



Intensive Care in Patients with Lung Cancer: A Multinational Study

Journal:	<i>Annals of Oncology</i>
Manuscript ID:	ANNONC-2014-0637
Manuscript Type:	Original Article
Date Submitted by the Author:	12-Apr-2014
Complete List of Authors:	<p>Soares, Marcio; D'Or Institute for Research and Education, Clinical Research TOFFART, Anne-Claire; Centre Hospitalier Universitaire A Michallon, Thoracic Oncology Unit Timsit, J-F; University Hospital Albert Michallon, 38043 Grenoble Cedex, France, medical ICU; INSERM/UJF U 823-Albert Bonniot institute, Groupe d'Epidemiologie des Cancers et des Affections Graves Burghi, gaston; Hospital Maciel, ICU Irrazabal, Celica; Instituto Medico Especializado Alexander Fleming, ICU Pattison, Natalie; Royal Brompton NHS Foundation Trust, ICU Tobar, Eduardo; Hospital Clinico Universidad de Chile, ICU Almeida, Bruno; Hospital A. C. Camargo, ICU Silva, Ulysses; Hospital do Câncer de Barretos - Fundação Pio XII, ICU Azevedo, Luciano; Hospital Sírio Libanês, ICU Rabbat, Antoine; CHU Hotel Dieu, Réanimation Lamer, Christian; Institut Mutualiste Montsouris, ICU Parrot, Antoine; Hopital TENON, APHP, ICU Souza-Dantas, Vicente; Instituto Nacional de Cancer, ICU Wallet, Florent; Hospices civils de Lyon, Centre Hospitalier Lyon Sud, Department of anesthesiology Blot, François; Gustave Roussy, ICU BOURDIN, GAEL; hopital de la croix rousse, ICU Piras, Claudio; Vitória Apart Hospital, ICU Delemazure, Julie; Groupe Hospitalier Pitié Salpêtrière, ICU Durand, Michel; CHU Grenoble, ICU Tejera, Darwin; Hospital de Clínicas, ICU Salluh, Jorge; Instituto Nacional de Cancer, Programa de Pós-Graduação em Oncologia Azoulay, Elie; CHU Saint Louis, Réanimation;</p>
Keywords:	Lung Cancer, Intensive care, Cancer-related complications, Multicenter study, Outcome

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

SCHOLARONE™
Manuscripts

Review

1
2
3
4 **Type of manuscript:** Original article.
5
6
7

8 **Intensive Care in Patients with Lung Cancer: A Multinational Study**
9

10 **Running-head:** Lung Cancer in Critical Care (LUCCA) Study
11
12
13

14
15 **Authors:** M. Soares ^{1,2}, A-C Toffart ³, J-F Timsit ⁴, G. Burghi ⁵, C. Irrazábal ⁶, N.
16
17 Pattison ^{7,8}, E. Tobar ⁹, B. F. C. Almeida ¹⁰, U. V. A. Silva ¹¹, L. C. P. Azevedo¹², A.
18
19 Rabbat ¹³, C. Lamer ¹⁴, A. Parrot ¹⁵, V. C. Souza-Dantas ¹⁶, F. Wallet ¹⁷, F. Blot ¹⁸, G.
20
21 Bourdin ¹⁹, C. Piras ²⁰, J. Delemazure ²¹, M. Durand ²², D. Tejera ²³, J. I. F. Salluh ^{1,2}, E.
22
23 Azoulay ²⁴, for the Lung Cancer in Critical Care (LUCCA) Study Investigators
24
25
26
27

28 **Affiliations**
29

30 ¹ Post-Graduation Program, Instituto Nacional de Câncer, Rio de Janeiro, Brazil
31

32 ² Department of Clinical Research, D'Or Institute for Research and Education, Rio de
33
34 Janeiro, Brazil
35

36 ³ Thoracic Oncology Unit, Hôpital A. Michallon Chu de Grenoble, Grenoble, France
37

38 ⁴ Medical Intensive Care Unit (ICU), Hôpital A. Michallon Chu de Grenoble, Grenoble,
39
40 France
41

42 ⁵ ICU, Hospital Maciel, Montevideo, Uruguay
43

44 ⁶ ICU, Instituto Medico Especializado Alexander Fleming, Buenos Aires, Argentina
45

46 ⁷ ICU, Royal Brompton NHS Foundation Trust, London, United Kingdom.
47

48 ⁸ ICU, Royal Marsden Hospital, London, United Kingdom
49

50 ⁹ ICU, Hospital Clinico Universidad de Chile, Santiago, Chile
51

52 ¹⁰ ICU, Hospital A. C. Camargo, São Paulo, Brazil
53
54
55
56
57
58
59
60

- 1
2
3
4¹¹ ICU, Fundação Pio XII - Hospital do Câncer de Barretos, Barretos, Brazil
5
6¹² ICU, Hospital Sírio Libanês, São Paulo, Brazil
7
8
9¹³ ICU, Hôtel Dieu de Paris, Paris, France
10
11¹⁴ ICU, Institut Mutualiste Montsouris, Paris, France
12
13¹⁵ Medical ICU, APHP-Hopital Tenon, Paris, France
14
15¹⁶ ICU, Instituto Nacional de Câncer - Hospital do Câncer I, Rio de Janeiro, Brazil
16
17¹⁷ Medical-Surgical ICU, Hospices Civils de Lyon Centre Hospitalier Lyon Sud, Lyon,
18
19 France
20
21¹⁸ ICU, Gustave Roussy, Villejuif, France
22
23¹⁹ Medical ICU, Hôpital de la Croix-Rousse, Lyon, France
24
25
26²⁰ ICU, Vitória Apart Hospital, Vitória, Brazil
27
28
29²¹ Medical ICU, Groupe Hospitalier Pitié Salpêtrière, Paris, France
30
31²² Surgical ICU, Hôpital A. Michallon Chu de Grenoble, Grenoble, France
32
33²³ ICU, Hospital de Clínicas, Montevideo, Uruguay
34
35²⁴ Medical ICU, Saint-Louis Teaching Hospital, Paris, France
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Conflicts of interest: The authors have declared no conflicts of interest.

Corresponding Author:

Márcio Soares

D'Or Institute for Research and Education

Rua Diniz Cordeiro, 30 – 3º andar; Rio de Janeiro – RJ; Brazil; CEP 22281-100

Phone:/Fax: +55 21 3883-6000

E-mail: marciosoaresms@gmail.com

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

1
2
3
4 rates were very high in patients with intractable disease and poor PS. In this subgroup,
5
6 palliative care may be the best option.
7
8
9

10
11 **Key words:** Lung Cancer, intensive care, cancer-related complications, multicenter
12 study, outcome.
13
14

15 16 17 **Abbreviation List**

18 Confidence interval - CI

19 Electronic Supplementary Material - ESM

20 Eastern Cooperative Oncology Group - ECOG

21 Intensive care unit - ICU

22 Interquartile range – IQR

23 Length of stay - LOS

24 Non-small-cell lung cancer - NSCLC

25 Organ failure - OF

26 Performance status – PS

27 Renal replacement therapy - RRT

28 Small-cell lung cancer - SCLC

29 Sequential Organ Failure Assessment – SOFA

30 Simplified Acute Physiology Score - SAPS

31 Surveillance, Epidemiology, and End Results - SEER

32 Treatment limitation decisions – TLD
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 **Word Count: 2,732 (Text: 2,159 words; References: 573 words)**
5
6
7

8 **INTRODUCTION**

9

10
11
12
13 Lung cancer is the most frequently diagnosed malignancy and the leading cause
14 of cancer-related mortality worldwide.[1] Despite advances in the management, overall
15 long-term survival remains poor particularly in patients with non-resectable or
16 metastatic tumors.[2] Nevertheless, complete recovery or prolonged survival can be
17 achieved in some patients with non-small-cell lung cancer (NSCLC).[3-5]
18
19
20
21
22
23

24 Lung cancer patients account for approximately 8% of all ICU admissions of
25 patients with malignancies and 27% of those with solid cancer.[6,7] Over the last
26 decade, improvements in ICU outcomes of these patients were documented in studies
27 performed worldwide.[8-13] However, lung cancer patients are usually perceived as
28 having substantially worse ICU outcomes compared to other cancer patients. Therefore,
29 ICU admission for life-threatening events is still widely viewed as unlikely to benefit
30 these patients, particularly when ventilatory support is needed.[14,15]
31
32
33
34
35
36
37
38

39 The available information about lung cancer patients requiring ICU admission
40 comes chiefly from single-center studies reporting ICU or hospital mortality rates in
41 small groups of patients.[8-15] Recently, however, two studies used administrative
42 databases to evaluate the outcomes of lung cancer patients admitted to the ICU.[16,17]
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60 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]

1
2
3
4 Here, our objective was to study a large population of critically ill patients with
5 lung cancer admitted to European or South American ICUs, in order to describe their
6 clinical characteristics and outcomes and to identify factors associated with short- and
7 long-term mortality.
8
9
10
11
12
13
14
15
16

17 **PATIENTS AND METHODS**

18 **Design and Setting**

19
20
21
22 This prospective multinational cohort study was conducted in 22 ICUs in
23 Argentina (n=1), Brazil (n=5), Chile (n=1), France (n=10), the United Kingdom (n=2),
24 and Uruguay (n=3) throughout 2011. All participating investigators and centers are
25 listed in the eAppendix of the Electronic Supplementary Material (ESM). The study was
26 observational, with all clinical decisions left to the attending physicians. The study was
27 approved initially by the Brazilian National Ethics Committee (approval number
28 CONEP 15.790) and subsequently by local and national ethics committees in the
29 participating centers and countries. In the few centers that required informed consent for
30 the study, written informed consent was obtained from each patient or legal
31 representative before study inclusion.
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

50 **Patient Selection, Data Collection, and Definitions**

51 Consecutive patients aged ≥ 18 years with a diagnosis of lung cancer requiring
52 ICU admission at the participating centers were evaluated. We did not include patients
53 with ICU stays shorter than < 24 h, complete cancer remission for more than 5 years,
54
55
56
57
58
59
60

1
2
3
4 previous ICU admission, malignancies other than primary lung cancer, or unwillingness
5
6 to participate in the study.
7

8
9 Demographic, clinical, and laboratory data collected included hospital location
10 before ICU, reason for ICU admission, Eastern Cooperative Oncology Group
11 performance status (ECOG-PS),[18] Simplified Acute Physiology Score (SAPS) II,[19]
12 Sequential Organ Failure Assessment (SOFA) score,[20] and comorbidities with
13 determination of the Charlson Comorbidity Index [21]. The use during the ICU stay of
14 ventilatory support (invasive and non-invasive mechanical ventilation) for longer than
15 24h, vasopressors, and renal replacement therapy (RRT) were recorded. The following
16 cancer-related data were collected: histological type, cancer stage, anticancer treatments
17 (radiation, chemotherapy, and surgical resection), cancer-related complications, and
18 cancer status (newly diagnosed, recurrent/progressive, or in remission). In patients with
19 non-small cell lung cancer (NSCLC), disease stage was evaluated using the TNM
20 classification, with limited disease defined as stage I-IIIa and extensive disease as stage
21 IIIb-IV. Lung cancer was considered a reason for ventilatory support in patients with
22 bilateral lung involvement, carcinomatous lymphangitis, or tumor masses causing
23 airway obstruction.[8] All patients were followed up until hospital discharge. In
24 addition, hospital survivors were followed up until 6 months after ICU admission.
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 **Data entry and processing**

47

48 Data were collected using a web-based standardized electronic case report form
49 developed specifically for the study. All investigators and research coordinators had
50 access to the website, which contained all the study documents including a manual
51 detailing the data-collection requirements and definitions. The investigators could
52
53
54
55
56
57
58
59
60

1
2
3
4 contact the steering committee members and country coordinators by telephone and
5
6 email if needed. Local investigators completed a form reporting the ICU and hospital
7
8 characteristics and were responsible for supervising data collection and checking data
9
10 completeness and quality. Data were screened by a single investigator (MS) for missing
11
12 information, implausible and outlying values, errors in logic, and lack of detail; this
13
14 investigator contacted the local investigators as needed to resolve these issues.
15
16
17
18
19

20 **Statistical Analysis**

21
22 Continuous variables were reported as mean±SD or median (25%-75%
23
24 interquartile range, IQR). Patients were managed in different centers, giving the data a
25
26 multilevel structure. We used a shared frailty model to identify factors associated with
27
28 death (PROC PHREG SAS 9.3). Risk factors for 30-day and 6-month mortality were
29
30 estimated using a Cox proportional hazards frailty model. The center effect was handled
31
32 as a random effect in the model. Variables included in the multivariate model were
33
34 those yielding *P* values <0.25 in univariate frailty models. Center- and patient-related
35
36 variables yielding *P* values <0.05 in the multivariate context were kept in the model.
37
38 Survival curves were plotted using the Kaplan-Meier method. All statistical analyses
39
40 were performed using SAS 9.3 (SAS Institute, Cary, NC, USA). *P* values less than 0.05
41
42 were considered significant.
43
44
45
46
47
48
49

50 **RESULTS**

51 52 53 54 55 **Characteristics of participating hospitals and ICUs** 56 57 58 59 60

1
2
3
4 The main characteristics of the 22 participating hospitals and ICUs are listed in
5
6 Table 1. Lung cancer patients accounted for 3.5% (716/20,351; range: 0.4%-17.8%) of
7
8 all ICU admissions during the study period. The median number of patients admitted
9
10 per center during the study year was 18 (IQR, 7-50; range, 3-138) and the median
11
12 number of patients included in the study per center was 15 (IQR, 6-29; range, 2-69).
13
14 The study flowchart is given in eFigure 1 of the ESM.
15
16
17
18
19

20 **Patient characteristics**

21
22 Tables 2 and 3 report the main characteristics of the 449 patients included in the
23
24 study. The main reasons for ICU admission were postoperative complications (41%),
25
26 acute respiratory failure (23%) and sepsis (21%).
27

28
29 There were 394 (88%) patients with NSCLC and 55 (12%) patients with SCLC.
30
31 The most frequent histological type was adenocarcinoma (57%). Median time since
32
33 cancer diagnosis was 74 (IQR, 22-185) days. Previous anticancer treatments included
34
35 surgical resection (17%), radiation therapy (22%), and single-drug or combination
36
37 chemotherapy (42%). More than half the patients had cancer-related complications at
38
39 ICU admission, with the most common being airway compromise by the tumor (Table
40
41 3).
42
43
44
45

46 **Outcome analysis**

47
48 The overall ICU, hospital, 30-day and 6-month mortality rates were 28%, 39%,
49
50 41% and 55%, respectively. Treatment-limitation decisions (TLD) were taken in 138
51
52 (31%) patients, after a median of 4 (1-11) days in the ICU admission, and 110 (80%) of
53
54
55
56
57
58
59
60

1
2
3
4 these patients died in the hospital. Of note, TLD were implemented on the first ICU day
5
6 in 38 (8%) patients. Table 2 compares the survivors and non-survivors.
7

8
9 The results of the univariate analyses to identify factors associated with 30-day
10 and 6-month mortality are reported in eTables 1 and 2 of the ESM. Center-related
11 variables assessed by univariate analysis were type of hospital, number of hospital beds,
12 type of ICU, and percentage of all ICU admissions contributed by lung cancer patients
13 during the study period. Patient-related data were age, type of ICU admission, hospital
14 length of stay before ICU admission, SOFA score, Charlson index, PS, TLD on the first
15 ICU day, type of lung cancer, cancer stage and status, and presence of cancer-related
16 complications.
17
18
19
20
21
22
23
24
25

26 Table 4 reports the results of the multivariate analyses. After adjustment for type
27 of admission and TLD taken on the first ICU day, the main determinants of 30-day and
28 6-month mortality were higher SOFA scores, poor PS, recurrent/progressive cancer, and
29 presence of cancer-related complications (airway compromise, deep vein thrombosis, or
30 superior vena cava syndrome). Admission to high-volume centers was associated with
31 lower mortality, particularly at 30 days. Histological type of cancer was not associated
32 with mortality. Figure 2 shows mortality rates according to the main combinations of
33 PS, cancer status, and treatment requirements. Survival curves for all patients and
34 subsets defined based on prognostic factors are provided in the ESM (eFigures 2a to 2f).
35
36
37
38
39
40
41
42
43
44
45
46
47
48

49 **Emergency anticancer treatments during the ICU stay**

50 Twenty-five (NSCLC=14; SCLC=11) patients received emergency anticancer
51 treatments (chemotherapy, n=20; radiation therapy, n=4; both, n=1) in the ICU. In
52 17/25 (68%) patients, the reason for emergency anticancer treatment was extensive
53
54
55
56
57
58
59
60

1
2
3
4 disease causing severe acute complications being the most frequent airway compromise
5 (56%) and large pleural/pericardial effusion (44%). No severe treatment-related
6 complications occurred during the ICU stay. ICU, hospital, and 6-month mortality rates
7
8
9
10
11 in these 25 patients were 36%, 44%, and 68%, respectively.

12 13 14 15 **Picture of hospital survivors**

16
17 Of the 449 patients, 275 were discharged alive from the hospital, 246 (89%) with
18 NSCLC and 29 (11%) with SCLC. Among them, 200 (73%) were known to be alive at
19 6 months and 72 (26%) had died; vital status was unknown for 3 (1%) patients. Cancer
20 recurrence or progression occurred in 53 (26%) hospital survivors. Anticancer
21 treatments were recommended to 108 (39%) hospital survivors and administered to 102;
22 anticancer treatment was not recommended to 121 (44%) patients and information on
23 this item was not available for 46 (17%) patients. In the 102 treated patients, the
24 treatments used were variable combinations of surgical resection (7%), radiation
25 therapy (34%), and chemotherapy (80%). In 35 (34%) patients, the initial anticancer
26 treatment plan required reduction or modification. Post-hospital mortality was non-
27 significantly lower in the patients given the initial treatment plan than in the other
28 patients (17% vs. 32%, $P=0.065$). Poor PS was the only factor associated with a lower
29 probability of receiving the initial treatment plan (odds ratio, 0.20; 95% confidence
30 interval, 0.05-0.87; $P=0.032$).
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 Among the 200 patients alive at 6 months, 142 (71%) were at home, 30 (15%)
49 were hospitalized, and 14 (7%) were in hospice care; the location was unknown for 12
50 (6%) patients. PS at 6 months was 3-4 in 19 (9.5%) survivors.
51
52
53
54
55
56
57
58
59
60

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,

1
2
3
4 closer collaboration between oncologists and intensivists, or more efficient ICU triage
5
6 policies.
7

8
9 At ICU admission, about half the patients had cancer-related complications,
10 some of which required emergency treatment. Thus, 25 patients received emergent
11 chemotherapy and/or radiation therapy in the ICU. These treatments were not associated
12 with increased mortality or acute toxicities, although their impact on the long term-
13 outcome is unclear. Hospital and six-month mortality rates of 44% and 68%,
14 respectively, in these 25 patients suggest that rescue anticancer treatment started in the
15 ICU may be of benefit in highly selected patients.
16
17
18
19
20
21
22
23

24 Strengths of our study include the large number of patients from different
25 countries admitted not only in referral cancer centers, but also in general hospitals.
26 Patient recruitment over a single year minimized the possible influence of changes in
27 treatment modalities over time. A limitation of our study is that we included patients
28 admitted to a convenience sample of centers in six countries. Therefore, our population
29 cannot be considered representative of all lung cancer patients admitted to the ICU. In
30 addition, we obtained data only for the first 6 months after ICU admission. Information
31 on longer-term outcomes is needed. Finally, we did not collect data on quality of life.
32
33
34
35
36
37
38
39
40
41

42 In conclusion, in this multinational study, ICU admission provided substantial
43 survival rates in patients with good PS and non-recurrent/progressive disease, including
44 those who had severe acute complications such as sepsis, multiple organ failure, and
45 need for ventilatory support. In addition, more than a third of the hospital survivors
46 received anticancer treatment. PS before ICU admission was associated with both
47 mortality and ability to receive optimal anticancer treatment after hospital discharge. On
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 the other hand, mortality rates were very high in patients with intractable disease and
5
6 poor PS. In this subgroup, palliative care may be the best option.[22,23]
7
8
9

10 11 12 13 **ACKNOWLEDGEMENTS**

14
15 **Financial support:** This work was supported by grants from the National Council for
16
17 Scientific and Technological Development (CNPq) and Fundação Carlos Chagas Filho
18
19 de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) and by departmental
20
21 funds from the D'Or Institute for Research and Education and Instituto Nacional de
22
23 Câncer, Brazil.
24
25

26
27
28 **Author contributions:** Study concept and design: MS, JIFS and EA; Acquisition of
29
30 data: all authors; Analysis and interpretation of data: MS, ACT, JFT; Drafting of the
31
32 manuscript: MS, JIFS, ACT, JFT, EA; Critical revision of the manuscript for important
33
34 intellectual content: all authors; Statistical expertise: ACT and JFT; Study supervision:
35
36 MS, EA; Approval of the final version of manuscript: all authors. Dr. Soares had full
37
38 access to all data in the study and takes responsibility for the integrity of the data and
39
40 the accuracy of the analysis.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

REFERENCES

- 1) Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893-2917.
- 2) Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin* 2011;61: 69–90.
- 3) Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542-2550.
- 4) Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22:1589-1597.
- 5) Reck M, Heigener DF, Mok T, et al. Management of non-small-cell lung cancer: recent developments. *Lancet* 2013;382:709-719.
- 6) Soares M, Caruso P, Silva E, et al. Characteristics and outcomes of patients with cancer requiring admission to intensive care units: A prospective multicenter study. *Crit Care Med* 2010;38:9-15.
- 7) Azoulay E, Moreau D, Alberti C, et al. Predictors of short-term mortality in critically ill patients with solid malignancies. *Intensive Care Med* 2000;26:1817-1823.
- 8) Soares M, Darmon M, Salluh JI, et al. Prognosis of lung cancer patients with life-threatening complications. *Chest* 2007;131:840-846.
- 9) Adam AK, Soubani AO. Outcome and prognostic factors of lung cancer patients admitted to the medical intensive care unit. *Eur Respir J* 2008;31:47-53.

- 10) Roques S, Parrot A, Lavole A, et al. Six-month prognosis of patients with lung cancer admitted to the intensive care unit. *Intensive Care Med* 2009;35:2044-2050.
- 11) Toffart AC, Minet C, Raynard B, et al. Use of intensive care in patients with nonresectable lung cancer. *Chest* 2011;139:101-108.
- 12) Andréjak C, Terzi N, Thielen S, et al. Admission of advanced lung cancer patients to intensive care unit: A retrospective study of 76 patients. *BMC Cancer* 2011;11:159.
- 13) Chou KT, Chen CS, Su KC, et al. Hospital outcomes for patients with stage III and IV lung cancer admitted to the intensive care unit for sepsis-related acute respiratory failure. *J Palliat Med* 2012;15:1234-1239.
- 14) Ewer MS, Ali MK, Atta MS, et al. Outcome of lung cancer patients requiring mechanical ventilation for pulmonary failure. *JAMA* 1986;256:3364-3366.
- 15) Lin YC, Tsai YH, Huang CC, et al. Outcome of lung cancer patients with acute respiratory failure requiring mechanical ventilation. *Respir Med* 2004;98:43-51.
- 16) Bonomi MR, Smith CB, Mhango G, et al. Outcomes of elderly patients with stage IIIB-IV non-small cell lung cancer admitted to the intensive care unit. *Lung Cancer* 2012;77:600-604.
- 17) Slatore CG, Cecere LM, Letourneau JL, et al. Intensive care unit outcomes among patients with lung cancer in the surveillance, epidemiology, and end results-medicare registry. *J Clin Oncol* 2012;30:1686-1691.
- 18) Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655.

- 1
2
3
4 19) Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score
5 (SAPS II) based on a European/North American multicenter study. JAMA
6 1993;270:2957-2963.
7
8
9
10 20) Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure
11 Assessment) score to describe organ dysfunction/failure. Intensive Care Med
12 1996;22:707-710.
13
14
15
16 21) Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic
17 comorbidity in longitudinal studies: development and validation. J Chronic Dis
18 1987;40:373-383.
19
20
21
22
23 22) Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with
24 metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
25
26
27
28 23) Azoulay E, Demoule A, Jaber S, et al. Palliative noninvasive ventilation in
29 patients with acute respiratory failure. Intensive Care Med 2011;37:1250-1257.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

For Peer Review

Electronic Supplementary Material (ESM)

e-Appendix: LUCCA study investigators and participating centers

eTable 1. Univariate analyses of center-related characteristics associated with 30-day and 6-month mortality.

eTable 2. Univariate analyses of patient-related characteristics associated with 30-day and 6-month mortality.

eFigure 1. Study flowchart

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

eFigure 2b. Survival according to number of patients with lung cancer admitted in ICUs in 2011

eFigure 2c. Survival according to performance status

eFigure 2d. Survival according to cancer stage

eFigure 2e. Survival according to cancer status

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

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

Variables	n (%) or median (IQR)
<i>Hospital characteristics</i>	
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%)
<i>ICU characteristics</i>	
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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

2

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%)	<i>P</i> 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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

3

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%)	<i>P</i> 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)	4·10 ⁻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%)	-	-	

^aData are mean±SD, median (25%-75% IQR), or n (%).^bSurvival 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^dLung 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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

4

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%)	<i>P</i> 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)	4·10 ⁻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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

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%)	<i>P</i> 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	-	-	

^aSurvival 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

^cOne patient received both chemotherapy and radiation therapy.

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ICU, intensive care unit

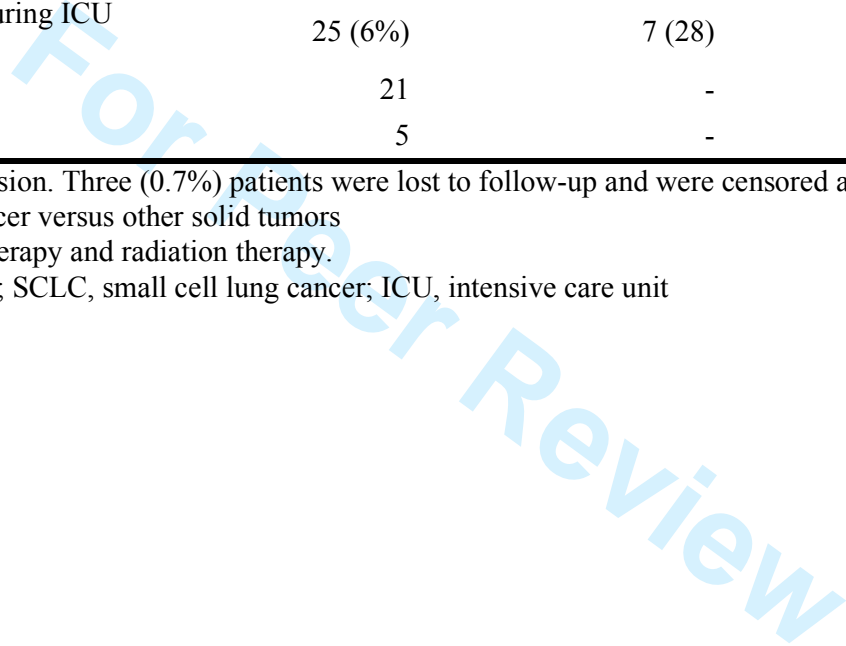


Table 4. Cox proportional hazards frailty models of characteristics associated with 30-day and six-month mortality (n=449)^a

Variables	Censored at 30 days		Censored at 6-months	
	Hazard Ratio (95%CI)	<i>P</i> value	Hazard Ratio (95%CI)	<i>P</i> 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	-	

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

Variables	Censored at 30 days		Censored at 6-months	
	Hazard Ratio (95%CI)	<i>P</i> value	Hazard Ratio (95%CI)	<i>P</i> 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)	

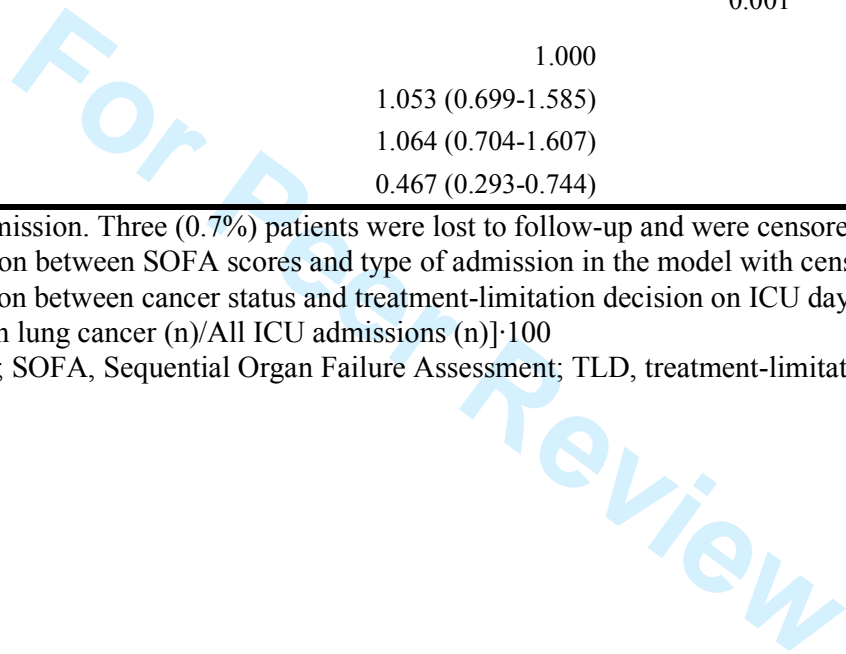
^aSurvival 6 months after ICU admission. Three (0.7%) patients were lost to follow-up and were censored at hospital discharge.

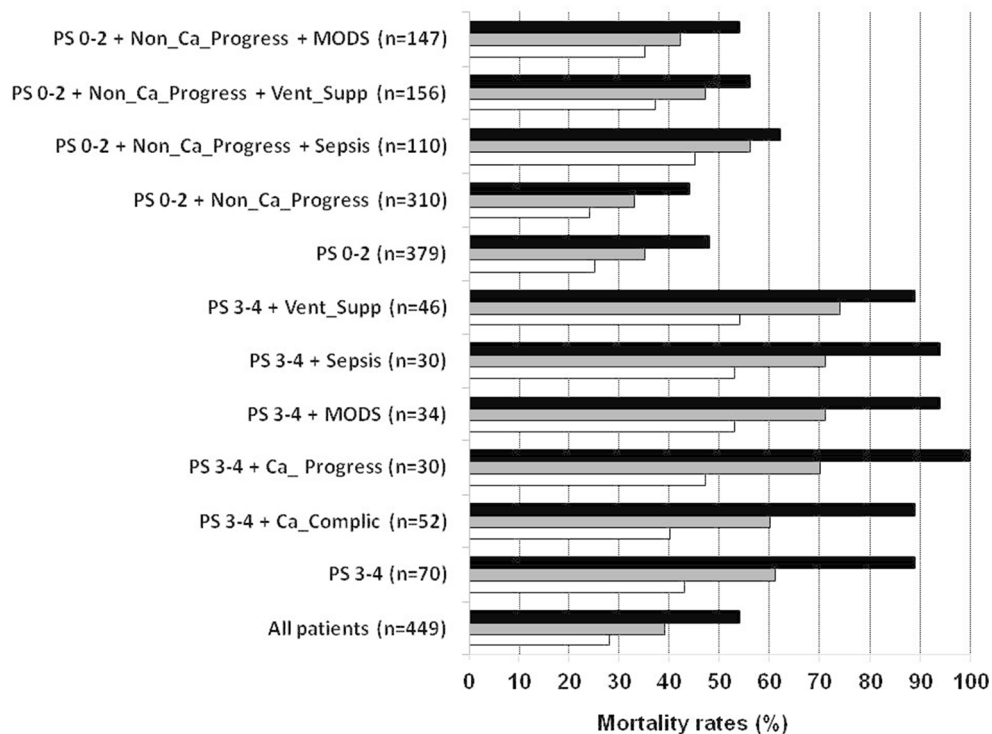
^bThere was a significant interaction between SOFA scores and type of admission in the model with censoring at 6 months (*P*=0.009).

^cThere 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





254x190mm (96 x 96 DPI)

Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ELECTRONIC SUPPLEMENTARY MATERIAL**Intensive Care in Patients with Lung Cancer: A Multinational Study**

Authors: M. Soares, A-C Toffart, J-F Timsit, G. Burghi, C. Irrazábal, N. Pattison, E. Tobar, B. F. C. Almeida, U. V. A. Silva, L. C. P. Azevedo, A. Rabbat, C. Lamer, A. Parrot, V. C. Souza-Dantas, F. Wallet, F. Blot, G. Bourdin, C. Piras, J. Delemazure, M. Durand, D. Tejera, J. I. F. Salluh, E. Azoulay, for the Lung Cancer in Critical Care (LUCCA) Study Investigators.

Address for correspondence and reprints:

Márcio Soares

D'Or Institute for Research and Education

Rua Diniz Cordeiro, 30 – 3º andar; Rio de Janeiro – RJ; Brazil; CEP 22281-100

Phone/Fax: +55 21 3883-6000

E-mail: marciosoaressms@gmail.com

e-Appendix: LUCCA Study Investigators and Participating Centers

Steering Committee: Márcio Soares, Jorge I. F. Salluh, Jean-François Timsit, Élie Azoulay.

Argentina: Instituto Medico Especializado Alexander Fleming, Buenos Aires (Célica Irrazábal, Pierina Bachetti); **Brazil:** Instituto Nacional de Câncer, Rio de Janeiro (Vicente C. Souza-Dantas, Mauro M. Zamboni, Aureliano Sousa), Hospital A. C. Camargo, São Paulo (Bruno F. C. Almeida, Lúcio S. Santos, Pedro Caruso), Fundação Pio XII - Hospital de Câncer de Barretos, Barretos (Ulysses V. A. Silva), Hospital Sírio Libanês, São Paulo (Luciano C. P. Azevedo, Guilherme P. P. Schettino), Vitória Apart Hospital, Vitória (Cláudio Piras, Stéphanie B. Piras, Albano S. M. T. Silva); **Chile:** Hospital Clinico Universidad de Chile, Santiago (Eduado Tobar, Nivia Estuardo); **France:** Gustave Roussy, Villejuif (François Blot, Bruno Raynard), APHP-Hopital Tenon, Paris (Antoine Parrot), Hospices Civils de Lyon Centre Hospitalier Lyon Sud, Lyon (Florent Wallet), Institut Mutualiste Montsouris, Paris (Christian Lamer), Groupe Hospitalier Pitié Salpêtrière, Paris (Alexandre Duguet, Alexandre Demoule, Julie Delemazure, Julien Mayaux, Thomas Similowski), Hôpital A. Michallon Chu de Grenoble, Grenoble (Surgical ICU: Michel Durand, Geraldine Dessertaine, Pr Jean François Payen; Medical ICU: Anne-Claire Toffart, Jean-François Timsit), Hôpital de la Croix-Rousse, Lyon (Gael Bourdin, Claude Guerin), Hôtel Dieu de Paris, Paris (Antoine Rabbat; Aurélie Lefebvre), Hopital Saint Louis, Paris (Élie Azoulay); **United Kingdom:** Royal Marsden Hospital, London (Natalie Pattison), Royal Brompton NHS Foundation Trust, London (Natalie Pattison); **Uruguay:** Hospital Maciel, Montevideo (Gastón Burghi, Darwin Tejera), Asociación Española Primera de Socorros Mutuos, Montevideo (Darwin Tejera, Gastón Burghi), Hospital de Clínicas, Montevideo (Gastón Burghi, Darwin Tejera).

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

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

Variables	Censored at 30 days		Censored at 6 months	
	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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

4

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

Variables	Censored at 30 days		Censored at six months	
	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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

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

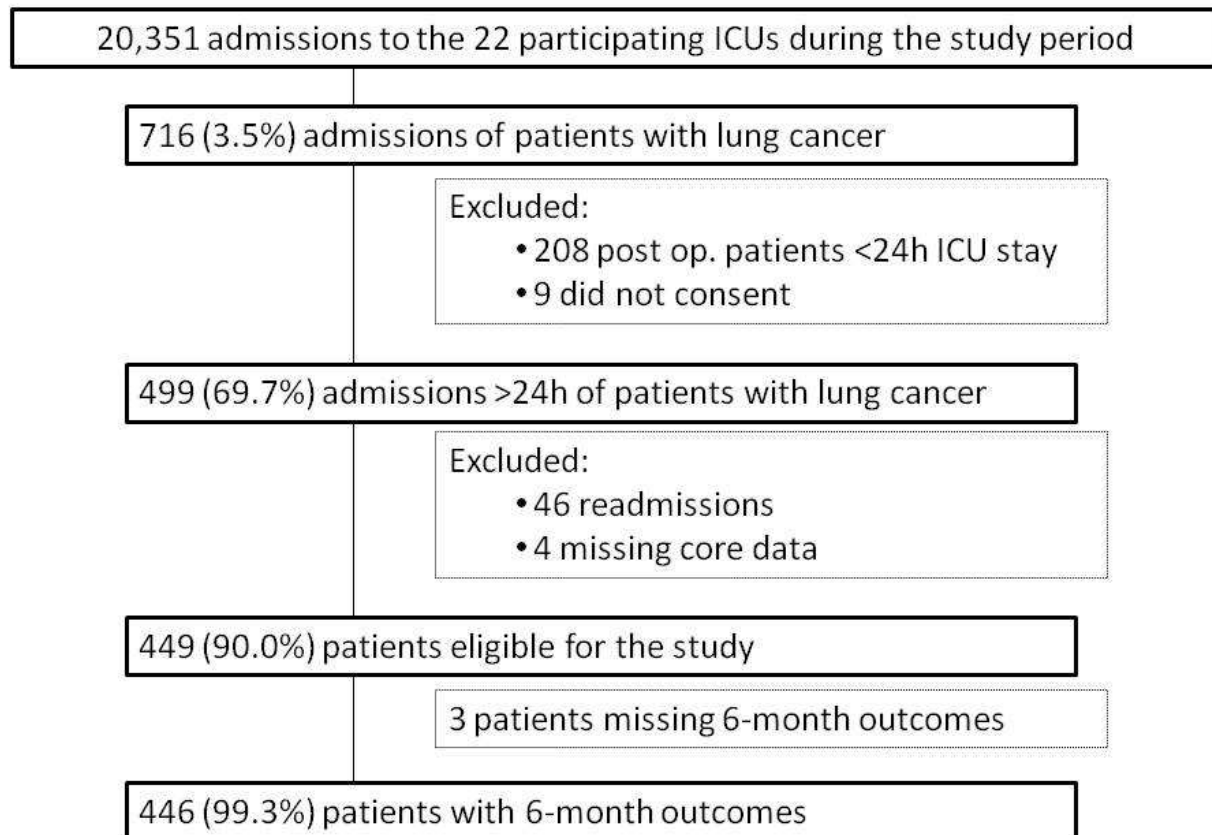
Variables	Censored at 30 days		Censored at six months	
	HR (95%CI)	<i>P</i> value	HR (95%CI)	<i>P</i> value
<i>Cancer-related characteristics</i>				
Type of lung cancer		0.179		0.602
Adenocarcinoma	1		1	
Squamous-cell	1.058 (0.748-1.498)		0.977 (0.721-1.323)	
Other	1.268 (0.581-2.770)		1.019 (0.491-2.114)	
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.

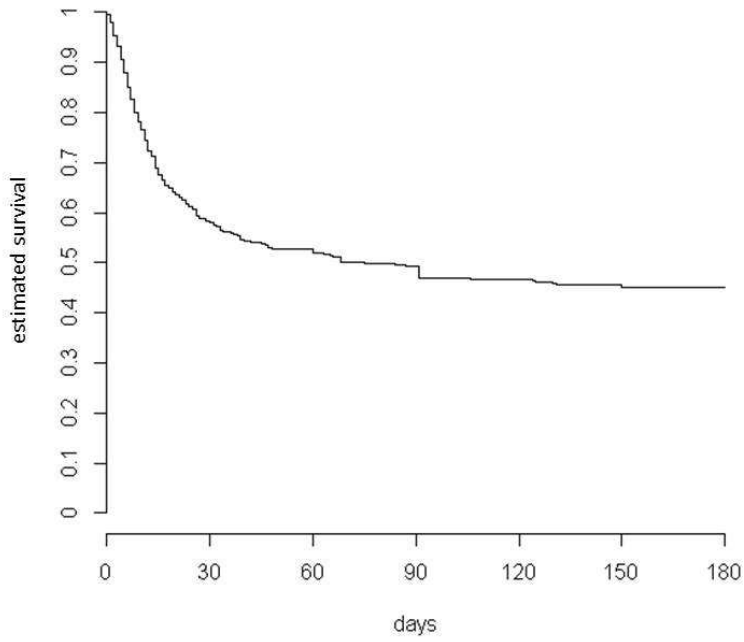
HR, hazard ratio; CI, confidence interval; SCLC, small cell lung cancer; ICU, intensive care unit

eFigure 1. Study flowchart

Study Flowchart



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



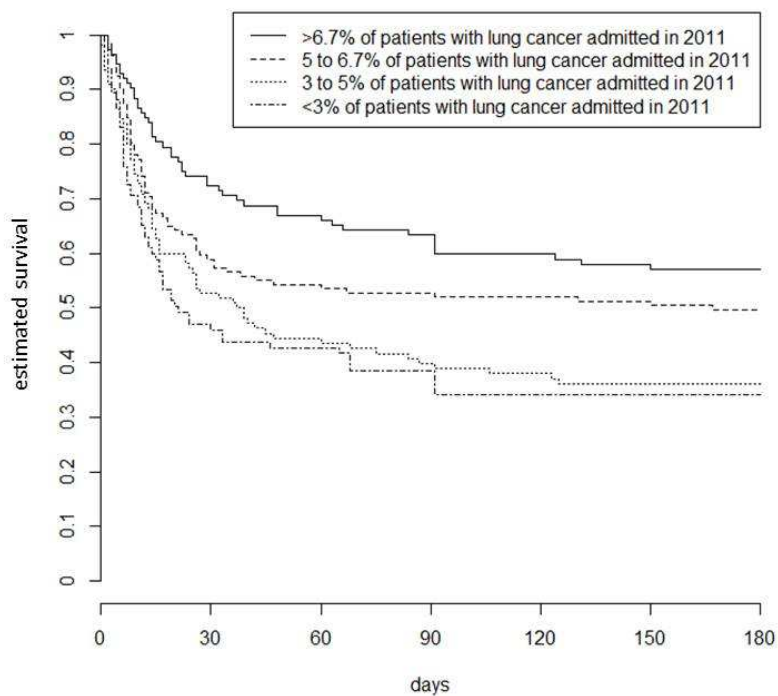
n at risk	d0	d30	d60	d90	d120	d150	d180
	449	260	234	219	208	203	200

Review

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

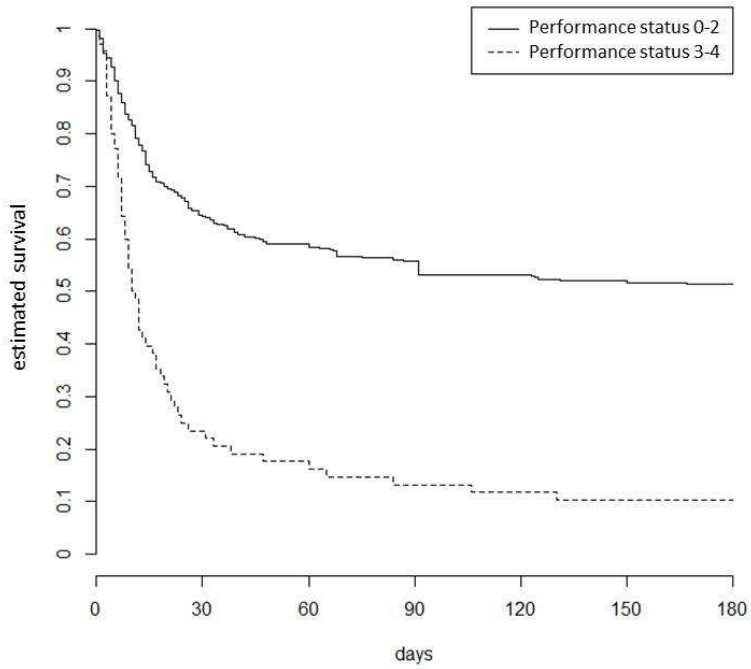
8

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.



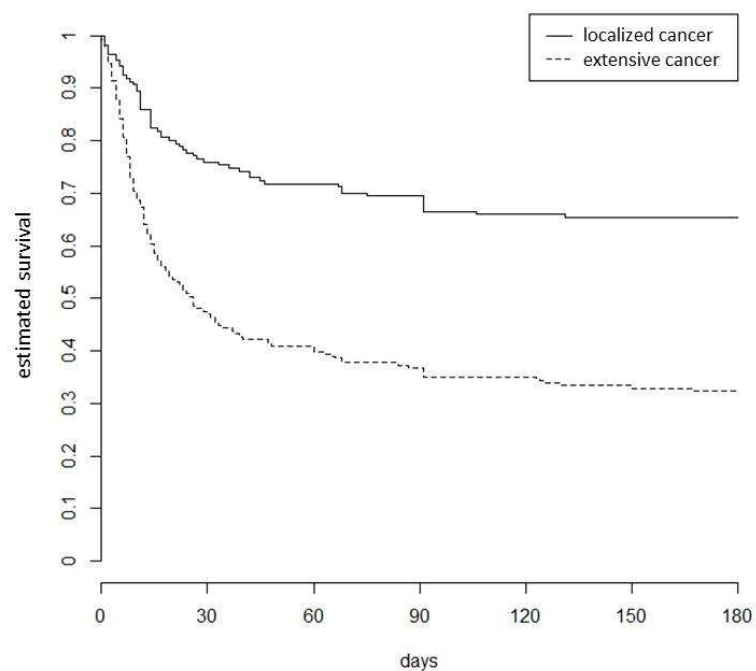
n at risk	d0	d30	d60	d90	d120	d150	d180
PS 0-2	379	244	222	210	200	196	193
PS 3-4	70	16	12	9	8	7	7

Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

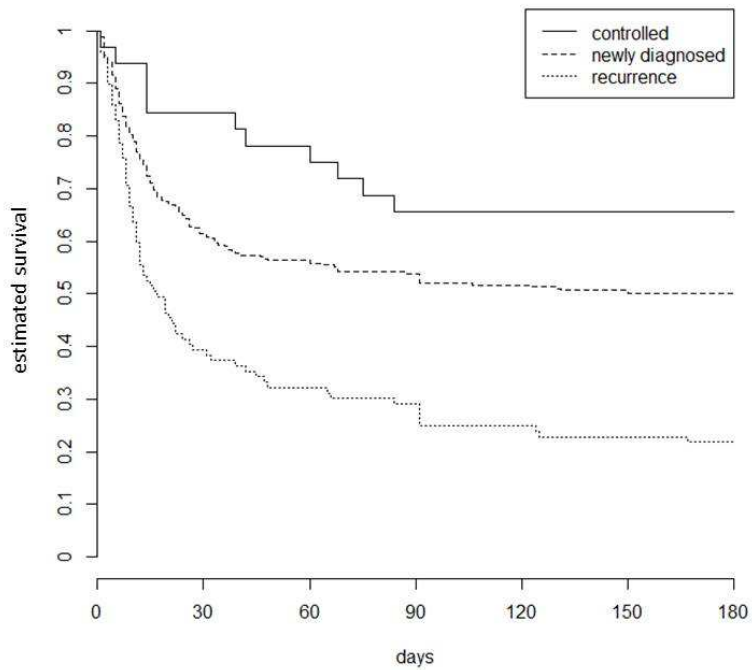
10

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

Soares et al. Lung Cancer in Critical Care (LUCCA) Study.

eFigure 2e. Survival according to cancer status.

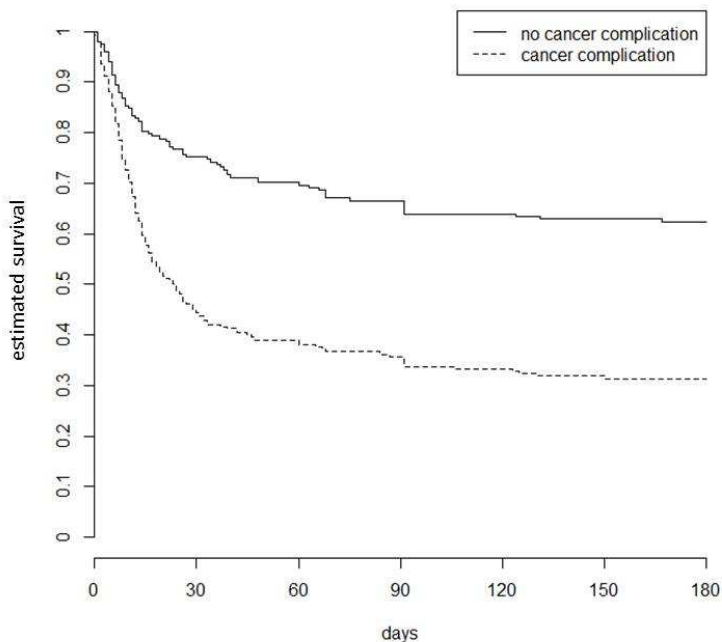


n at risk	d0	d30	d60	d90	d120	d150	d180
Controlled	32	27	25	21	21	21	21
Newly diagnosed	318	194	178	170	163	160	158
Recurrence	99	39	31	28	24	22	21

Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60