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Predictive factors of death in primary lung cancer patients on admission to the intensive care unit

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Abstract *Objective*: To assess the lung cancer patient's prognosis in the intensive care unit with early predictive factors of death.
Design: Retrospective study from July 1986 to February 1996.
Setting: Medical intensive care unit at a university hospital.
Patients: Fifty-seven patients with primary lung cancer admitted to our medical intensive care unit (MICU).
Measurements and results: Data collection included demographic data (age, sex, underlying diseases, MICU admitting diagnosis) and evaluation of tumor (pathologic subtypes, metastases, lung cancer staging, treatment options). Three indexes were calculated for each patient: Karnofsky performance status, Simplified Acute Physiology Score (SAPS) II, and multisystem organ failure score (ODIN score). Mortality was high in the MICU: 66 % of patients died during their MICU stay, and hospital mortality reached 75 %. In multivariate analysis, acute pulmonary disease and Karnofsky performance status < 70 were associated with a poor MICU and post-MICU prognosis. For the survivors, long-term survival after MICU discharge depended exclusively on the severity of the lung cancer.
Conclusions: We confirmed the high mortality rate of lung cancer patients admitted to the MICU. Two predictive factors of death in MICU were identified: performance status < 70 and acute pulmonary disease.

Key words Lung cancer · Intensive care unit · Outcome assessment · Predictive factors of death

Introduction

For inoperable non-small-cell lung cancers and small-cell lung cancers, there is a 5-year survival rate of less than 5 % [1]. During the last two decades, only small improvements in survival have been reached, and intensive care can seem futile. Thus, the disease raises crucial and difficult questions concerning the benefit and drawbacks of critical care. This initial decision must be based on the expected reversibility of the precipitating event and on whether this reversibility can be achieved in the time frame allotted by the life-sustaining support measures. It is often extremely difficult to appreciate the respective weights of the functional impairment attributable either to reversible or to irreversible factors. Severe respiratory failure in lung cancer patients may be related to tumor progression but also to other factors, i.e., cardiac failure, pneumonia, weaning after surgery, which might improve. Moreover, tumor extension during treatment of non-malignant and/or infectious problems may preclude successful weaning from mechanical ventilators.

Assessment of the lung cancer patient's prognosis in the intensive care unit remains complicated despite the use of severity scores such as the Simplified Acute Physiology Score (SAPS), the SAPS II or the Acute Physiology and Chronic Health Evaluation (APACHE II). These scoring systems were developed using data from

Table 1 Characteristics of the patient population

Patients	$n = 57$
Underlying conditions	
Smoking habits	52 (91 %)
Pulmonary chronic obstructive disease	21 (36.8 %)
Tuberculosis	6 (10.5 %)
Emphysema	3 (5.3 %)
Bronchiectasis	2 (3.5 %)
Ischemic or hypertensive cardiomyopathy	33 (57.8 %)
Pathologic subtypes	51 (89.5 %)
Squamous cell carcinoma	28 (55 %)
Adenocarcinoma	10 (19.6 %)
Poorly differentiated carcinoma	8 (15.6 %)
Oat cell carcinoma	5 (9.8 %)
Tumor extension	53 (93 %)
Stage I or II	10 (19 %)
Stage III	18 (34 %)
Stage IV	25 (47 %)
Karnofsky performance status	53 (93 %)
≥ 70	28 (53 %)
< 70	25 (47 %)

trauma patients rather than from patients with an underlying malignancy, and none can be relied upon to predict the death of a lung cancer patient. There are few previous studies assessing predictive factors of death in patients with solid tumors upon admission to the intensive care unit. Previous studies have been limited to the examination of factors affecting the survival of patients with solid tumors and hematologic malignancies during their ICU sojourn. Early predictive factors of intensive care unit death will be useful when the decision regarding admission to an intensive care unit has to be made. We conducted a retrospective study to identify predictive factors of death in patients with primary lung cancer on admission to the intensive care unit.

Materials and methods

Patient population and data collection

During the 10-year period from July 1986 through February 1996, 57 patients with primary lung cancer were admitted to our medical intensive care unit (MICU). In our hospital, all lung cancer patients are eligible for MICU admission. Patients were transferred mainly from the departments of pneumology or thoracic surgery, because there is no intensive care unit in the department of pneumology, and the thoracic surgery department only receives uncomplicated post-operative patients. Data were collected retrospectively from both the MICU records and the referred unit records before MICU admission. For the patients with more than one MICU admission, only the first admission was included in the analysis to assure independence of observations.

Demographic data (age, sex, underlying diseases, MICU admitting diagnosis) were recorded for all patients. Other data collected included evaluation of tumor: pathologic subtypes, types and number of metastases, lung cancer staging TNM classification [2], treatment options from surgical resection and radiation therapy, to chemotherapy. Three indexes were calculated for each patient: SAPS II [3], based on the worst values of clinical and biological variables within the first 24 hours in the MICU; ODIN score [4], based on type and number of organ failures on admission; and the Karnofsky performance status. The Karnofsky index, evaluating quality of life, determines the ability of a patient to carry on normal activities in life by using a scale from 0 to 100 %. In this study, it was established within the 15 days preceding admission to hospital.

Statistical analysis

We used death as the measurement of outcome. First, we identified variables which were predictive of death during the MICU stay. Then we studied the in-hospital mortality after discharge from the MICU and the outcome of those patients having survived since hospital discharge. Univariate analysis involving dimensional data was conducted using Student's *t*-test, and categorical data were analyzed using Pearson's chi-square test and Fisher's test. A P value < 0.05 was used to indicate statistical significance. Variables found significant at $P < 0.1$ in univariate analysis were subjected to a backwards stepwise logistic regression adjusting for available prognostic factors of death in patients with lung cancer such as age, sex, and extension of tumor.

Patients discharged home were followed up from their last day in hospital (origin day) to 1 August 1996 (reference date). A survival curve with a 95 % confidence interval was computed, using the Kaplan-Meier method.

Results

Demographics

A total of 57 patients, with a mean age 64 ± 8 years, were admitted to the MICU over the period of our data collection. Three patients had two or three consecutive admissions. For those patients, only the first admission was analyzed. Of the 57, lung cancer disease had already been diagnosed for 48 (84.2 %) patients. For the nine patients, diagnosis of lung cancer was made in our MICU. Nine patients (15.8 %) had been previously treated for non-pulmonary cancer and were considered as cured.

The pathologic diagnosis of lung carcinoma was performed on endobronchial biopsies during bronchoscopy or on lung samples resected during surgery. Pathologic subtypes was known for 51 patients (89.5 %) (Table 1). Tumor extension was made at the time of diagnosis of lung cancer. It was evaluated with the lung staging classification in 53 patients (93 %). Following pathologic diagnosis, 23 patients (40 %) initially underwent surgery, 13 patients (23 %) radiotherapy, and 24 patients (42 %) chemotherapy. The performance status could not be evaluated for four patients. Twenty-five patients (47 %) had a Karnofsky performance status of less than 70.

Table 2 Reasons for admission of the 57 patients to the MICU

Reason	No. (%)
Acute pulmonary disease	39 (68.4)
Infection (pneumonia, acute bronchitis)	31 (54.4)
ARDS	2 (3.5)
Pulmonary embolism	2 (3.5)
Pneumothorax	3 (5.3)
Hemoptysis	2 (3.5)
Airway obstruction and atelectasis	1 (1.8)
Pleural effusion	1 (1.8)
Shock	14 (24.5)
Cardiogenic	6 (10.5)
Septic	8 (14.0)
Central nervous system dysfunction	6 (10.5)
Brain metastases	5 (8.7)
Ischemic stroke	1 (1.8)
Electrolyte abnormalities	6 (10.5)
Hypercalcemia	5 (8.7)
Hyponatremia	1 (1.8)
Hematological disorders	4 (7.0)
Aplasia	3 (5.3)
Disseminated intravascular coagulation	1 (1.8)
Iatrogenic	3 (5.3)
Acute respiratory failure after endoscopy	
Post-operative (all surgery)	9 (15.8)

The mean SAPS II was 53 ± 19. Reasons for MICU admission are listed in Table 2. Acute pulmonary disease was the most frequent reason of admission. Acute pulmonary disease includes mainly pneumonia. All pathologic disorders for each patient are listed. Patients could have one or more reasons for admission. Post-operative recovery after major surgery was made in a post-operative unit devoted to this in the hospital. However, seven patients who underwent surgery for their lung cancer developed severe pneumonia (five patients) or pulmonary embolism (two patients) requiring admission in our MICU. Two patients were admitted for septic shock after general surgery.

Mechanical ventilation was required for 52 patients (91.2 %). The other organ failures were distributed among the cardiac ($n = 17$; 29.8 %), hematologic ($n = 6$; 10.5 %), renal ($n = 6$; 10.5 %), and neurologic ($n = 5$; 8.7 %) sites. Eighteen patients (31.6 %) had one acute extra-respiratory failure, five (8.7 %) had two acute extra-respiratory failures, and two (3.5 %) had three acute extra-respiratory failures.

Death-predictive factors

Overall mortality in the MICU was 66.7 % and 75 % in hospital. Acute pulmonary disease, requiring intubation and mechanical ventilation, Karnofsky performance status < 70, and SAPS II were correlated with the MICU mortality rate in univariate analysis (Table 3). Initial tumor extension, pathologic subtypes, and the presence of metastases were not predictive factors of death in the MICU. On admission, and except for acute respiratory failure, there was no relationship between the type of organ failures and the observed MICU death, but the sample size was too small to draw a definite conclusion. However, in our series, all patients with neurologic failure died in hospital as did the patients with three organ failures or more. Hospital mortality was correlated with performance status and tumor extension in univariate analysis (Table 4).

In multivariate analysis, only acute pulmonary disease and the Karnofsky performance status were significantly associated with MICU and hospital mortality as shown in Table 5.

Table 3 Predictive factors of death in the MICU and in hospital using univariate analysis

Variables	Died $n = 38$	Survived $n = 19$
Tumor subtype		
Squamous cell carcinoma	19	9
Adenocarcinoma	6	4
Poorly differentiated carcinoma	5	3
Oat cell carcinoma	4	1
Unknown	4	2
Stage		
I or II	5	5
III or IV	30	13
Performance status		
≥ 70	14	14
< 70	21	4**
Acute pulmonary disease		
Yes	30	9**
No	8	10
Ventilated		
Yes	37	15*
No	1	4
Organ failure		
Cardiovascular	11	6
Renal	5	1
Central nervous system	4	1
Hematologic	3	3
Number of organ failures[a]		
1	11	7
2	3	2
3	2	0
SAPS II: mean (SD)	56.3 (20.02)	45.3 (16)*

[a] Number of organ failures associated with respiratory failure
$^{*}P < 0.05$; $^{**}P < 0.01$ (95 % confidence interval)

Table 4 Predictive factors of death in hospital using univariate analysis

Variables	Died (n = 43)	Survived (n = 14)
Tumor subtype		
Squamous cell carcinoma	21	7
Adenocarcinoma	7	3
Poorly differentiated carcinoma	7	1
Oat cell carcinoma	4	1
Unknown	4	2
Stage		
I or II	5	5
III or IV	35	8*
Performance status		
≥ 70	18	10
< 70	22	3*
Acute pulmonary disease		
Yes	32	7
No	11	7
Ventilated		
Yes	40	12
No	3	2
Organ failure		
Cardiovascular	12	5
Renal	5	1
Central nervous system	5	0
Hematologic	3	3
Number of organ failures[a]		
1	13	5
2	3	2
3	2	0
SAPS II: mean (SD)	55 (19.8)	45.3 (16.7)

[a] Number of organ failures associated with respiratory failure
*$P < 0.05$ (95 % confidence interval)

Table 5 Prediction of MICU and hospital mortality using multivariate analysis

	MICU mortality	Hospital mortality
Acute pulmonary disease	OR = 11.4 (1.43–90.8)*	OR = 21.6 (1.16–401.0)*
Karnofsky status < 70	OR = 10.7 (1.80–63.8)*	OR = 9.63 (1.01–91.7)*

*$P < 0.05$ (95 % confidence interval)

Survivors

Fourteen patients (25 %) survived and were subsequently discharged from the hospital after their MICU sojourn. Among surviving patients, tumor extension was unknown for one patient. Five patients had limited disease (stages I or II). The mean age was 64.2 years and all of them had a performance status ≥ 70. Pathologic subtypes included squamous cell carcinoma in three patients, adenocarcinoma in one patient, and one was unclassified. Three of them were admitted for acute pulmonary disease.

Eight patients had disseminated disease (stage III or IV). The mean age was 54 years and six had a performance status > 70. Pathologic subtypes were: four squamous cell carcinoma, two adenocarcinoma, one small-cell lung cancer, and one unclassified. The reason for admission was an acute pulmonary disease in only three cases. The estimated median survival times for these two subgroups were: 32 weeks for stage I or II, and 16 weeks for stage III or IV. Their estimated survival curves are shown in Fig. 1. Estimated survivals were not different using the Log-rank test.

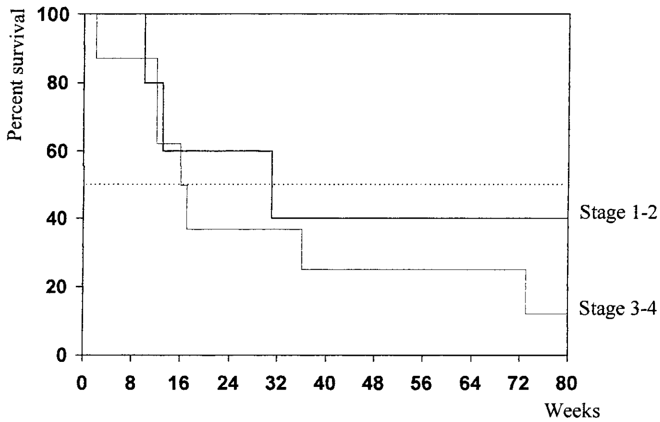

Fig. 1 Kaplan-Meier overall survival curves for the two groups after hospital discharge. *Dotted line* indicates median survival time

Discussion

There was an elevated mortality rate among patients with lung cancer admitted to our MICU; 38 patients (66.7 %) died in the MICU while overall hospital mortality was 43 (75 %), as five patients died after MICU discharge.

The reported mortality rate of cancer patients admitted to a medical intensive care unit is higher than that of concurrently admitted patients without cancer (55 % and 17 %, respectively) [5], but less than the mortality rate in patients with hematological malignancy admitted to an MICU [6, 7, 8]. A review of the literature reveals mortality rates between 72 % and 90 % for oncology patients requiring mechanical ventilation (MV). However, in a recent study [9], a 67 % mortality rate is reported for MV patients included in a population in whom nearly half had hematologic malignancies and/or bone marrow transplantation. This is one of the lowest reported mortality rates to date. In the same study, ICU mortality was 48 % in lung cancer patients. These more recent data raise the possibility that newer treatments and ventilatory strategies for MV oncology patients may be leading to improvements in outcome.

However, long-term survival after MICU discharge was poor. This is in accordance with the six-month survival rate, which ranges from 20 to 26 %, of patients admitted to the intensive care unit with solid tumor or hematological cancers [10]. In a 5-years survival analysis of 12,180 patients admitted to an intensive care unit [11], cancer was a strong determinant of a poor outcome in multivariate analysis. In our study, only 14 patients (25 %) survived to be discharged from hospital, and median survival time was 16 weeks for disseminated tumor. In this case, long-term survival after MICU discharge depended exclusively on the severity of the lung cancer, close to the median survival time usually reported to be between 14 and 26 weeks in this category of the cancer population [12, 13, 14].

There are four main reasons for admitting a cancer patient to an intensive care unit [15]: postoperative recovery and severe surgical complications; intensive anticancer treatment administration or monitoring; critical complications of cancer and its treatment; and acute disease unrelated to the neoplastic disease or its treatment. The mortality rate is different according to the reason of admission. In a retrospective study of 49 cardiac arrests in cancer patients, cardiac pulmonary resuscitation is always successful when cardiac arrest is the consequence of acute drug cardiovascular toxicity, and the majority of these patients survive their hospital stay [16]. On the other hand, when the cardiac arrest is the consequence of acute complications due to cancer, resuscitation is successful in only 25 % of the cases.

Acute pulmonary disease, such as pulmonary infections, was the most frequent reason for our ICU admission and was also a strong death-predictive factor (OR = 21.6; $P < 0.05$; CI 95 %). Other reasons for admissions (cardiologic, neurologic, hematological, and biological abnormalities) were not correlated with death, but this result should be discussed in the light of the sample size.

For mortality risk stratification in the intensive care unit, several severity indexes are used. These indexes, such as SAPS II and APACHE II [17], are calculated during the first 24 h. Although these indexes are useful in explaining ICU outcome variance, doubts have been expressed concerning their accuracy when applied to certain subgroups of patients. Thus, APACHE II scoring significantly underestimates the mortality risk in HIV-positive patients admitted to a medical ICU with a total lymphocyte count of < 200 cells/mm^3, and particularly with regard to patients admitted for pneumonia or sepsis [18]. In a cohort study of patients admitted to the intensive care unit [11], the reduction of survival was large in patients with cancer even among those patients with a low APACHE II at the time of ICU admission. The general ICU prognosis scoring system consistently underestimates the probability of hospital mortality for cancer patients admitted to an ICU. So, the relative accuracy and predictive abilities of those indexes in patients with lung cancer have yet to be established. In the SAPS II score, where cancer is recorded, the estimate of risk of death could be improved. In our study, SAPS II is a death-predictive factor in univariate analysis ($P < 0.05$), but not in multivariate analysis. In this population of patients, mortality after MICU discharge could not be accurately predicted with the SAPS II score. In a recent study, Groeger et al. [19] develop a model for probability of hospital survival at admission to the intensive care unit of patients with malignancy. They report a disease-specific multivariate logistic regression model based on 16 variables. More simply, in our study, a Karnofsky performance status of < 70 is a strong death-predictive index in both univariate and multivariate analysis. Performance status is commonly used to predict mortality in cancer patients and is a well-known variable associated with survival duration [12, 20]. For those patients, performance status appears to be a good predictive factor of hospital mortality, and is likely to be a prognostic variable not only of cancer patients.

As for the scores regarding organ failures on admission, we did not observe a relationship between the type and number of organ failures, using the ODIN model, and the death rate. However, it has been shown that the mortality rate increases with the cumulative number of organ failures [9, 21] during the MICU stay. The small number of patients in our study probably implies a potential lack of power of the analysis.

Decisions concerning the standard of care in the MICU will necessarily involve medical, as well as economic and ethical, considerations. In the current era of healthcare reform, there has been increased attention by both providers and consumers placed on the use of limited resources that do not provide commensurate increases in health benefits to patients. The majority of patients with solid tumors and hematological cancers admitted to the intensive care unit die before discharge, or if they survive the hospital admission, they spend a minimal amount of time before dying. This limited survival is achieved at considerable cost [10]. Despite separate educational programs conducted for oncologists and intensivists, the results of a recent study [22] demonstrated that the physician education intervention did not result in a change in the utilization of medical ICU resources by bone marrow transplant patients. Modification of physicians' practice habits remains difficult and requires objective data. We report two death-predictive factors, which should be validated in a prospective study. These death-predictive factors can aid the physician's clinical decision-making and should motivate the discussion regarding appropriate use of ICU resources.

In conclusion, we confirmed the high mortality rate of cancer patients admitted to the MICU: 66 % of patients died during their MICU stay, and hospital mortality reached 75 % in this study. A Karnofsky performance status < 70, and acute pulmonary disease, particularly pneumonia, were death-predictive factors in lung cancer patients.

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