REVIEW ARTICLE

Intensive care unit and lung cancer: when should we intubate?

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ABSTRACT

Lung cancer still remains the leading cause of cancer death among males. Several new methodologies are being used in the everyday practise for diagnosis and staging. Novel targeted therapies are being used and others are being investigated. However; early diagnosis still remains the cornerstone for efficient treatment and disease management. Lung cancer patients requires in many situations intensive care unit (ICU) admission, either due to the necessity for supportive care until efficient disease symptom control (respiratory distress due to malignant pleural effusion) or disease adverse effect management (massive pulmonary embolism). In any case guidelines indicating the patient that has to be intubated have not yet been issued. In the current review we will present current data and finally present an algorithm based on the current published information for lung cancer patients that will probably benefit from admission to the ICU.

KEY WORDS

Intensive care unit (ICU); lung cancer; respiratory distress

Introduction

Lung cancer still remains the leading cause of cancer death for males and the second most common cancer for females (1). There are currently several methods for lung cancer diagnosis such as the endobronchial ultrasound bronchoscopy, positron emission tomography and tissue biomarkers (2,3). Currently there also novel optical tools evaluated for rapid on site tissue specimen diagnosis (4). Novel treatments are also administered or are under development (5-13). However, early diagnosis and disease management are the cornerstone for efficient treatment (14,15). The current algorithm that is used for lung cancer patient treatment has prolonged the survival of these patients, including those not eligible for surgery (16). Therefore these patients present more often during their treatment

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complications attributed to the cancer disease or their treatment (17,18). The prolongation of patients not eligible for surgery reaches the 5 years in 16% of these patients (19). Treatment of lung cancer with radiation or tyrosine kinase inhibitors is also responsible for short term respiratory distress (20,21). Taken under consideration these factors and especially the advances in pharmacological treatment a larger number of patients are now eligible for admission in the intensive care unit (ICU) while before it was considered futile (22). There are currently novel non-invasive diagnostic and therapeutic techniques in the ICU making the short term admission of such a patient feasible (23). The ICU admission decision should be based on short-term and long-term outcome for the patient. The characteristics of the patients that would benefit from short-term or long-term are still not clarified. The ICU medical care is costly, burdensome and associated with increased risk (24). Until now the deterioration within the first 72 hours of the patient [measured with the logistic organ dysfunction score (LOD)] (25) has been identified as an early marker for worse survival and the use of vasopressors in combination with two-three organ system failures have been identified as a long term prediction factor for the intubated lung cancer patient (26). Moreover, other important factors identified to be negatively associated with survival where hemoptysis and acute respiratory failure upon admission. The mechanical ventilation and performance status (PS) ≥2 have been identified

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as independent factors indicating a worse prognosis for lung cancer patients (27). Furthermore, there is the subgroup of lung cancer patients which has been diagnosed and treated for a prolonged time and their disease related problems have been managed with different medications and non-invasive methods. Most importantly these patients have the time to decide how they want to be treated when their disease has progressed and the treatment options are no more efficient/availiable (28). We should also consider the fact that aggressive care in several situations does not provide the patient with the quality of life that deserves (29). Patient candidates for curative chemotherapy administration during ICU hospitalisation have not been yet identified. In the current review we will present published data for patients admitted in the ICU with two approaches: (I) patients admitted with known extensive disease or unknown however admitted (diagnosed upon admission); (II) patients with early stage lung cancer and (III) ICU as palliative care for lung cancer patients.

Search methods

We performed an electronic article search through PubMed, Google Scholar, Medscape, and Scopus databases, using combinations of the following keywords: ICU and lung cancer, ICU and cancer. All types of articles (randomized controlled trials, clinical observational cohort studies, review articles, case reports) were included. Selected references from identified articles were searched for further consideration, without language limitation.

Intensive care and lung cancer patients

In the study by Adam *et al.* (26), 139 patients were included retrospectively. The mean age of the patients was 64.2 years [96 non-small cell lung cancer (NSCLC), 18 small cell lung cancer (SCLC) and 1 mesothelioma] and two evaluation scores were used: (I) acute physiology and chronic health evaluation III and (II) simplified acute physiology score (SAPS) III. The following data were recorded: (I) mechanical ventilation application; (II) positive blood cultures; (III) use of vasopressors; (IV) high serum lactate; (V) cardiac support and (VI) two-three organ system failures. The multivariate analysis demonstrated that the most important factors affected the final outcome (mortality) were the use of vasopressors and the presence of more than two organ failures. In another study by Roques *et al.* (27), 105 patients with mean age 64.8 years were included (87 NSCLC and 18 SCLC) and the following scores were used for patient assesment: (I) sequential organ failure assessment score (SOFA) and (II) SAPS II. Sixty-eight NSCLC patients had extensive stage disease (IIIB-IV). Only 30 patients after hospital discharge received chemotherapy treatment. The following factors were identified as prognostic:

(I) mechanical ventilation and (II) PS ≥2 and (III) acute respiratory failure. The authors state that when PS ≤2 and the patient has stable disease then the outcome will be positive for the patient. However, stable disease in a patient with extensive disease is a combination that narrows the candidates and we should not forget that ICU hospitalisation triggers other mechanisms which can induce adverse effects such as, thrombosis. In the study by Toffart *et al.* (25) again Eastern Cooperative Oncology Group (ECOG)-PS <2 along with the LOD were established as prognostic factors for the outcome of these patients. In specific the reduction of LOD score within the first 72 hours of ICU admission was associated with severe outcome. The administration of chemotherapy in lung cancer patients was investigated as a prognostic factor in 20 SCLC patients (8 limited disease/12 extensive disease). The patients were evaluated with the adjusted Manchester score [0-4]. Five patients received chemotherapy while being intubated and 2 of them were free of tumour recurrence 7 months later. Patients who did not received chemotherapy died within 40 days. The patients administered chemotherapy were weaned-off early. A variety of chemotherapy agents were used and therefore no clear conclusions can be drawn which would be the best regimen for SCLC patients under these conditions. The Manchester score is a valuable tool for decision making for administering chemotherapy in patients admitted to the ICU and ICU admission (30). Moreover; other factors affecting lung cancer patients such as; infections, congestive heart failure and unidentifiable causes were assessed in a large study of 203 oncology patients (31). Mechanical ventilation was correlated with increased mortality (75.4%). The predictive factors were: (I) invasive aspergillosis; (II) unidentifiable diagnosis; (III) use of vasopressors; (IV) late initiation of mechanical ventilation; and (V) failure of non-invasive mechanical ventilation. Patients intubated due to with pulmonary oedema had the best prognosis and outcome. In the largest study including 49,373 lung cancer patients the mechanical ventilation was found to be the determinant factor affecting the outcome of these patients. Most patients were observed to die within 6 months of admission (32). In another large study with 1,134 older patients (>65) with extensive IIIB-IV stage NSCLC the following factors were recorded: sepsis, respiratory, cardiac, neurological and renal failure. Sepsis and >65 years of age were identified as the major prognosis factors. Survivors required multiple hospitalisations after ICU discharge and the 1 year mortality was observed to be 90% (33). Sepsis from gram-negative bacteria upon ICU admission has been also identified as a major factor for increased mortality among lung cancer patients in another large study of 563 patients (34). In the study by Kress *et al.* (35) with 348 patients included, the following factors were identified as predictive: (I) respiratory distress; (II) hepatic and (III) cardiovascular failure. Another large study comparing several types of cancers was carried out 2,009 including 3,147 patients

Table 1. Intensive care unit and lung cancer studies.

Author	No. patients	Lung cancer	Factors	Ref
Adam *et al.*	139 (7 years)	NSCLC, SCLC, Mesothelioma	Mechanical ventilation application, positive blood cultures, use of vasopressors, high serum lactate, cardiac support and two-three organ system failures	(26)
Roques *et al.*	105 (9 years)	NSCLC, SCLC	Mechanical ventilation, performance status ≥2, acute respiratory failure	(27)
Jennes *et al.*	20 (8 years)	SCLC	Chemotherapy, Manchester score	(30)
Azoulay *et al.*	203 (5 years)	Oncology patients	Ventilation, invasive aspergillosis,	(31)
Soubani *et al.*	Review	Review	Review	(23)
Petrella *et al.*	154 (4 years)	NSCLC	Creatinine and respiratory complications higher in the BMI	(38)
Reichner *et al.*	47 (2 years)	NSCLC	Advanced stage and mechanical ventilation	(39)
Slatore *et al.*	49,373 (15 years)	NSCLC, SCLC, OTHER	Mechanical ventilation	(32)
Bononi *et al.*	1,134 (6 years)	NSCLC	Sepsis, Age >65	(33)
Keating *et al.*	2,913 (2 years)	NSCLC/Colorectal	Age >65	(29)
Rosolem *et al.*	563 (4 years)	Oncology patients	SOFA, PAPS II, Sepsis (Gram-negative)	(34)
Toffart *et al.*	103 (7 years)	NSCLC, SCLC, other	SOFA, LOD	(25)
Okiror *et al.*	425 (6 years)	NSCLC	Brunelli scoring system	(40)
Park *et al.*	316 (2 years)	NSCLC	Low FEV1, cardiac co-morbidities	(41)
Fernandes *et al.*	189 (14 months)	NSCLC	COPD, Anemia, Hypoxia, Age	(42)
Kress *et al.*	348 (3 years)	Oncology	Respiratory, hepatic, cardiovascular	(35)
Soares *et al.*	143 (6 years)	NSCLC, SCLC, others	Respiratory failure, number of organ failures, severity of co-morbidities	(43)
Taccone *et al.*	3,147 [2002]	Oncology	Three organ failure determinant factor	(36)
Mendoza *et al.*	147 (18 months)	Oncology	Metastatic disease and vasopressors	(37)
Bakitas *et al.*	322 (5 years)	Oncology	ESAS, FACITPC, CESDS	(44)
Delgado-Guay *et al.*	1,637 (1 year)	Oncology	Severe distress, ESAS, MDAS	(28)

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ESAS, edmonton symptom assessment scale; MDAS, memorial delirium assessment scale; CESDS, Center for Epidemiological Studies Depression Scale; FACITPC, Functional Assessment of Chronic Illness Therapy for Palliative Care; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; SOFA, sequential organ failure assessment; LOD, logistic organ dysfunction score; BMI, body mass index; PAPS II, simplified acute physiology score.

(Sepsis Occurrence in Acutely Ill Patients-SOAP) (36). The determinant prognostic factor was the three organ failure. In the study by Mendoza *et al.* (37), 147 oncology patients were included and the most important factors affecting the prognosis of ICU admitted cancer patients were: (I) use of vasopressors and (II) metastatic disease (Table 1).

ICU and early stage lung cancer

Early stage lung cancer is another category of patients and a different mentality for ICU admission should be applied. In the study by Petrella *et al.* (38), an effort was made to identify the factors affecting the ICU admission outcome in surgically resected NSCLC patients. In specific the body mass index (BMI) was recorded and a cut off value of 25 kg/m^2 was applied. Several other values such as, creatinine, forced expiratory value

in 1 second (FEV1), Carbon Monoxide Diffusing Capacity (DLCO), histology and pathological stage, sex, cigarette history, preoperative albumin and total protein. The major results from this study indicate that the creatinine levels and the respiratory complications were 5.3 times higher in the BMI group >25 kg/m^2. In the study by Okiror *et al.* (40), 425 patients were included with mean age 65 years. The respiratory functions were not identified as a prognostic marker for ICU outcome and the Brunelli score which was used, did not offer the expected results as an evaluation method for ICU outcome. In the study by Park *et al.* (41), 425 patients were included and the following factors were identified as prognostic postoperatively: (I) low FEV1 and cardiac co-morbidities. The type of surgery and the scoring systems (American Society of Anesthesiology, Charlson Co-morbidity Index) that were used were not identified as prognostic factors for the ICU outcome. Moreover in the

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study by Park *et al.* (41), two groups were identified: (I) early complications and (II) late complications. In the first group the major factors identified were the low expected FEV1 and the cardiac co-morbidity. In the second group the advanced age, low expected FEV1 and the cardiac co-morbidity were identified as prognostic factors. In the study by Fernandes *et al.* (42), 189 patients were included. The major factors identified as prognostic were: (I) anaemia; (II) age (≥65); (III) hypoxia and (IV) chronic obstructive pulmonary disease (COPD). In the SOAP study early lung cancer patients had increased rate of sepsis after surgery (36) (Table 1).

ICU as palliative care for lung cancer patients

In an effort to identify the cancer patients that would benefit from palliative care intervention the ENABLE II study was conducted. The quality of life was measured with three scoring systems: (I) Center for Epidemiological Studies Depression Scale (CESDS); (II) Edmonton Symptom Assessment Scale (ESAS); and (III) Functional Assessment of Chronic Illness Therapy for Palliative Care (FACITPC). However, it was observed that palliative care intervention did not reduce the days of hospitalisation in the ICU or hospital wards and time in the emergency department (44). In another study by Delgado-Guay *et al.* (45), 1,637 oncology patients with median age of 60 years were included. The major findings were delirium, dyspnea, pain, fatigue and anxiety. The major pharmacologic and non-pharmacologic findings were: opioid management, steroids, antipsychotics and counselling. The patients were informed for withdrawal of mechanical ventilation, do not resuscitate conversion and withdrawal of bi-level-positive airway pressure. The two questionnaires used were the ESAS and Memorial Delirium Assessment Scale (MDAS). The pharmacological and non-pharmacological recommendations contributed in the quality of life of the patients and in several patients reduced the emotional distress (Table 1).

Discussion

Pulmonary physicians play a key role in the admission of lung cancer patients since they are also responsible for the 'end of life' decision making in several situations when the patient cannot be weaned-off the mechanical ventilation. The pulmonary physicians based on their expertise along with the anaesthesiologists are usually called to decide regarding the outcome of a lung cancer patient requiring intensive medical care. This is observed for patients with known lung cancer, while in the situation where a patient has not been yet diagnosed with lung cancer the decision is usually made by the internal medicine doctors (39). Older patients with extensive lung cancer usually receive less aggressive treatment in comparison to younger patients (<65 years) (29). Patients with lung cancer and

pulmonary oedema should be intubated since positive outcome is expected, although the characteristics of these patients have not been clearly defined (disease stage and response) (31). We should state at this point that cardiovascular failure is a negative prognostic factor for early and extensive stage lung cancer patients and although it has previously stated that patients with pulmonary oedema should be intubated because of favourable outcome, we should firstly identify and clarify the characteristics of patients with coronary heart disease (35,41). The BMI >25 kg/m^2 can be used as a predictive factor for early lung cancer patients admitted to the ICU (38). The low postoperative FEV1 can be also used as a predictive factor for early stage lung cancer patients admitted to the ICU (41). We should consider administering chemotherapy at least for SCLC which has a fast growth rate and the respiratory failure is due to obstruction from the lesion (endobronchial or intrathoracic pressure to the airways). The mechanical ventilation and not the cancer *per se* is the most important prognostic factor for lung cancer patients admitted to the ICU (43). Additionally, failure of more than 3 organs is attributed to 75% of mortality rate (36). Hepatic metastatic disease has the worse prognosis among other distant metastasis (35). The use of vasopressors and metastatic disease was also observed to affect the prognosis of the patients (37). Economical studies regarding these patients should be performed dividing them in patients with early lung cancer, patients >65 years and patients to treat based on the fact that they will benefit early from chemotherapy during their ICU hospitalisation (46). In the study by Au *et al.* (47), patient's characteristics with COPD were compared with lung cancer patients. In specific a record was made with the two groups of patients regarding the cost of ICU admission. It was observed that the COPD patients visited their care providers several times more than the lung cancer patients for reasons other than their disease and when intubated their length of stay in the ICU was at least prolonged by 2 weeks. Also, the odds of a patient with COPD to be intubated are twice as much higher than a lung cancer patient. Therefore the cost of a patient with COPD is much higher. The COPD patients, however, were observed to receive less palliative care in comparison to lung cancer patients (47). These observations vary geographically and depend of the center's experience that the patients are admitted for care (Table 2). We recommend based on the published literature that the LOD score is used as a predictive factor for extensive stage lung cancer patients (25) and the Manchester score when we want to administer chemotherapy in ICU admitted lung cancer patients (30). The early stage lung cancer patients can be probably identified as a separate group of patients and different evaluation factors for ICU admission should be applied. In specific pneumonectomy has been observed to induce postoperatively acute respiratory distress syndrome (ARDS) and patients which had a large pericardial effusion have been observed to develop acute cardiac decompensation (23). There

Table 2. Intensive care unit admission and outcome.

Admission

- ❖ Respiratory failure
- ❖ Obstruction
- ❖ Mechanical ventilation
- ❖ Non-invasive ventilation failure
- ❖ Vasopressors
- ❖ Performance status ≤2
- ❖ Number of organ failure
- ❖ SCLC
- ❖ Hemoptysis
- ❖ Pulmonary embolism
- ❖ Pleural effusion
- ❖ SVC

Outcome

- ❖ Early chemotherapy administration
- ❖ SOFA
- ❖ Manchester
- ❖ PAPS II
- ❖ LOD
- ❖ Invasive aspergillosis
- ❖ Stable disease

are other situations that are related with cancer treatment; In specific radiation pneumonitis is an inflammatory process where the administration of corticosteroids can assist the respiratory function of the patient. The admission in the ICU could be considered for these patients mandatory, since it could provide them the time to recover and regain part of their respiratory capacity (20). Another treatment related situation is observed when several chemotherapeutic agents are administered. The following agents used in oncologic patients nowadays have been identified to induce ARDS; tyrosine kinase inhibitors, docetaxel, paclitaxel, etoposide, mitomycin, methotrexate and bevacizumab. The ARDS caused from these agents can be treated again with corticosteroids and in several situations admission in the ICU provides a window for these patients to regain their respiratory capacity. However, the identification of an infection from a pneumonitis in a neutropenic patient still remains a challenge for the clinician and we should have caution. Neutropenia on its own it is not a negative prognostic factor (36). There are data regarding NSCLC and SCLC patients admitted in the ICU, however, there are limited data regarding patients with mesothelioma. A future study presenting data regarding these patients would be most welcomed. Nutrition while ICU hospitalisation is a subject that has not been thoroughly investigated in correlation with lung cancer patients and whether it affects the outcome of these patients. Upon lung

cancer diagnosis and specifically for extensive stage, the caregiver should discuss thoroughly with the patient the course of the disease and options. The patient and relatives should be aware of the complications and treatment management. Still there are no guidelines for lung cancer patient admission to the ICU and the burden for this decision is usually for the caregiver who provides the oncologic treatment to take. Future studies and committees should establish the criteria for ICU admission for lung cancer patients, taking into account also the quality of life of the patient.

Acknowledgements

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