Respiratory Medicine (2004) **98**, 43–51

ELSEVIER

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Outcome of lung cancer patients with acute respiratory failure requiring mechanical ventilation

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Received 20 January 2003; accepted 24 July 2003

KEYWORDS
Lung cancer;
Acute respiratory failure;
Mechanical ventilation;
Outcome;
Weaning;
Intensive care unit

Summary To assess the weaning outcome of lung cancer patients with acute respiratory failure (ARF) requiring mechanical ventilation, we retrospectively analyzed the database of the respiratory intensive care unit at a university-affiliated tertiary care hospital.

Charts were reviewed for cancer status, biochemistries before respiratory failure, causes of respiratory failure, acute physiology and chronic health evaluation (APACHE) III score, ventilatory settings, data recorded during spontaneous breathing, duration of ventilator days, and weaning outcome. Ninety-five consecutive respiratory failure events in 81 patients were recorded from January 1, 1995 through June 30, 1999.

Twenty-six episodes ended with successful weaning (27.4%). Age, gender, and cancer status did not affect the weaning outcome. Serum albumin level, APACHE III score, highest fractional inspired O_2 (FiO_2) and highest positive end-expiratory pressure, organ failure, ability to shift to partial ventilatory support, and duration of mechanical ventilation could significantly influence the weaning outcome statistically. The overall hospital mortality rate was 85.2%.

Our results suggested that lung cancer patients with ARF will have a better chance to wean if the initial APACHE III score was less than 70, use of FiO_2 never exceeded 0.6, or less than 2 additional organ systems failed during the treatment course.

Introduction

Acute respiratory failure (ARF) is a common complication in patients with lung cancer and implies a poor prognosis. Mechanical ventilation in these patients presents dilemmas in medical management, philosophy, and ethics. It can be lifesaving on the one hand or be the beginning of a long and painful death on the other. Despite the progress in treating lung cancer and managing respiratory failure, a definite strategy for lung cancer patients with respiratory failure is still not established. To identify those who would have benefits from the ventilatory support is therefore crucial. Reviewing the literature reveals only one article concerning the outcome of lung cancer patients with ARF.[1]

Respiratory failure in critically ill cancer patients indicate poor prognosis.[2–8] Mortality in the intensive care unit (ICU) ranged from 54.5% to 91.1%[1,4] and hospital mortality varied from 63.2% to 95.6%.[2,9–13] The mortality rate in lung cancer

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0954-6111/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2003.07.009

patients associated with ARF is much higher as compared with those induced by other diseases, such as pneumonia, chronic obstructive pulmonary disease (COPD), and septic shock.[14–17] Pertinent literatures suggested thoroughly considering initiation or withholding and withdrawing the life support because of the high mortality rate and the expense of intensive care in critical cancer patients.[6,14] However, there are no acceptable guidelines to help managing critically ill lung cancer patients with ARF.

A variety of factors may cause respiratory failure among lung cancer patients. COPD is a common concomitant disease,[18–20] since most of the patients with lung cancer have been heavy smokers. The rate of lung cancer patients with COPD reported in previous studies ranged from 22.0% to 64.6%.[19–20] Therefore, either lung cancer itself or other reversible conditions such as infections and bronchospasm may contribute to ARF. To separate the degree of functional impairment attributable to reversible etiologies from that caused by irreversible factors is extremely difficult.[1]

Many factors affecting the outcome in different cancer patients had been proposed. These factors, which attracted some controversy, included acute physiology and chronic health evaluation (APACHE) II[3,6,9,11,16] and III[8,12] scores, simplified acute physiological score,[22] cancer type,[10] hepatic,[7,23] cardiovascular,[7,13] renal,[23] and neurological failures,[8,23] persisted leucopenia,[9,23] thrombocytopenia,[23] disseminated intravascular coagulation (DIC),[13] an increasing number of organ system dysfunctions,[2,6,9,11,13,14,21,23] septic shock,[8,11,22] pulmonary infiltrates on chest radiograph,[3,17] requirement of a high fractional inspired O_2 (FiO_2),[16] duration of mechanical ventilation,[1,5] length of ICU stay,[6,22] and low serum albumin.[16,17]

Most of the authors had focused on the outcome of mortality. However, to use mechanical ventilation does not imply terminal illness. Clinical experience reveals that some patients may be weaned from a mechanical ventilator even in an advanced cancer stage. Identifying the predictors of the ability to liberate from mechanical ventilation will be very helpful for clinicians. This study aimed to disclose clinical variables associated with successful weaning from mechanical ventilation among lung cancer patients with ARF.

Materials and methods

Data were retrospectively collected in a university-affiliated tertiary care hospital from January 1, 1995 to June 30, 1999. The investigation included all patients with lung cancer requiring mechanical ventilation for more than 24 h. Ninety-five episodes in 81 patients were eligible for data analysis from a total of 1497 ICU admissions. Factors recorded included: (1) demographic data; (2) cancer status; (3) relevant laboratory values and clinical conditions before respiratory failure; (4) causes of respiratory failure; (5) conditions during mechanical ventilation, including APACHE III score, tidal volume (V_T), maximal inspiratory pressure (Pi_{max}), highest FiO_2, highest positive end-expiratory pressure (PEEP), ability to shift from full mechanical ventilatory support to partial support mode within 48 h, and duration of mechanical ventilation; organ system(s) dysfunction, in addition to the respiratory system, during mechanical ventilation; and[6] weaning outcome and mortality.

Pathology or cytology determined the cell type of tumors and the cells were classified as small cell or non-small cell types. The cancer stage was recorded by the TNM (T: primary tumor, N: regional lymph nodes, M: distant metastasis) system[24] based on the status before respiratory failure. The location of tumors was defined as central, for tumors located up to the segmental orifice, or peripheral, for all other locations. Airway obstruction was defined as occlusion of airway by tumors documented during bronchoscopic examination, or the appearance of obstructive pneumonitis on chest radiograph.

The arterial blood gas and blood chemistry values were those obtained in the last evaluation before ARF. Documented diseases such as COPD were retrieved from the medical records as associated diseases.

The cause of respiratory failure was also recorded. Disease progression was defined as respiratory failure caused by airway obstruction due to tumor mass or diffuse tumor invasion of the lungs. Systolic blood pressure lower than 90 mmHg and not of cardiac origin or sepsis was categorized as shock group. Respiratory failure caused by congestive heart failure or cardiac dysarrhythmia was defined as cardiac origin.

Data from the first profile taken during mechanical ventilation determined the 'after respiratory failure' evaluations. The APACHE III score calculated according to the system of Knaus et al.[25] was obtained within 24 h after mechanical ventilation was initiated.

The criteria for organ failure were modified from previous investigations,[6,14] and were evaluated at least 48 h before death. Cardiovascular failure implied life-threatening cardiac dysarrhythmia, or congestive heart failure. Diagnosing renal failure required a serum creatinine above 2 mg/dl or a 24-h urine output of less than 600 ml. Gastrointestinal failure was defined as upper gastrointestinal bleeding requiring transfusion of more than two units of blood and prolonged ileus (>5 days). A Glasgow coma scale score[26] of less than 6 without sedation was taken to indicate neurological failure. Hematological failure required a platelet count below 50,000 mm^3, a WBC count below 1000 mm^3, the presence of DIC, and a hematocrit below 20%.

All patients in our ICU were screened routinely each morning between 9:00 and 9:30 by the respiratory therapists. The Pi_{max} and was measured by a haloscale during a 30-s spontaneous breathing test and V_T was obtained by dividing the minute ventilation by the respiratory frequency. The weaning protocol was the same for all patients in our ICU. The decision of shifting ventilatory setting to partial support mode was judged by in-charge attending physician. When a low-level pressure support ventilation (6–8 cm H_2O) was successful, a 2-h T-piece trial was arranged accordingly. The patient was liberated from ventilator if he or she could tolerate the spontaneous breathing test. If the patient could not tolerate the low-level pressure support mode, the T-piece trial would be used for weaning, in which the length of T-piece trial was increased, with alternating periods of ventilatory support and the T-piece trial. The decision to perform extubation was made by the patient's attending physician. If the respiratory distress developed, such as diaphoresis, conscious disturbance, agitation, and increased partial pressure of arterial carbon dioxide accompanied by a pH of 7.30 or less, the patients would be reintubated.

The outcome was subclassified into weaned, defined as survival for more than 72 h after liberating from mechanical ventilation, and unweaned groups. The correlation of the variables with the weaning outcome was analyzed statistically.

Statistics

Data are presented as mean ± standard deviation (SD). Two-tailed Student's *t* test was employed for comparisons between groups for continuous variables. Discrete variables were examined by the chi-square test first. If 25% of the cells had expected counts of less than 5, they were re-examined with Fisher's exact test. $P<0.05$ was considered statistically significant. Statistically significant variables in univariate analysis, patient age, and gender were then examined by logistic regression analysis. The grouping cut-off levels were adjusted according to the mean levels of the weaned and unweaned groups. All statistical computations were performed by SAS software (SAS Institute Inc, Cary, NC).

Results

Ninety-five respiratory episodes in 81 patients with lung cancer complicated by respiratory failure were treated with mechanical ventilation during the study period (Table 1). Twelve patients had two respiratory failure episodes and one had three episodes. The interval between respiratory episodes ranged from 15 to 74 days (mean 49.55 days). Males predominated. All 22 small cell lung cancers were in extensive stage disease and were categorized as stage IV disease. The weaning rate was 27.4%. Among the 12 patients who could be discharged from our hospital, two patients were

Table 1 Demographic data.

No. of patients	81
Age (years)	
Mean	67.46 ± 10.01
Range	31–88
Sex	
Male	81 (85.3%)
Female	14 (14.7%)
Cell type	
Small cell	22 (23.2%)
Non-small cell	73 (76.8%)
Squamous cell	29 (30.5%)
Adenocarcinoma	32 (33.7%)
Large cell	1 (1.1%)
Non-Small cell	11 (11.6%)
Stage	
Stage I	1 (1.1%)
Stage II	3 (3.2%)
Stage III	35 (36.8%)
Stage IV	56 (58.9%)
Weaned	
Yes	26 (27.4%)
No	69 (72.6%)
Outcome	
ICU mortality	59 (72.8%)
Hospital mortality	69 (85.2%)
Survivor	12 (14.8%)

Data were expressed as mean ± SD.

Table 2 Cancer status before respiratory failure.

	Weaned (26)	Unweaned (69)	*P* value
Cell type			
Non-small cell	19 (26.0%)	54 (74.%)	0.59
Small cell	7 (31.8%)	15 (68.2%)	
Stage			
Stage I–III	10 (25.6%)	29 (74.4%)	0.75
Stage IV	16 (28.6%)	40 (71.4%)	
Location (two missing data)			
Central	12 (30.0%)	28 (70.0%)	0.56
Peripheral	13 (24.5%)	40 (75.5%)	
Obstruction (two missing data)			
Yes	12 (24.5%)	37 (75.5%)	0.58
No	13 (29.6%)	31 (70.4%)	
Time between lung cancer diagnosis and respiratory failure (days)	106.31±215.25	156.04±263.53	0.35
Previous treatment			
None	15 (31.3%)	33 (68.7%)	0.27
C/T* alone	2 (10.5%)	17 (89.5%)	
R/T† alone	6 (37.5%)	10 (62.5%)	
C/T+R/T	3 (25.0%)	9 (75.0%)	

Values expressed as mean±SD unless otherwise indicated. Data were not available for all patients.
*Chemotherapy.
†Radiotherapy.

still alive at the time of data collection. The survival time of the other 10 patients ranged from 6 to 302 days (mean 61.53 days).

Because the number was too small (1 stage II and 3 stage II), cancer stage I–III disease were included in stage I–III group. Table 2 summarizes the cancer status of the patients before respiratory failure. All factors had no influence on the probability of weaning. 12 lung cancer patients were diagnosed after respiratory failure. Half of our patients did not receive chemotherapy or radiotherapy. In addition, no chemotherapy or endobronchial treatment was done in our patients when the ARF was related to progression of the cancer.

Table 3 lists the blood chemistry and gas values before respiratory failure in the two groups. Only the serum albumin level differed significantly in these two groups of patients. The mean age and gender did not vary between the weaned and the unweaned groups. The presence of COPD or diabetes mellitus did not affect the probability of successful weaning.

Table 4 summarizes the causes of respiratory failure. The various causes revealed no significant differences.

The mean APACHE III score was significantly lower in the weaned group than in the unweaned group (Table 5). The unweaned group exhibited higher mean V_T and lower Pi_{max} than the weaned group but the difference was insignificant. The highest FiO_2 and PEEP required during mechanical ventilation were significantly higher in those who were not successfully weaned. The duration of mechanical ventilation was found to be significantly longer in the unweaned group. Patients whose mechanical ventilator mode could be switched to partial support within 48 h displayed a better prognosis.

Cardiovascular failure, gastrointestinal failure and neurological failure were all associated with poor weaning outcome. Moreover, the mean number of failed organ systems was higher in the unweaned group (data not shown).

Table 6 lists the result of logistic regression. The APACHE III score, shifting to partial support mode with 48 h after respiratory failure, high FiO_2, duration of mechanical ventilation, and number of organs failed were positive predictors.

We also analyzed factors affecting hospital mortality (data not shown). Prognostic factors are those which reflect underlying chronic condition

Table 3 Conditions before respiratory failure.

	Weaned	Unweaned	*P* value
Age	68.85±8.10	66.94±10.65	0.35
Gender			
Male	22 (27.2%)	59 (72.8%)	0.91
Female	4 (28.6%)	10 (71.4%)	
Associated diseases			
COPD			
Yes	12 (35.3%)	22 (64.7%)	0.20
No	14 (23.0%)	47 (77.0%)	
DM			
Yes	3 (33.3%)	6 (66.7%)	0.67
No	23 (26.7%)	63 (73.3%)	
Biochemical profile			
Sodium (meq/dl)	136.96±8.40	134.13±7.20	0.14
Potassium (meq/dl)	3.65±1.00	4.07±1.04	0.08
Calcium (meq/dl)	8.32±1.04	8.47±1.38	0.57
Albumin (g/dl)	3.06±0.43	2.57±0.51	<0.001
Arterial blood gas			
pH	7.38±0.13	7.34±0.13	0.27
PaO_2 (mmHg)	77.23±38.03	68.32±25.74	0.28
$PaCO_2$ (mmHg)	49.82±22.11	52.30±22.40	0.63
HCO_3 (meq/l)	28.23±8.90	27.90±8.27	0.87

Values expressed as mean±SD unless otherwise indicated. Data were not available for all patients. COPD denotes chronic obstructive pulmonary disease, DM diabetes mellitus, PaO_2 the partial pressure of arterial oxygen, $PaCO_2$ the partial pressure of arterial carbon dioxide, and HCO_3 the concentration of arterial bicarbonate.

Table 4 Causes of respiratory failure.

Etiology	Weaning outcome		*P* value
	Weaned	Unweaned	
Cancer progression	4	13	0.87
Chemotherapy	2	4	
Shock	0	3	
Sepsis	5	14	
PPU*	0	1	
Pneumonia	11	24	
COPD†	3	7	
Cardiac origin	1	3	
Subtotal	26	69	

*Perforated peptic ulcer.
†Chronic obstructive pulmonary disease.

such as the ability to wean, serum albumin level, duration of mechanical ventilation and ICU stay, and the occurrence of cardiovascular failure. But factors reflecting acute status such as the APACHE III score during mechanical ventilation were not correlated well with the prognosis.

Discussion

This study, like Ewer's work,[1] aimed at the weaning outcome but not the mortality per se, which was a different approach from the previous studies. In the long run, we considered that the weaning outcome could be treated as a form of immediate outcome and the mortality as a final outcome. The immediate outcome for such patients who had an untreatable disease was of more concern than the final outcome to the intensive care physicians, the families, and even the patients themselves.

Despite aggressive intensive care, the weaning and survival rates of our patients were low, which confirmed the report by Snow.[23] Even when lung cancer patients can be weaned, their long-term survival remains poor. The result also demonstrated that the mortality rate of cancer patients with ARF remains high despite significant advances in supportive management in ICU and ventilatory strategies in recent years.[27]

In our study, the serum albumin level, highest FiO_2, PEEP required during mechanical ventilation, the presence of cardiovascular, gastrointestinal

Table 5 Parameters after respiratory failure.

	Weaned	Unweaned	*P* value
APACHE III score*	52.23 ± 21.05	72.65 ± 23.08	<0.001
Weaning profile			
Tidal volume (ml)	221.82 ± 116.24	216.60 ± 103.07	0.86
Pi_{max} (cm H_2O)	30.32 ± 11.50	33.02 ± 11.40	0.36
Highest FiO_2	0.54 ± 0.20	0.78 ± 0.23	<0.001
Highest PEEP (cm H_2O)	5.62 ± 3.03	8.12 ± 3.73	0.002
Duration of ventilator (days)	7.35 ± 6.94	18.33 ± 23.55	<0.001
Partial support mode†			
Yes	18 (50.0%)	18 (50.0%)	0.01
No	8 (13.6%)	51 (86.4%)	

Values expressed as mean ± SD unless otherwise indicated. Data were not available for all patients. FiO_2 denotes the partial pressure of arterial oxygen, and PEEP the positive end-expiratory pressure.
*Scores on the acute physiological and chronic health evaluation (APACHE) III can range from 0 to 299. Higher scores indicate a worse outcome.
†Shift to partial support mode within 48 h after initiation of mechanical ventilation.

Table 6 Result of logistic regression.

Variable	Standardized estimate	Odd ratio	*P* value
Gender	−0.026	0.87	0.93
Age	0.29	1.05	0.40
APACHE III score	−0.90	0.93	0.03
Albumin	0.57	6.71	0.06
Partial support*	0.57	8.20	0.046
Highest FiO_2	−0.95	0.001	0.008
Total organ failure	−1.26	0.135	0.02
MV duration	−1.47	0.88	0.03

APACHE III denotes acute physiological and chronic health evaluation III, FiO_2 the partial pressure of arterial oxygen, MV the mechanical ventilation.
*Shift to partial support mode within 48 h after initiation of mechanical ventilation.

failure, neurological failures, the sum of organ failures, duration of mechanical ventilation, and APACHE III score influenced the weaning outcome. Patient's age, as in Ewer's[1] report, and gender did not influence the weaning outcome. Most authors agreed that age[1,5,8,10,16,22,23,28] and gender[5,6] are not significant predictors of mortality. In one study, age did affect the mortality.[12] Different disease categories, disease severity, different institutions, and, possibly, different analytic methods may have caused the different results. Another, more reasonable explanation suggests that age does not contribute significantly to patient outcome independently from organ system dysfunction.[6]

The cancer status, including the cell type, stage, and previous treatments, did not influence the result. According to Ewer et al.,[1] the tumor cell type does not correlate to successful weaning. This may be because respiratory failure itself in lung cancer patients indicates just as ominous an outcome as in other cancer patients.[2,3,6–8]

Among other parameters documented before respiratory failure, only serum albumin level carries prognostic significance. The weaned group exhibited higher albumin level. Albumin is frequently utilized to estimate the nutritional status of patients and hypoalbuminemia represents, to some degree, the status of malnutrition. Malnutrition influences respiratory function in a number of adverse ways. Studies have demonstrated that malnutrition decreases the ventilatory response to hypoxia,[29] diminishes muscle mass and thickness, and reduces respiratory muscle strength and endurance.[30,31] Malnutrition also alters host defenses and predisposes the patient to nosocomial pneumonia, which places an additional load on the respiratory system.[29] Studies have demonstrated that low serum albumin levels were associated with poor prognosis in different disease states.[16,17] Albumin may be administered to patients with hypoalbuminemia for various reasons. A recently published meta-analysis[32] indicates that administering albumin does not influence mortality. However, it has not been determined whether correcting the albumin level will improve weaning outcome in critically ill lung cancer patient.

The analysis of the causes of ARF did not allow us to identify the subgroups bearing a better prognosis. Those patients whose ARF was caused by cancer exhibited a higher mortality rate.[14] However, we could not prove the prognostic difference between the groups. The result is comparable to a previous study.[1] The fact that the respiratory failure itself indicated poor outcome in cancer patients may explain it.[2–8]

The number of dysfunctional organ systems has been identified as an important indicator of prognosis in critically ill patients.[2,6,9,11,13,14,22,23] The unweaned group in this study also displayed a higher mean number of dysfunctional organ systems. The study of Dees and colleagues[11] indicated that patients with three failed organ systems had mortality rates as high as 84%. In our study, no patient with three or more failed organ systems in addition to the respiratory system survived. On the other hand, the absence of organ failure does not guarantee successful weaning. Among the organ systems, cardiovascular, gastrointestinal, and neurological failures were associated with less favorable outcome in this study.

The highest FiO_2 and PEEP needed, and the ability to shift to partial ventilatory support but not the V_T or Pi_{max} were prognostic predictors. These factors reflected the severity of the patients' respiratory insufficiency. A previous article[16] revealed that the non-survivals in general medical ICU needed higher FiO_2. However, no previous record, at least in cancer patients, mentioned the ability to shift to partial ventilatory mode as a predictor of weaning outcome. The duration of mechanical ventilation was shorter in our weaning group. However, whether the duration of mechanical ventilation can predict mortality in cancer patients is a controversial issue.[1,5,10,12] The duration of mechanical ventilation is closely related to the general condition of the individual patient. The major determinant of the duration of ventilatory days should be severity, reversibility, and the time needed to recover from the acute problems causing respiratory failure. It should not simply be an issue of shorter or longer duration of mechanical ventilation. Other possible explanation for the controversy is the lack of a suitable weaning protocol in some studies.

Increased APACHE III or modified APACHE III score reflected positive predictors, as mentioned above. The unweaned group had higher score, just as other studies reported upon mortality.[8,12] Similar findings were noted with APACHE II.[3,9] In Staudinger's group, all patients with APACHE III scores above 80 died at ICU.[8] In our group, by contrast, two were weaned among those whose scores exceeded 80 (2/24). A single variable, even the APACHE III score, is insufficient to predict the outcome for an individual patient.

Although the lung cancer treatment plans have made progress and many new ventilator strategies have also been developed in recent years, the prognosis for patients with lung cancer complicated by respiratory failure remains unfavorable. Since no single factor including the APACHE III score should determine decisions about therapy prolongation,[8] we analyzed the weaning outcome based on the combination of APACHE III score, highest FiO_2, and total number of organ systems failed. In this model, no one (0/10) could be weaned from ventilator if APACHE III score exceeded 70, highest FiO_2 were greater than 0.6, and more than two additional organs failed. Since those who could not be weaned from ventilator eventually died, this model also predicted the mortality.

Avoiding intubation should be an important issue in patients bearing this untreatable disease. Non-invasive ventilation may avert intubation and serious complication caused by intubation in selected immunocompromised patients.[33] It may also be a palliative support in end-stage cancer patients. But how to select patients who would most benefit from this approach remains unclear. On the basis of our data, only serum albumin level recorded before respiratory failure was a significant predictor of weaning outcome.

This analysis has some drawbacks. First, these subjects were lung cancer patients treated in a tertiary academic medical center and the severity of their illness may be differed from those in other hospitals. Indications for initiating mechanical ventilation may also differ between institutions, and the outcome may be favorable in other settings because the patients suffer less severe illnesses. Moreover, the 95 respiratory events were derived from 81 patients. The influence on the data of the individuals having more than one episode of respiratory failure would be greater than that of the other patients. But if only the first or last respiratory episode were recorded, the sampling bias will occur. We therefore treated respiratory failures in the same patients as different events. Actually, we also analyzed the data excluding those who experienced more than one respiratory failure event, and this change produced a similar result (data not shown).

In addition, this analysis was directed at the weaning outcome but not the mortality. As mentioned above, published data were limited. We therefore compared our results with those regarding mortality. Moreover, our results are limited by the retrospective design and the small sample size. Nevertheless, our results provide scientific guides for physicians who take care of critically ill cancer patients for prognosis explanation and decision making. This will, of course, need further large-scale prospective randomized studies to verify. At last, although our model may predict outcome in groups of critically ill lung cancer patients, the decision to each patient should be made independently in each case.

Conclusions

Even with the disappointed result, 27.4% of ARF episodes could be weaned. The weaned group had higher albumin level, less ventilatory support, lower APACHE III score, and less failed organs.

In this study, lung cancer patients with respiratory failure who have less than two organs failure during the course, use FiO_2 in mechanical ventilation less than 0.6, and have initial APACHE III score less than 70 will have a better chance to be weaned from mechanical ventilation. We believe this retrospective study provides a scientific data and a different viewpoint for managing lung cancer patients with ARF.

Acknowledgements

The authors would like to thank Chia-Lin Li for her assistance in statistical work.

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