer admitted to European or South American ICUs, in order to describe their clinical characteristics and outcomes and to identify factors associated with short- and long-term mortality.

PATIENTS AND METHODS

Design and Setting

This prospective multinational cohort study was conducted in 22 ICUs in Argentina (n=1), Brazil (n=5), Chile (n=1), France (n=10), the United Kingdom (n=2), and Uruguay (n=3) throughout 2011. All participating investigators and centers are listed in the eAppendix of the Electronic Supplementary Material (ESM). The study was observational, with all clinical decisions left to the attending physicians. The study was approved initially by the Brazilian National Ethics Committee (approval number CONEP 15.790) and subsequently by local and national ethics committees in the participating centers and countries. In the few centers that required informed consent for the study, written informed consent was obtained from each patient or legal representative before study inclusion.

Patient Selection, Data Collection, and Definitions

Consecutive patients aged ≥18 years with a diagnosis of lung cancer requiring ICU admission at the participating centers were evaluated. We did not include patients with ICU stays shorter than <24 h, complete cancer remission for more than 5 years,

previous ICU admission, malignancies other than primary lung cancer, or unwillingness to participate in the study.

Demographic, clinical, and laboratory data collected included hospital location before ICU, reason for ICU admission, Eastern Cooperative Oncology Group performance status (ECOG-PS),[18] Simplified Acute Physiology Score (SAPS) II,[19] Sequential Organ Failure Assessment (SOFA) score,[20] and comorbidities with determination of the Charlson Comorbidity Index [21]. The use during the ICU stay of ventilatory support (invasive and non-invasive mechanical ventilation) for longer than 24h, vasopressors, and renal replacement therapy (RRT) were recorded. The following cancer-related data were collected: histological type, cancer stage, anticancer treatments (radiation, chemotherapy, and surgical resection), cancer-related complications, and cancer status (newly diagnosed, recurrent/progressive, or in remission). In patients with non-small cell lung cancer (NSCLC), disease stage was evaluated using the TNM classification, with limited disease defined as stage I-IIIa and extensive disease as stage IIIb-IV. Lung cancer was considered a reason for ventilatory support in patients with bilateral lung involvement, carcinomatous lymphangitis, or tumor masses causing airway obstruction.[8] All patients were followed up until hospital discharge. In addition, hospital survivors were followed up until 6 months after ICU admission.

Data entry and processing

Data were collected using a web-based standardized electronic case report form developed specifically for the study. All investigators and research coordinators had access to the website, which contained all the study documents including a manual detailing the data-collection requirements and definitions. The investigators could

contact the steering committee members and country coordinators by telephone and email if needed. Local investigators completed a form reporting the ICU and hospital characteristics and were responsible for supervising data collection and checking data completeness and quality. Data were screened by a single investigator (MS) for missing information, implausible and outlying values, errors in logic, and lack of detail; this investigator contacted the local investigators as needed to resolve these issues.

Statistical Analysis

Continuous variables were reported as mean±SD or median (25%-75% interquartile range, IQR). Patients were managed in different centers, giving the data a multilevel structure. We used a shared frailty model to identify factors associated with death (PROC PHREG SAS 9.3). Risk factors for 30-day and 6-month mortality were estimated using a Cox proportional hazards frailty model. The center effect was handled as a random effect in the model. Variables included in the multivariate model were those yielding *P* values <0.25 in univariate frailty models. Center- and patient-related variables yielding *P* values <0.05 in the multivariate context were kept in the model. Survival curves were plotted using the Kaplan-Meier method. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). *P* values less than 0.05 were considered significant.

RESULTS

Characteristics of participating hospitals and ICUs

The main characteristics of the 22 participating hospitals and ICUs are listed in Table 1. Lung cancer patients accounted for 3.5% (716/20,351; range: 0.4%-17.8%) of all ICU admissions during the study period. The median number of patients admitted per center during the study year was 18 (IQR, 7-50; range, 3-138) and the median number of patients included in the study per center was 15 (IQR, 6-29; range, 2-69). The study flowchart is given in eFigure 1 of the ESM.

Patient characteristics

Tables 2 and 3 report the main characteristics of the 449 patients included in the study. The main reasons for ICU admission were postoperative complications (41%), acute respiratory failure (23%) and sepsis (21%).

There were 394 (88%) patients with NSCLC and 55 (12%) patients with SCLC. The most frequent histological type was adenocarcinoma (57%). Median time since cancer diagnosis was 74 (IQR, 22-185) days. Previous anticancer treatments included surgical resection (17%), radiation therapy (22%), and single-drug or combination chemotherapy (42%). More than half the patients had cancer-related complications at ICU admission, with the most common being airway compromise by the tumor (Table 3).

Outcome analysis

The overall ICU, hospital, 30-day and 6-month mortality rates were 28%, 39%, 41% and 55%, respectively. Treatment-limitation decisions (TLD) were taken in 138 (31%) patients, after a median of 4 (1-11) days in the ICU admission, and 110 (80%) of

these patients died in the hospital. Of note, TLD were implemented on the first ICU day in 38 (8%) patients. Table 2 compares the survivors and non-survivors.

The results of the univariate analyses to identify factors associated with 30-day and 6-month mortality are reported in eTables 1 and 2 of the ESM. Center-related variables assessed by univariate analysis were type of hospital, number of hospital beds, type of ICU, and percentage of all ICU admissions contributed by lung cancer patients during the study period. Patient-related data were age, type of ICU admission, hospital length of stay before ICU admission, SOFA score, Charlson index, PS, TLD on the first ICU day, type of lung cancer, cancer stage and status, and presence of cancer-related complications.

Table 4 reports the results of the multivariate analyses. After adjustment for type of admission and TLD taken on the first ICU day, the main determinants of 30-day and 6-month mortality were higher SOFA scores, poor PS, recurrent/progressive cancer, and presence of cancer-related complications (airway compromise, deep vein thrombosis, or superior vena cava syndrome). Admission to high-volume centers was associated with lower mortality, particularly at 30 days. Histological type of cancer was not associated with mortality. Figure 2 shows mortality rates according to the main combinations of PS, cancer status, and treatment requirements. Survival curves for all patients and subsets defined based on prognostic factors are provided in the ESM (eFigures 2a to 2f).

Emergency anticancer treatments during the ICU stay

Twenty-five (NSCLC=14; SCLC=11) patients received emergency anticancer treatments (chemotherapy, n==20; radiation therapy, n=4; both, n=1) in the ICU. In 17/25 (68%) patients, the reason for emergency anticancer treatment was extensive

disease causing severe acute complications being the most frequent airway compromise (56%) and large pleural/pericardial effusion (44%). No severe treatment-related complications occurred during the ICU stay. ICU, hospital, and 6-month mortality rates in these 25 patients were 36%, 44%, and 68%, respectively.

Picture of hospital survivors

Of the 449 patients, 275 were discharged alive from the hospital, 246 (89%) with NSCLC and 29 (11%) with SCLC. Among them, 200 (73%) were known to be alive at 6 months and 72 (26%) had died; vital status was unknown for 3 (1%) patients. Cancer recurrence or progression occurred in 53 (26%) hospital survivors. Anticancer treatments were recommended to 108 (39%) hospital survivors and administered to 102; anticancer treatment was not recommended to 121 (44%) patients and information on this item was not available for 46 (17%) patients. In the 102 treated patients, the treatments used were variable combinations of surgical resection (7%), radiation therapy (34%), and chemotherapy (80%). In 35 (34%) patients, the initial anticancer treatment plan required reduction or modification. Post-hospital mortality was non-significantly lower in the patients given the initial treatment plan than in the other patients (17% vs. 32%, P=0.065). Poor PS was the only factor associated with a lower probability of receiving the initial treatment plan (odds ratio, 0.20; 95% confidence interval, 0.05-0.87; P=0.032).

Among the 200 patients alive at 6 months, 142 (71%) were at home, 30 (15%) were hospitalized, and 14 (7%) were in hospice care; the location was unknown for 12 (6%) patients. PS at 6 months was 3-4 in 19 (9.5%) survivors.

DISCUSSION

This multinational study obtained prospective data in a large population of lung cancer patients admitted to the ICU. Lung cancer patients accounted for 3.5% of all ICU admissions. Their mortality rates were comparable to those in unselected cancer patients requiring ICU admission in previous multicenter studies.[6,7] Slightly over one-third of hospital survivors received anticancer treatments after discharge. Most of 6-month survivors were living at home.

In recent years, several specialized centers reported improved outcomes after ICU admission of lung cancer patients.[8-13] Two studies were published recently using administrative databases that contained no information on many relevant clinical characteristics.[16,17] In contrast to earlier studies, we considered both center- and patient-related variables in our assessment of factors potentially associated with mortality. After adjustment for medical vs. surgical ICU admission and TLD on the first ICU day, in addition to the severity of acute organ dysfunctions, three main factors were associated with increased 6-month mortality: poor PS before ICU admission, recurrent or progressive cancer, and presence of serious cancer-related complications (airway compromise, deep vein thrombosis, or superior vena cava syndrome). PS before ICU admission was closely associated with 30-day and 6-month mortality across the range of clinical presentations. In addition, a poor PS also predicted inability to receive the initial anticancer treatment plan in hospital survivors. Importantly, admission to high-volume centers was associated with lower mortality. This effect may be related to experience,

closer collaboration between oncologists and intensivists, or more efficient ICU triage policies.

At ICU admission, about half the patients had cancer-related complications, some of which required emergency treatment. Thus, 25 patients received emergent chemotherapy and/or radiation therapy in the ICU. These treatments were not associated with increased mortality or acute toxicities, although their impact on the long term-outcome is unclear. Hospital and six-month mortality rates of 44% and 68%, respectively, in these 25 patients suggest that rescue anticancer treatment started in the ICU may be of benefit in highly selected patients.

Strengths of our study include the large number of patients from different countries admitted not only in referral cancer centers, but also in general hospitals. Patient recruitment over a single year minimized the possible influence of changes in treatment modalities over time. A limitation of our study is that we included patients admitted to a convenience sample of centers in six countries. Therefore, our population cannot be considered representative of all lung cancer patients admitted to the ICU. In addition, we obtained data only for the first 6 months after ICU admission. Information on longer-term outcomes is needed. Finally, we did not collect data on quality of life.

In conclusion, in this multinational study, ICU admission provided substantial survival rates in patients with good PS and non-recurrent/progressive disease, including those who had severe acute complications such as sepsis, multiple organ failure, and need for ventilatory support. In addition, more than a third of the hospital survivors received anticancer treatment. PS before ICU admission was associated with both mortality and ability to receive optimal anticancer treatment after hospital discharge. On

the other hand, mortality rates were very high in patients with intractable disease and poor PS. In this subgroup, palliative care may be the best option.[22,23]

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Author contributions: Study concept and design: MS, JIFS and EA; Acquisition of data: all authors; Analysis and interpretation of data: MS, ACT, JFT; Drafting of the manuscript: MS, JIFS, ACT, JFT, EA; Critical revision of the manuscript for important intellectual content: all authors; Statistical expertise: ACT and JFT; Study supervision: MS, EA; Approval of the final version of manuscript: all authors. Dr. Soares had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

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FIGURE LEGENDS

Figure. ICU (white bars), hospital (gray bars), and 6-month (black bars) mortality rates according to clinical presentation in critically ill patients with lung cancer. PS, performance status; Ca_Progress, cancer recurrence or progression; Ca_Complic, cancer-related complications; MODS, multiple organ dysfunction syndrome; Non_Ca_Progress, no recurrence or progression of the cancer; Vent_Supp, ventilatory support.

Electronic Supplementary Material (ESM)

Table 1– Characteristics of participating centers (n=22)

Variables	n (%) or median (IQR)
Hospital characteristics	
Type of hospital	
University/affiliated	14 (64%)
Private	8 (36%)
Hospital beds	345 (215 – 723)
<200	5 (23%)
200-499	8 (36%)
≥500	9 (41%)
Hospital facilities	
Intermediate/step-down unit	15 (68%)
Oncology department	22 (100%)
Radiation therapy unit	16 (73%)
Chemotherapy	20 (91%)
Bone marrow transplant unit	16 (73%)
ICU characteristics	
Type of ICU	
General	18 (82%)
Oncological	4 (18%)
Closed ICU	19 (86%)
ICU beds	15 (12 – 20)
≤10	4 (18%)
11-20	13 (59%)
>20	5 (23%)
Persons involved in ICU-admission triage decisions	
ICU physician	20 (91%)
Attending oncologist	9 (41%)
ICU nurse	1 (4%)
Family/patient	4 (18%)
ICU admissions of patients with lung cancer in 2011	
% total admissions contributed by patients with lung cancer (quartiles) [a]	
<3%	12 (55%)
3% - 5%	4 (18%)
5% - 6.7%	3 (14%)
>6.7%	2 (9%)

ICU, intensive care unit; IQR, 25%-75% interquartile range

[a][ICU admissions of patients with lung cancer (n)/All ICU admissions (n)]·100

Table 2. Main patient characteristics and comparison of 6-month survivors and nonsurvivors[a,b]

Variables	All patients (n=449)	Survivors (n=203, 45%)	Nonsurvivors (n=246, 55%)	*P* value[c]
Characteristics at ICU admission				
Age (years)	63.8 ± 11.7	62.7 ± 11.9	64.7 ± 11.6	0.096
Gender				
Female	148 (33%)	67 (45%)	81 (55%)	0.986
Male	301 (67%)	136 (45%)	165 (55%)	
Type of admission				
Surgical	182 (41%)	132 (73%)	50 (27%)	$<10^{-4}$
Medical	267 (59%)	71 (27%)	196 (73%)	
Hospital LOS prior to ICU admission (days)	1 (0-4)	1 (0-2)	2 (0-6)	0.004
SAPS II (points)	46.1 ± 19.1	36.5 ± 13.9	54.1 ± 19.1	$<10^{-4}$
SOFA score – First ICU day (points)	5 (3-8)	4 (2-6)	6 (4-11)	$<10^{-4}$
Charlson Comorbidity Index (points) [d]	0 (0-1)	0 (0-1)	0 (0-1)	
0-2	414 (92%)	186 (45%)	228 (55%)	0.678
>2	35 (8%)	17 (49%)	18 (51%)	
Performance status				
0-2	379 (84%)	195 (51%)	184 (49%)	$<10^{-4}$
3-4	70 (16%)	8 (11%)	62 (89%)	
Organ support during ICU stay				
Ventilatory support on day 1	239 (53%)	79 (33%)	160 (67%)	$<10^{-4}$
Vasopressors on day 1	128 (29%)	34 (27%)	94 (73%)	$<10^{-4}$
Dialysis on day 1	20 (4%)	4 (20%)	16 (80%)	0.021

Table 2. Main patient characteristics and comparison of 6-month survivors and nonsurvivors[a,b] (continued)

Variables	All patients (n=449)	Survivors (n=203, 45%)	Nonsurvivors (n=246, 55%)	*P* value [c]
Outcome data				
Treatment-limitation decisions	138 (31%)	8 (6%)	130 (94%)	$<10^{-4}$
Treatment-limitation decisions on day 1	38 (8%)	3 (8%)	35 (92%)	$<10^{-4}$
ICU LOS (days)	4 (2-10)	4 (2-7)	6 (3-11)	$4 \cdot 10^{-4}$
Hospital LOS (days)	14 (8-26)	13 (7-22)	16 (8-27)	0.188
Survival censoring at 6 months (days)	48 (11-180)	-	-	
ICU mortality	126 (28%)	-	-	
Hospital mortality	174 (39%)	-	-	
30-day mortality	186 (41%)	-	-	
Six-month mortality [b]	246 (55%)	-	-	

[a]Data are mean±SD, median (25%-75% IQR), or n (%).
[b]Survival 6 months after ICU admission. Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.
[c]*P* values for survivors versus nonsurvivors
[d]Lung cancer was not considered when computing the Charlson Comorbidity Index.
ICU, intensive care unit; LOS, length of stay; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; IQR, interquartile range

Table 3. Cancer-related data and comparison of 6-month survivors and nonsurvivors[a]

Variables	All patients (n=449)	Survivors (n=203, 45%)	Nonsurvivors (n=246, 55%)	*P* value[b]
Type of lung cancer				
NSCLC	394 (88%)	181 (46)	213 (64)	
Adenocarcinoma	258 (57%)	118 (46)	140 (54)	0.850
Squamous cell	120 (27%)	55 (46)	65 (54)	
Other	16 (4%)	8 (50)	8 (50)	
SCLC	55 (12%)	22 (40)	33 (60)	
Cancer stage				$<10^{-4}$
Limited	171 (38%)	112 (66)	59 (35)	
Extensive	278 (62%)	91 (33)	187 (67)	
Cancer status				$<10^{-4}$
Controlled/remission	32 (7%)	21 (66)	11 (34)	
Newly-diagnosed	318 (71%)	160 (50)	158 (50)	
Recurrence/progression	99 (22%)	22 (22)	77 (78)	
Cancer-related complications at ICU admission	251 (56%)	79 (31)	172 (69)	$<10^{-4}$
Airway compromise by tumor	116 (26%)	36 (31)	80 (69)	$4{\cdot}10^{-4}$
Chemotherapy and/or radiation toxicity	55 (12%)	14 (25%)	41 (75%)	0.002
Deep vein thrombosis	35 (8%)	4 (11%)	31 (89%)	$<10^{-4}$
Neutropenia	26 (6%)	4 (15%)	22 (85%)	0.002
Superior vena cava syndrome	20 (5%)	4 (20)	16 (80)	0.021
Intracranial mass effect	21 (5%)	5 (24%)	16 (76%)	0.044
Hypercalcemia	7 (2%)	1 (14%)	6 (86%)	0.132

Table 3. Cancer-related data and comparison of 6-month survivors and nonsurvivors [a] (continued)

Variables	All patients (n=449)	Survivors (n=203, 45%)	Nonsurvivors (n=246, 55%)	*P* value[b]
Spinal cord compression	7 (7%)	0	7 (100%)	0.017
Other	67 (15%)	27 (40%)	40 (60%)	0.411
Emergency anticancer treatments during ICU stay[c]	25 (6%)	7 (28)	18 (72)	0.0752
Chemotherapy	21	-	-	
Radiation therapy	5	-	-	

[a]Survival 6 months after ICU admission. Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.
[b]*P* values for patients with lung cancer versus other solid tumors
[c]One patient received both chemotherapy and radiation therapy.
NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ICU, intensive care unit

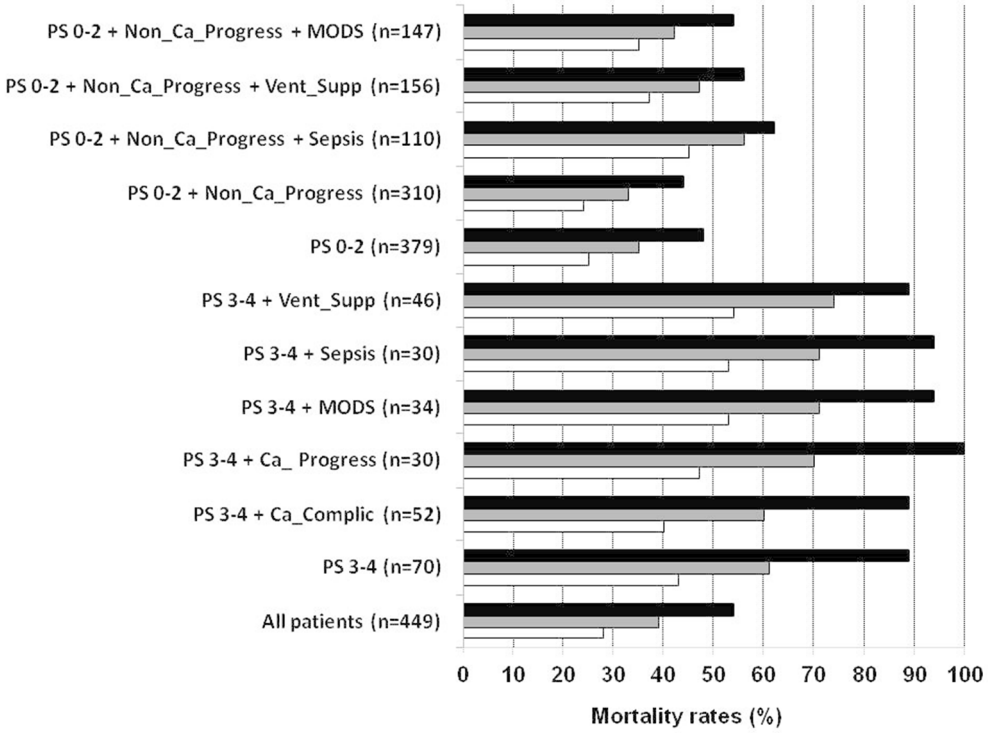
Table 4. Cox proportional hazards frailty models of characteristics associated with 30-day and six-month mortality (n=449)[a]

	Censored at 30 days		Censored at 6-months	
Variables	Hazard Ratio (95%CI)	*P* value	Hazard Ratio (95%CI)	*P* value
Type of admission				
Surgical	1.000		-	
Medical	1.675 (1.113 – 2.521)	0.013	-	
SOFA score for all patients (points)	1.112 (1.076 – 1.150)	<0.001	-	
SOFA score for medical patients[b]	-		1.125 (1.093 – 1.159)	<0.001
SOFA score for surgical patients[b]	-		1.090 (1.025 – 1.159)	0.006
Performance status				
0-2	1.000		1.000	
3-4	2.083 (1.470 – 2.953)	<0.001	2.342 (1.680 – 3.265)	<0.001
Cancer status according to TLDs on ICU day 1[c]		<0.001		<0.001
Controlled /remission without TLDs (n=31)	1.000		1.000	
Newly-diagnosed without TLDs (n=294)	2.482 (0.902 – 6.828)		1.484 (0.765 – 2.876)	
Recurrence/progression without TLDs (n=86)	3.690 (1.313 – 10.373)		2.509 (1.261 – 4.994)	
Controlled/remission with TLDs (n=1)	214.077 (20.621 – 2,222.411)		149.678 (15.610 – 1,435.223)	
Newly-diagnosed with TLDs (n=24)	6.589 (2.180 – 19.912)		4.603 (2.067 – 10.251)	
Recurrence/progression with TLDs (n=13)	10.795 (3.421 – 34.071)		6.119 (2.502 – 14.969)	
Cancer-related complications at ICU admission				
Airway compromise by tumor	1.671 (1.208 – 2.313)	0.002	1.541 (1.150 – 2.066)	0.004
Deep vein thrombosis	1.711 (1.109 – 2.637)	0.015	1.873 (1.244 – 2.822)	0.003
Superior vena cava syndrome	1.738 (1.006 – 3.000)	0.047	-	

Table 4. Cox proportional hazards frailty models of characteristics associated with 30-day and six-month mortality (n=449)[a] (continued)

	Censored at 30 days		Censored at 6-months	
Variables	Hazard Ratio (95%CI)	*P* value	Hazard Ratio (95%CI)	*P* value
% total admissions contributed by patients with lung cancer in 2011[d]		0.001		0.026
<3%	1.000		1.00	
3%-5%	1.053 (0.699-1.585)		1.123 (0.630 – 2.003)	
>5%-6.7%	1.064 (0.704-1.607)		0.955 (0.478 – 1.909)	
>6.7%	0.467 (0.293-0.744)		0.559 (0.307 – 1.017)	

[a]Survival 6 months after ICU admission. Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.
[b]There was a significant interaction between SOFA scores and type of admission in the model with censoring at 6 months (*P*=0.009).
[c]There was a significant interaction between cancer status and treatment-limitation decision on ICU day 1 in both models (*P*=0.002).
[d][ICU admissions of patients with lung cancer (n)/All ICU admissions (n)]·100
95%CI, 95% confidence interval; SOFA, Sequential Organ Failure Assessment; TLD, treatment-limitation decision; ICU, intensive care unit



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ELECTRONIC SUPPLEMENTARY MATERIAL

Intensive Care in Patients with Lung Cancer: A Multinational Study

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eTable 1. Univariate analyses of center-related characteristics associated with 30-day and 6-month mortality (n=449)[a]

	Censored at 30 days		Censored at 6 months	
Variables	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Hospital characteristics				
Type of hospital				
University/affiliated vs. private	1.140 (0.703-1.847)	0.290	1.272 (0.781-2.074)	0.104
Hospital beds		0.057		0.020
<200	1		1	
200-499	1.592 (0.857-2.958)		1.778 (0.965-3.277)	
≥500	1.858 (0.962-3.587)		2.020 (1.060-3.850)	
Hospital facilities				
Intermediate / step down unit	0.930 (0.554-1.562)	0.421	0.999 (0.584-1.707)	0.805
Radiation therapy unit	1.279 (0.738-2.214)	0.188	1.177 (0.674-2.058)	0.245
Bone marrow transplant unit	1.160 (0.689-1.951)	0.291	1.218 (0.717-2.067)	0.170
ICU characteristics				
Type of ICU: oncological vs. general	1.117 (0.616-2.024)	0.358	1.022 (0.549-1.903)	0.559
ICU beds		0.463		0.408
≤10	1		1	
11 – 20	1.009 (0.536-1.902)		0.865 (0.453-1.649)	
>20	1.179 (0.583-2.383)		0.953 (0.458-1.984)	
% admissions of patients with lung cancer in 2011 [b]		0.004		0.014
<3%	1		1	
3% to 5%	0.897 (0.560-1.435)		1.011 (0.584-1.752)	
5% to 6.7%	0.693 (0.418-1.150)		0.666 (0.348-1.276)	
> 6.7%	0.432 (0.258-0.726)		0.532 (0.301-0.941)	

ICU, intensive care unit; HR, hazard ratio; CI, confidence interval

[a] Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.

[b] [ICU admissions of patients with lung cancer (n) /All ICU admissions (n)]·100

eTable 2. Univariate analyses of patient-related characteristics associated with 30-day and 6-month mortality (n=449)[a]

	Censored at 30 days		Censored at six months	
Variables	HR (95%CI)	P value	HR (95%CI)	*P* value
Characteristics at ICU admission				
Age (years)		0.895		0.893
<57	1		1	
57-64	0.898 (0.592-1.360)		1.069 (0.737-1.550)	
65-71	0.878 (0.569-1.357)		1.052 (0.716-1.547)	
>71	0.992 (0.661-1.490)		1.151 (0.797-1.663)	
Male vs. Female	0.997 (0.732-1.359)	0.986	1.020 (0.777-1.339)	0.883
Medical vs. surgical admission	3.610 (2.478-5.260)	<0.001	4.163 (2.982-5.813)	<0.001
Hospital LOS before ICU admission (days)		0.006		2.10^{-4}
0	1		1	
0-3	0.850 (0.577-1.253)		0.747 (0.527-1.058)	
≥4	1.506 (1.041-2.177)		1.491 (1.076-2.065)	
SAPS II (per point)	1.037 (1.030-1.045)	<0.001	1.039 (1.032-1.046)	<0.001[4]
SOFA score (per point)	1.123 (1.088-1.159)	<0.001	1.120 (1.089-1.153)	<0.001
Charlson Comorbidity Index: >2 vs. 0-2	0.803 (0.449-1.435)	0.447	0.856 (0.519-1.411)	0.529
Performance status: 3-4 vs. 0-2	3.267 (2.325-4.592)	<0.001	3.593 (2.613-4.941)	<0.001
Organ support on ICU day 1				
Mechanical ventilation (IMV + NIV)	2.747 (1.987-3.797)	<0.001	2.340 (1.776-3.083)	<0.001
Vasopressors	2.254 (1.666-3.051)	<0.001	2.132 (1.625-2.796)	<0.001
Dialysis	2.145 (1.183-3.890)	0.011	2.212 (1.287-3.802)	0.004
Treatment limitation decisions on day 1	4.213 (2.755-6.443)	<0.001	3.902 (2.612-5.828)	<0.001

[a] Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.

HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; LOS, length of stay; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation; TLD, treatment-limitation decisions

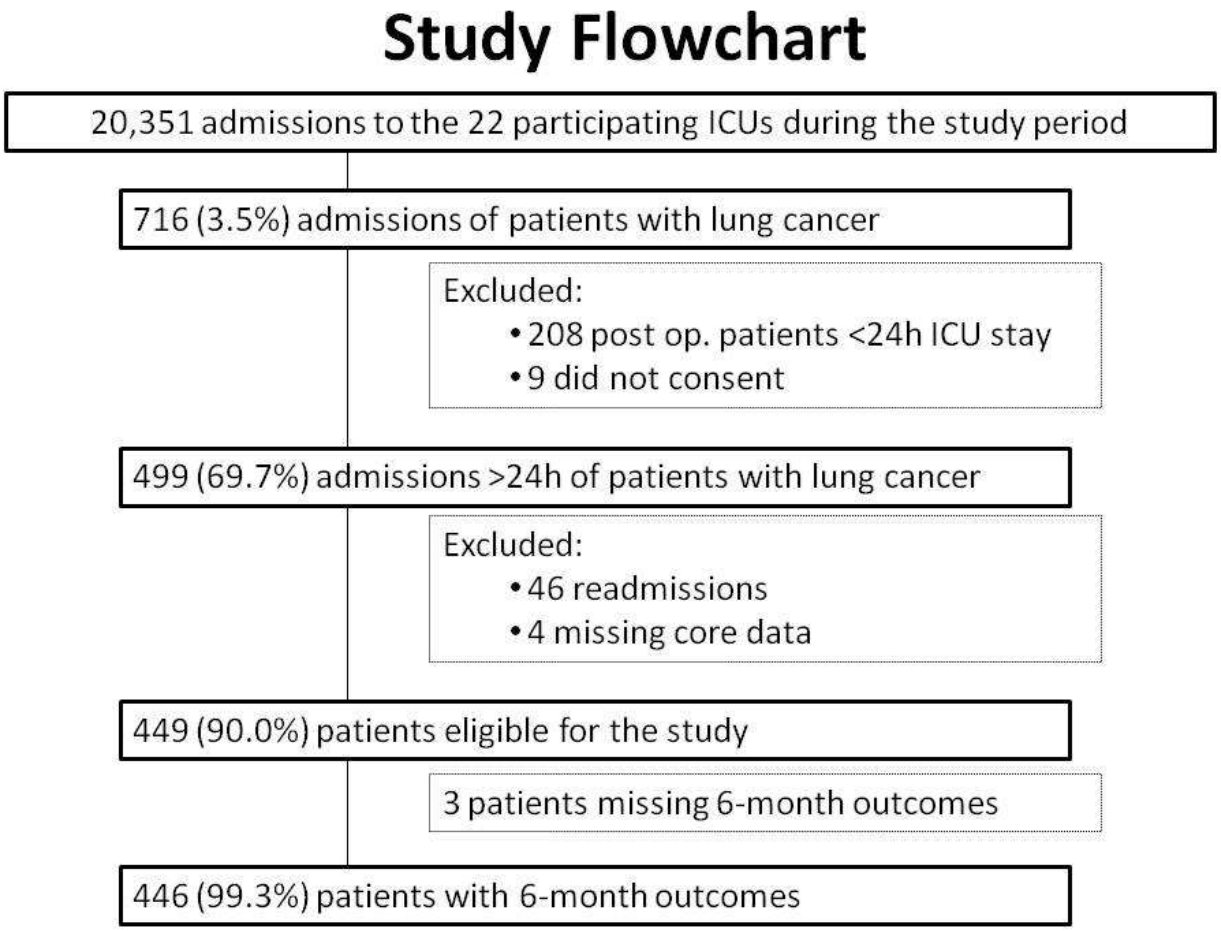
eTable 2. Univariate analyses of patient-related characteristics associated with 30-day and 6-month mortality (n=449)[a]

	Censored at 30 days		Censored at six months	
Variables	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Cancer-related characteristics				
Type of lung cancer		0.179		0.602
Adenocarcicnoma	1		1	
Squamous-cell	1.058 (0.748-1.498)		0.977 (0.721-1.323)	
Other	1.268 (0.581-2.770)		1.019 (0.491-2.114)	
SCLC	1.595 (1.043-2.440)		1.289 (0.868-1.913)	
Extensive disease	2.652 (1.861-3.777)	<0.001	2.496 (1.845-3.377)	<0.001
Cancer status		<0.001		<0.001
Controlled/remission	1		1	
Uncontrolled, newly-diagnosed	3.054 (1.236-7.545)		1.998 (1.069-3.732)	
Uncontrolled, recurrence/progression	5.651 (2.243-14.233)		3.936 (2.060-7.519)	
Cancer-related complications at ICU admission	2.727 (1.950-3.815)	<0.001	2.533 (1.903-3.371)	<0.001
Airway compromise by cancer	2.090 (1.535-2.845)	<0.001	1.933 (1.462-2.556)	<0.001
Chemotherapy and/or radiation toxicity	1.747 (1.188-2.571)	0.004	1.633 (1.147-2.326)	0.006
Deep vein thrombosis	2.503 (1.619-3.869)	<0.001	2.654 (1.778-3.963)	<0.001
Neutropenia	1.575 (0.929-2.672)	0.088	1.817 (1.150-2.871)	0.010
Superior vena cava syndrome	2.513 (1.463-4.317)	8.10^{-4}	2.185 (1.296-3.683)	0.003
Intracranial mass effect	1.265 (0.668-2.393)	0.453	1.414 (0.823-2.431)	0.198
Emergent anticancer treatments during ICU stay	0.971 (0.534-1.766)	0.919	1.134 (0.690-1.864)	0.610

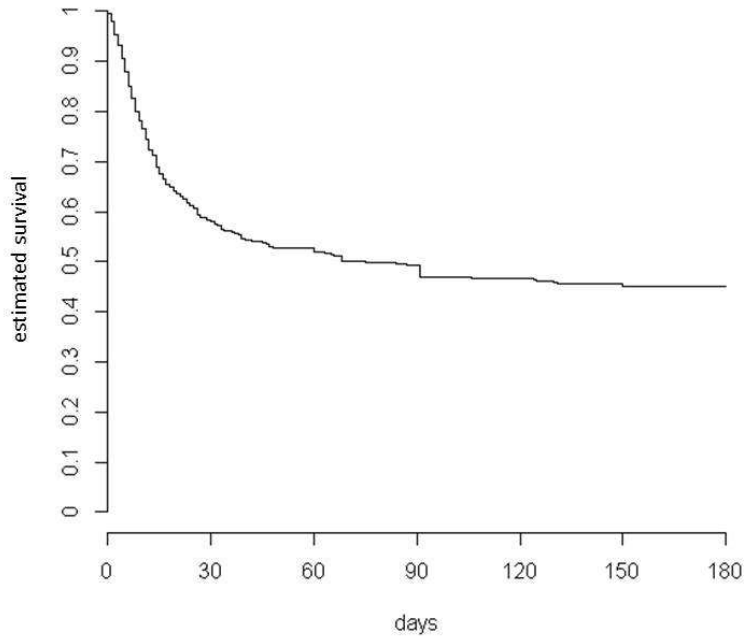
[a] Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.

HR, hazard ratio; CI, confidence interval; SCLC, small cell lung cancer; ICU, intensive care unit

eFigure 1. Study flowchart

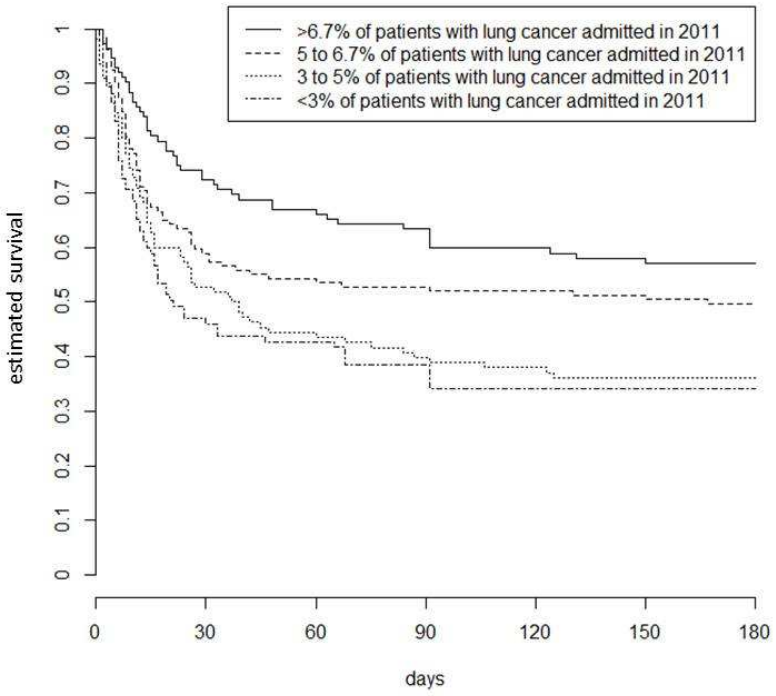


eFigure 2a. Survival curve for all patients (n=449)



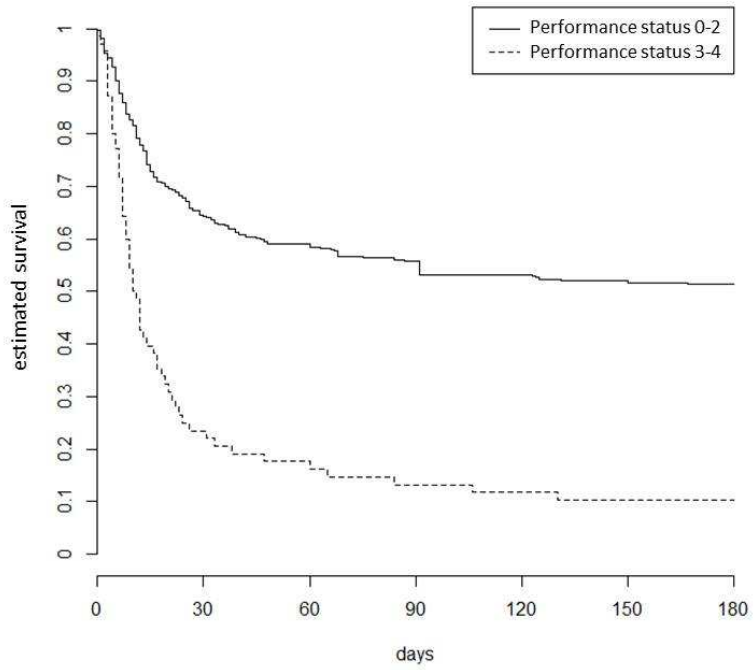
n at risk	d0	d30	d60	d90	d120	d150	d180
	449	260	234	219	208	203	200

eFigure 2b. Survival according to proportion of ICU patients with lung cancer among all ICU admissions in 2011



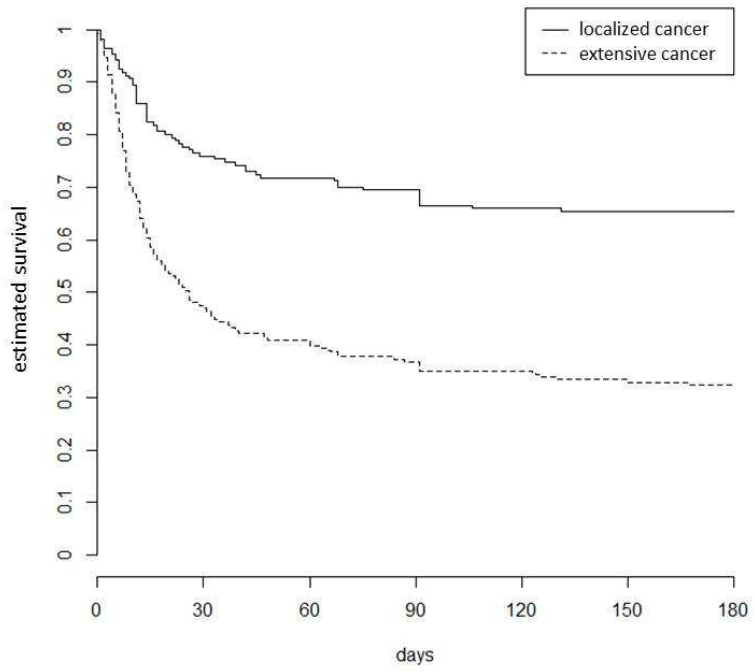
n at risk	d0	d30	d60	d90	d120	d150	d180
>6.7%	112	81	75	71	67	65	64
5 to 6.7%	132	77	71	69	68	67	65
3 to 5%	110	58	48	43	41	39	39
<3%	95	44	40	36	32	32	32

eFigure 2c. Survival according to performance status.



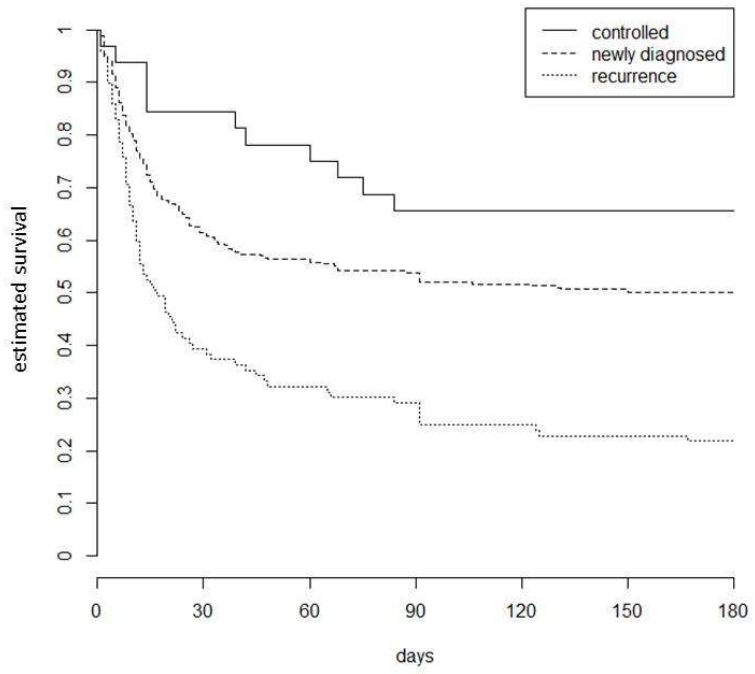
n at risk	d0	d30	d60	d90	d120	d150	d180
PS 0-2	379	244	222	210	200	196	193
PS 3-4	70	16	12	9	8	7	7

eFigure 2d. Survival according to cancer stage.



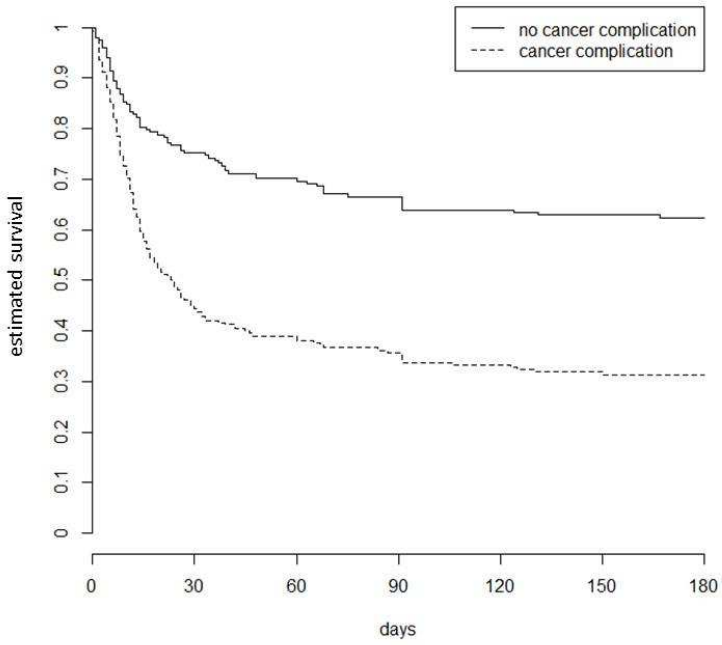
n at risk	d0	d30	d60	d90	d120	d150	d180
Localised	171	129	122	118	112	111	111
Extensive	278	131	112	101	96	92	89

eFigure 2e. Survival according to cancer status.



n at risk	d0	d30	d60	d90	d120	d150	d180
Controlled	32	27	25	21	21	21	21
Newly diagnosed	318	194	178	170	163	160	158
Recurrence	99	39	31	28	24	22	21

eFigure 2f. Survival according to cancer complication at ICU admission.



n at risk	d0	d30	d60	d90	d120	d150	d180
No cancer complication	198	148	137	130	125	123	122
Cancer complication	251	112	97	89	83	80	78