An Observational Study Evaluating the Performance of LENT Score in the Selected Population of Malignant Pleural Effusion from Lung Adenocarcinoma in Singapore

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Keywords

Cancer (lung) · Pleural effusion · Survival · Epidermal growth factor receptor · Eastern Cooperative Oncology Group

Abstract

Background: Patients with malignant pleural effusion (MPE) secondary to lung cancer have been associated with poor prognosis historically. LENT score developed to risk-stratify unselected patients with MPE predicts prognosis of <6 months in patients with lung cancer. **Objective:** To assess the performance of LENT score in predicting prognosis in selected population of MPE secondary to lung adenocarcinoma alone. **Methods:** A retrospective observational study was conducted by reviewing the medical records of patients managed for MPE in the year 2012. **Results:** Seventy patients with lung adenocarcinoma presenting with MPE were studied. The median (range) LENT score at initial diagnosis was 5 (2–7), and the median survival 7.9 (0.13–40) months. Thirty-nine patients received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKIs). The median LENT score and median survival was 4 (2–7) and 14.4 months, respectively, in this group. Those in high-risk category by LENT in this group ($n = 19$) had a median survival and 6-month survival of 17.4 months and 73.6%, respectively. Thirty-one pa-

tients were treated with conventional chemotherapy. The median LENT score and median survival was 5 (2–7) and 4.1 (0.13–34.3) months, respectively, in this group. The median survival and 6-month survival rate in patients in high-risk category and moderate-risk category by LENT score was 6.2 months and 52.7%, and 11.4 months and 70.5%, respectively. **Conclusion:** LENT score underestimates prognosis in patients having MPE secondary to lung adenocarcinoma. This disparity particularly applies to the lung adenocarcinoma patients carrying EGFR mutation. Hence, LENT score may not be applicable to, or may need modification before applying to such patients.

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Introduction

Up to half of the patients with various metastatic malignancies develop para-malignant or malignant pleural effusion (MPE) [1, 2]. In the case of lung malignancy, 15% have a pleural effusion at the initial diagnosis of lung cancer [3]. It is known that MPE recurs rapidly, sometimes within a month after an initial thoracentesis [2]. The management of these patients is thus twofold, one targeted at the cancer itself such as chemotherapy, radiotherapy or tyrosine ki-

nase inhibitor (TKI), and the other targeted at the prevention of recurrence of MPE in future, after initial drainage, by employing chemical pleurodesis, tunneled pleural catheter, pleurectomy, or pleuroperitoneal shunt [2, 4–8].

Choice of these strategies hinges on predicted survival and presence or absence of lung entrapment. Ability to predict survival helps prioritize therapeutic options for MPE, enabling better match with patient's circumstances. Identifying patients with poorest survival carries potential for improved quality of life by shifting focus on minimizing discomfort and inconvenience toward the end of their life. Identifying patients with good survival on the other hand carries potential for improved quality of life by minimizing discomfort and morbidity associated with recurrence of MPE by providing prevention strategies like pleurodesis or tunneled pleural catheter. To this end, there are several factors that predict poor survival of unselected patients with MPE [9–13]. These are high pleural fluid lactate dehydrogenase (LDH; >1,500 IU/L), high eastern cooperative oncology group (ECOG) score (3–4), high neutrophil: lymphocyte ratio (>9), cancer type (lung), low pleural fluid pH (<7.28), and high sVEGFR-1 pleural fluid level [9–13].

However, none of the above stated predictors are sufficiently accurate, leaving patients exposed to errors in decision making. Adding to this insufficiency, conversely, in selected cancer type such as lung cancer, epidermal growth factor receptor (EGFR) mutation and EGFR-TKI therapy predicts longer survival [14, 15]. Consequently, in search for a better predictor, LENT score was developed and recently published by Clive et al. [9] to risk-stratify unselected patients with MPE. LENT prognostic score is a composite score formed by the combination of pleural fluid LDH, ECOG status, serum NLR, and tumor type [9]. It classifies patients into low, moderate, and high-risk groups based on the duration of survival [9]. Ninety seven percent of patients belonging to high risk group reportedly die within 6 months when stratified based on the LENT scoring system [9].

Since LENT scoring system was developed for a diverse unselected population, we performed this study to assess the performance of LENT score in the “selected” population of lung adenocarcinoma. This is a common cancer which presents not uncommonly with MPE. We hypothesized that since survival trends show improvement in lung cancer, especially adenocarcinoma, by virtue of the discovery of cancer-driving mutations and targeted therapy, LENT scoring system may underestimate prognosis in this group of patients.

Material and Methods

The aim of this study was to assess the performance of LENT score in predicting prognosis in selected population of MPE secondary to lung adenocarcinoma.

Patients hospitalized and managed for MPE in the year 2012 were studied. Patients diagnosed with MPE from adenocarcinoma lung between January 1, 2012 and December 31, 2012 at our center were identified from our department database using the ICD code for MPE. Out of these, patients having MPE from adenocarcinoma lung were filtered out, followed by the review of electronic medical records. Data were collected on age, gender, side of pleural effusion, serum LDH, serum protein, pleural LDH, pleural protein, pleural fluid differential cell count, cytology, ECOG status, pleural biopsy result, and survival. All patients reviewed were managed as in-patients as only those presenting first time with the pleural effusion were assessed, and these required admission due to either symptoms or need for work-up such as thoracentesis and pleural drainage. Survival was calculated from the date of diagnosis of MPE and date of death. Follow-up data were available for all patients. LENT score was calculated for each patient according to the published literature [9]. Data were also analyzed by modifying the LENT score by substituting “0” for “2” in the “T” domain of the LENT score. Institutional Review Board approval was obtained for this study with the waiver of consent.

Data Analysis

We used SPSS software, version 17 (SPSS, Chicago, IL, USA) for all statistical analyses. The results were compared using a Wilcoxon 2-sample test or Fisher exact test. *p* values were 2-sided and considered indicative of a significant difference if <0.05.

Results

A total of 100 patients with MPE were identified, of which MPE was secondary to lung adenocarcinoma in 70 patients. These were analyzed for the present study. There were no missing data for any of the variables as all patients underwent pleural fluid analysis in a standardized manner, with results keyed into the electronic system making the retrieval easy. Mortality data were also available for each patient with the help of national electronic health record system. All patients were well enough to receive some form of cancer-specific therapy regardless of the performance status.

The median (range) age was 72 (38–92) years. There were 37 (53%) males, and 39 (55.7%) patients exhibited activating mutation in EGFR and received TKI's. The median LENT score was 5 (2–7), and the overall survival was 241 (4–1,216) days. The duration of follow-up was 7.9 (0.13–40) months (Table 1).

In sub-group analysis, the median (range) LENT score was 4 (2–7), and 5 (2–7) in the sub-group treated with EGFR-TKIs, and sub-group treated with conventional

Table 1. Demographic features, clinical features, and pleural fluid biochemistry of patients with MPE from adenocarcinoma lung ($n = 70$)

Variables	$n = 70$
Age, years	72 (38–92)
Gender, male	37 (53)
Epidermal growth factor receptor mutation	39 (55.7)
Survival, days	241 (4–1,216)
Treated with TKI's	39 (55.7)
Treated with conventional chemotherapy	31 (44.2)
ECOG status	2 (0–4)
Pleural fluid lactate dehydrogenase	929 (267–3,800)
Blood neutrophil lymphocyte ratio	4.8 (1–59)
LENT score	5 (2–7)

Data is presented as n (%), or median (range).

MPE, malignant pleural effusion; ECOG, Eastern Cooperative Oncology Group; TKI's, tyrosine kinase inhibitors.

chemotherapy ($p = 0.44$), respectively. The median (range) survival was 437 (16–1,216) days, and 125 (4–1,043) days in the sub-group ($n = 39$) treated with EGFR-TKIs, and sub-group ($n = 31$) treated with conventional chemotherapy ($p = 0.003$), respectively (Fig. 1).

Nearly half of the patients, 51.4% (36/70), belonged to the high-risk category based on LENT score, and the other half, 48.5% (34/70), belonged to moderate-risk category, with none in low-risk category. Patients in the high-risk category, which is a LENT score ≥ 5 ($n = 36$), in the whole group, had a median survival of 190.5 days, and more than half, 52.7% (19/36), survived >6 months. In those belonging to the moderate-risk category, which is a LENT score 2–4 ($n = 34$), the median survival was 346 days, and 70.5% (24/34) survived >6 months. In the sub-group treated with targeted therapy ($n = 39$), 19 (48.7%) had a LENT score of ≥ 5 , with a median survival of 530 days, and 73.6% (14/19) survived >6 months (Table 2).

Thirty nine (55.7%) patients had activating mutation in EGFR in our cohort. EGFR mutations have been reported in 72.5% of patients with MPE from adenocarcinoma lung in the Korean population [16]. A positive association between EGFR mutation and the presence of MPE, suggesting a role of EGFR mutations in the formation of MPE has also been reported from China [17]. Due to this, we hypothesize that since significant number of patients of adenocarcinoma lung presenting with MPE will have EGFR mutation enabling longer survival, the “2” in the “T” domain of LENT score substituted with “0” will improve its accuracy. Hence, we decided to substitute “0” for “2” in

the “T” domain of the LENT score. After substituting “0” for “2” in the “T” domain of LENT score, 4.2% (3/70) belonged to high-risk category, 70% (49/70), belonged to moderate-risk category, and 25.7% (18/70) belonged to low-risk category. The median survival and survival rate at 6 months in high-, moderate-, and low-risk groups was 113 days and 33.3% (1/3), 208 days and 53% (26/49), and 491 days and 83.3% (15/18), respectively (Table 2). In the sub-group treated with targeted therapy ($n = 39$), 1 had a LENT score of ≥ 5 , 27 had a LENT score of 2–4, and 11 had a LENT score of 0–1 with a median survival and survival rate at 6 months of 113 days, and 0%, 357 days and 77.7%, and 655 days and 91%, respectively.

Discussion

We illustrated that the actual survival in patients having MPE from lung adenocarcinoma was higher than predicted by the LENT score. Modification of the LENT score by substituting “0” for “2” in the “T” domain improved its accuracy in this cohort.

LENT score was developed as a risk stratification system to predict survival in MPE, calculated based on pleural fluid LDH, ECOG status, serum NLR, and tumor type [9]. Patients with a combination of high pleural fluid LDH, high ECOG status, high NLR, and cancer type other than mesothelioma, renal cell carcinoma, hematological cancer, gynecological cancer, and breast cancer, score highest according to the LENT scoring system [9]. Lung cancer was assigned highest risk category among cancer types based on the poor median survival of 74 (60–92) days in the validation cohort of the LENT scoring system [9].

However, with the discovery of mutational drivers of lung cancer such as EGFR mutation, and the advent of EGFR-TKI therapy since 2009, survival rates have improved dramatically in lung cancer patients carrying activating EGFR mutation [18–22]. Prior to the advent of TKI's, the median survival used to be 6.5–8 months in patients with MPE from lung cancer [23]. However, the median survival in those receiving TKI's has been reported as 14 months with a survival rate at 1 year of 52.9% [15]. These findings are consistent with the findings in our cohort.

The median survival in our cohort was 241 days, which was better than the survival of 74 days reported by Clive et al. [9] in their cohort. Among those who received TKI's, the median survival was 437 days, even higher than the survival reported in the “lung cancer” group by Clive et al. [9] in their LENT validation cohort. The median survival in our whole cohort was close to mesothelioma, the

Table 2. Comparison of median survival and survival rate at 6 months based on LENT score in the current study, with the published literature [9]

	Clive et al. [9] (<i>n</i> = 203) (LENT score)	Current study (<i>n</i> = 70) (LENT score)	Current study (<i>n</i> = 70) (modified LENT score)
Survival, days			
High risk (LENT ≥ 5)	44 (22–77)	190.5 (4–1,216)	113 (27–209)
Moderate risk (LENT 2–4)	130 (47–467)	346 (18–1,193)	208 (4–1,216)
Low risk (LENT 0–1)	319 (228–549)	–	491 (32–1,193)
Survival rate at 6 months			
High risk (LENT ≥ 5)	3*	19 (52.7)	1 (33.3)
Moderate risk (LENT 2–4)	47*	24 (70.5)	26 (53)
Low risk (LENT 0–1)	86*	–	15 (83.3)

Data presented in median (range), and percentages or *n* (%).

* Number of patients not provided in the LENT paper.

Fig. 1. a Box plot showing the median LENT score in the whole group, sub-group treated with EGFR-TKIs, and sub-group treated with conventional chemotherapy. **b** Box plot showing the median (solid horizontal line) survival in the whole group, sub-group treated with targeted therapy (EGFR-TKIs), and sub-group treated

with conventional chemotherapy. Despite similar LENT scores between whole group, sub-group treated with EGFR-TKIs, and sub-group treated with conventional chemotherapy, survival was significantly longer in the TKI group compared to chemotherapy group. TKI, tyrosine kinase inhibitor.

cancer type associated with best survival in the study by Clive et al. [9]. Furthermore, the survival in the sub-group of patients who received TKI's in our cohort was higher than even mesothelioma.

Based on LENT score, most patients in our cohort fell in the high-risk or moderate-risk category with none in

the low-risk group. Based on this score, the survival rate at 6 months of patients falling in these categories should be 3, 47, and 86%, respectively [9]. However, the proportion of patients surviving >6 months in the high-risk and moderate-risk groups of our cohort was 52.7 and 70.5%, respectively, much higher than that reported of 3

and 47%. In patients who belonged to the high-risk group and were treated with TKI's, the survival rate was even higher, 73.6% at 6 months, much higher than the 3% quoted in the LENT study.

This study indicates that it may be more appropriate for patients with lung adenocarcinoma and activating EGFR mutation to be assigned the score of "0" instead of "2" in the "T" domain of the LENT score. Without this, the LENT score may underestimate prognosis and falsely assign poor prognosis to this group of patients depriving them of appropriate treatment modalities.

When we re-calculated the LENT score by assigning "0" instead of "2" in the T domain of the LENT scoring system, the risk profile changed. The least number of patients now belonged to the high-risk category as compared to when the score of "2" was assigned to the "T" domain. The highest number of patients (two-thirds) now belonged to moderate-risk category, and a quarter belonged to the low-risk category. The proportion of patients surviving >6 months in the high-risk, moderate-risk, and low-risk groups of our cohort was 33.3, 53, and 83.3% with the modification of the LENT scoring system.

Hence, the LENT score was found to have limitations in predicting survival in patients having MPE from lung adenocarcinoma, especially in those treated with EGFR TKI's. On the same note, while it can be argued that assigning "0" instead of "2" in the "T" domain may be more appropriate for patients with adenocarcinoma and EGFR mutation, for those with adenocarcinoma without EGFR mutation, assigning "1" instead of "0" in place of "2" may be more appropriate, and is a possible area to explore in the future.

Lung cancer being the cancer associated with the worst prognosis, has attracted significant progress in the development of novel therapies in recent years as a battle against it. Identification of several mutational drivers such as EGFR, ALK, ROS1 etc., with corresponding targeted therapies have significantly changed the survival statistics of lung cancer. In addition, immunotherapy carries potential to further improve the survival in lung cancer patients [24]. In view of these advances, the LENT score may indeed need modification for this group of patients. Similar findings have been published by investigators from Japan who reported 14 (87.5%) patients in the high-risk group based on LENT score but could use TKI's for survival longer than 6 months [25].

However, it is noteworthy to highlight that the prevalence of EGFR mutation in Singapore is 40%, whereas the

prevalence in countries LENT was derived from is 12% in UK, 12% in Australia, and 15% in Netherland [26]. This imposes geographical limitations on applying the LENT score. Authors would like to draw the readers' attention to this fact when interpreting our findings. Nevertheless, our study elucidates the limitations of the prognostic scores, demonstrating that they need to be revised and re-validated with the therapeutic advances to keep up with them. Future studies with prospective validation in other Asian countries, and impact analysis to see if the LENT score really alters outcomes will help to improve the clinical decision making [27].

Our study has the limitation of being a single center experience with a retrospective observational design. However, the main strength of our study is that it was conducted on a homogenous population of adenocarcinoma lung, thus increasing the precision with which it can be applied to this group of patients. Additionally, patients with lung adenocarcinoma with MPE have a higher EGFR mutation detection rate compared to patients with lung adenocarcinoma presenting as a solitary mass or nodule. The EGFR mutation rate in MPEs of lung adenocarcinoma has been reported to be as high as 70% [28]. Consequently, greater proportions of patients with adenocarcinoma and a MPE phenotype are eligible for TKI therapy. Hence, based on our findings, modifying or not modifying the LENT score may impact 70% of patients with MPEs from lung adenocarcinoma.

In conclusion, the actual survival in patients having MPE from lung adenocarcinoma is higher than that predicted by LENT score. The LENT score may underestimate prognosis in such patients and needs to be modified to improve its accuracy in this group of patients.

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Ethics Approval and Consent to Participate

Ethics approval was obtained from the institutional review board.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure Statement

J.A., A.V., R.S.D., and R.W.L. have no potential conflicts of interest to report.

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Authors' Contributions

A.V. and J.A. conceived the study, collected the data, analyzed the data, and drafted the manuscript. R.S.D. collected and analyzed the data, and R.W.L. reviewed and revised the study.

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