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Does the LENT score risk-stratify patients with malignant pleural mesothelioma? An observational study

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Abstract

Background: Malignant pleural mesothelioma (MPM) is a rare, highly aggressive and deadly disease with a poor patient life expectancy. A few years ago, the main challenge was the histological diagnosis of this disease; at present, the search for the best therapeutic strategy is now a priority. However, an optimal therapeutic strategy is not yet clear, despite growing efforts in the treatment armamentarium and research, and at the era of tailored and individualized treatment, tools to predict patient survival are needed for therapeutic decision-making. Among them, the LENT scoring system was developed to predict prognosis in patients with malignant pleural effusion. The aim of this study was to assess the performance of the LENT score in predicting prognosis in patients with MPM.

Methods: A retrospective observational study was conducted by analyzing the prospective collected databases of patients undergoing medical thoracoscopy in a single center with a final diagnosis of MPM confirmed by the MESOPATH National Reference Center.

Results: A total of 41 patients with MPM were studied. All patients underwent platinum-based chemotherapy combined with pemetrexed ± bevacizumab. No high-risk category patients were found using the LENT scoring system in this cohort. The median (range) LENT score at the time of medical thoracoscopy was 0 (0–3) and the median survival was 15.5 (2–54) months for the entire cohort. The median survival of low-risk and moderate-risk category patients was 21.4 months (2–54, 32 patients) and 6.7 months (2–19, nine patients), respectively. A total of 27 patients with MPM of epithelial subgroup had a median LENT score of 1 (0–2) with a 26 (2–54) months median survival. The median LENT score and median survival of nonepithelial mesothelioma patients (biphasic MPM subgroup, eight patients; sarcomatoid MPM subgroup, six patients) were 0 (0–3) and 11 (2–52) months, respectively.

Conclusions: Applied to a homogenous cohort of MPM patients, the LENT score underestimated prognosis and was not useful per se for the management of this disease, as evidenced in the epithelial mesothelioma subgroup of patients in our study.

KEYWORDS
pleural effusion, pleural mesothelioma, predictive medicine, survival

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare, highly aggressive and deadly disease with a poor patient life

expectancy. A few years ago, the main challenge was the histological diagnosis of this disease; at present, the search for the best therapeutic strategy is now a priority.[1] However, an optimal therapeutic strategy is not clear yet, despite growing

efforts in the treatment armamentarium and research and at the era of tailored and individualized treatment, tools to predict patient survival are needed for therapeutic decision-making and to prioritize the best therapeutic option.[2] Efforts have recently been made to predict the survival of patients with malignant pleural effusion with several clinical and biological factors predicting poor survival but none are accurate enough.[3–6] Therefore, various systems have been built to better predict survival in patients with malignant pleural effusion (MPE). Among them, the LENT scoring system has been developed and recently validated on the basis of an international cohort stratifying patients to predict prognosis in patients with malignant pleural effusion in low-, moderate-, and high-risk groups. This score combines pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance status, serum neutrophil-to-lymphocyte ratio, and tumor type.[7] However, this score indirectly takes into account inflammation-based parameters which have been associated with overall prognosis in various cancer types,[3,8] and was created for an unselected population regarding the potential presence of oncogenic drivers, chemotherapy treatment, tumor burden, and histological type, in particular MPM, which may impact on patient survival.

This study was performed to assess the performance of the LENT score in a population of patients with confirmed MPM diagnosed by medical thoracoscopy, who were all treated with the same protocol of chemotherapy.

METHODS

This retrospective observational study enrolled patients diagnosed with malignant pleural effusion from mesothelioma at our center (Hôpital Nord – Marseille – France) identified through our hospital database. The prerequisite to be enrolled in this study were a diagnosis of MPM assessed by medical thoracoscopy as previously described,[9] histological confirmation by the MESOPATH National Reference Center,[10] therapeutic management with chemotherapy combining platinum derivatives, pemetrexed (with folic acid and vitamin B12 supplementation) with or without bevacizumab,[11] and informed consent which was obtained according to our institutional policies. Data collected were age, gender, asbestos-exposure, smoking behavior, side of pleural effusion, pleural lactate dehydrogenase (LDH), serum neutrophil and lymphocyte counts, ECOG status, histological subtype, pleural symphysis (talc poudrage), and survival assessed from the date of diagnostic thoracoscopy and date of death. LENT score for each patient was calculated according to the literature.[7] Categorical variables are presented using frequencies with percentages. Continuous variables are summarized using median with interquantile range. All analysis were performed with the Prism software (GraphPad Software Inc.). The p-values were two-sided and considered indicative of a significant difference if <0.05.

TABLE 1 Demographic features, clinical features, and biochemistry of mesothelioma patients

Variables	$n = 41$
Age, years	73 (43–87)
Gender, male	33 (80%)
Asbestos exposure	36 (88%)
Smoking behavior	
Smoker	26 (63%)
Never smoker	15 (37%)
Side of pleural effusion	
Right	17 (41%)
Left	24 (59%)
ECOG status	0 (0–2)
Histological subtype	
Epithelial	27 (66%)
Nonepithelial	14 (34%)
Pleural symphysis (talc poudrage)	20 (48%)
LENT score	
Overall	0 (0–3)
Epithelial MPM	1 (0–2)
Nonepithelial MPM	0 (0–3)
Survival, months	
Overall	15.5 (2–54)
Low-risk category (32 patients)	21.4 (2–54)
Moderate-risk category (nine patients)	6.7 (2–19)

Note: Data is presented as n (%), or median (range). ECOG, Eastern Cooperative Oncology Group; MPM, malignant pleural mesothelioma.

RESULTS

A total of 41 mesothelioma patients were analyzed in the present study. There were no missing data for any of the variables at diagnosis and follow-up was completed for all patients and consequently mortality data were available. Demographic and clinical features as well as blood and pleural biochemistries of patients are listed in Table 1. All patients underwent chemotherapy and six patients received immunotherapy as a second-line treatment. There were 33 (80%) males, all with occupational asbestos exposure. Three females had also been exposed to asbestos. The median (range) age of patients was 73 (43–87) with the majority (63%) being smokers. The side effect of pleural effusion was well balanced. Regarding the histological subtype, epithelial MPM was found for 27 (66%) patients and pleural symphysis was performed in 20 (48%) patients. The median LENT score of the overall cohort was 0 (0–3) and overall survival was 15.5 (2–54) months. All mesothelioma patients had a low (score: 0–1; 32 patients) or moderate (score: 2–4; 9 patients) LENT score. No high LENT score was found in this population. Overall median survival for this cohort was 15.5 months (2–54 months). Patients' median survival was 21.4 months (2–54 months) and 6.7 months[2–19] in cases of low and moderate LENT score,
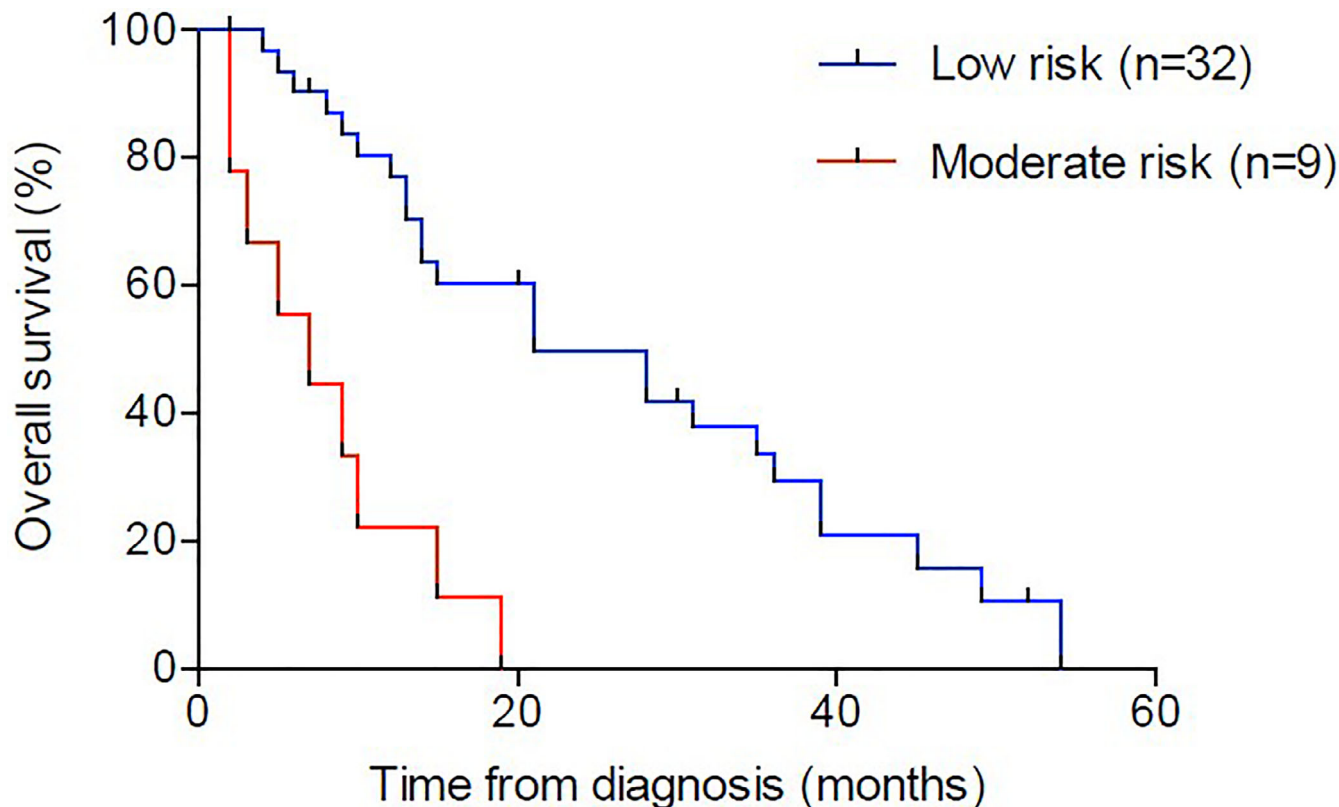
FIGURE 1 Survival curves according to the LENT score

respectively ($p < 0.001$). In comparison, estimated survival based on LENT score for these two subgroups was 10.6 (7.6–18.3) and 4.3 months (1.6–15.6) (Figure 1).

No significant difference related to median survival was found between patients undergoing pleural symphysis with talc (20 patients) and the other group without symphysis, 21 (7–45) months and 13 (2–54) months ($p = 0.3$), respectively. Conversely, the usual significant survival difference was found between the 27 epithelial and 14 nonepithelial mesothelioma patients with median survival of 26 (2–54) and 11 (2–52) ($p = 0.03$), respectively (Figure 2).

DISCUSSION

The results of our study, addressing a dedicated and homogeneous cohort of mesothelioma patients diagnosed by medical thoracoscopy and undergoing the same therapeutic strategy, showed that the actual survival of mesothelioma patients was higher than predicted by the LENT score. Indeed, in the original study leading to the design of this score,[7] the patients with a low-risk LENT score had a median survival of 10.6 (7.6–18.3) months and a median survival of 4.3 (1.6–15.6) months in cases of a moderate-risk score, in comparison to 21.4 (2–54) months and 6.7[2–19] months, respectively, in our study. One could argue that our population was different to the "all-comers" design of the
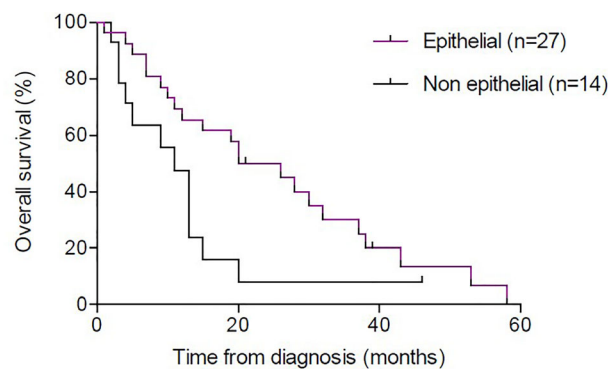

FIGURE 2 Kaplan–Meier survival curves according to mesothelioma subtype

LENT score cohort, as our patients were in good condition and fit enough to undergo a thoracoscopic procedure followed by chemotherapy. Indeed, the LENT scoring system was originally built based on three collective databases (one in the UK and two cohorts - Australian and Dutch) to identify patients with malignant pleural effusions (MPE). Among them, only 21% of patients had mesothelioma. Apart from 17% of breast cancer patients with a known better prognosis, the others were poor prognostic cancer patients including 30% with lung cancer. Patients with mesothelioma at diagnosis usually have quite good ECOG

PS status which does not preclude medical thoracoscopy (under local or general anesthesia as previously published) which is the gold standard for the diagnosis of MPM and the majority of the time a dedicated systemic treatment is feasible. According to the literature, mesothelioma patients are usually fit for such a diagnostic work-up, although in some cases percutaneous image-guided biopsies can be performed, as well as therapeutic management.

This validated risk stratification system may be useful and clinically relevant in building a therapeutic strategy for patients with malignant pleural effusion in comparison to various other prognostic parameters and scoring systems, although it was created for an unselected population regardless of particular histological subtype and pleural tumor burden. In the study by Clive and colleagues who collected 789 patients from three national cohorts (Australian, Dutch, UK), the population of mesothelioma patients (170 patients) was not analyzed per se regarding the risk LENT score, but the data (survival and potential prognostic parameters) extracted from this histological subgroup were used to build a predictive model.[7] Therefore, the LENT score, which allocates score "0" (lower-risk tumor types) for mesothelioma and hematological malignancy, score "1" (moderate-risk tumor types) for breast cancer, gynecological cancer, renal cell carcinoma, and score "2" (high-risk tumor types) for lung cancer and other types of tumor, does not separate mesothelioma subtype, for example, epithelial and nonepithelial types. However, a negative association between biphasic or sarcomatoid mesothelioma subtypes and survival is well known.[2,12–15] In our study, a significant difference in survival was found between the 27 epithelial mesothelioma and 14 nonepithelial mesothelioma patients with median survival of 26 (2–54) and 11 (2–52) months, respectively ($p = 0.03$), in comparison to 11.3 (8.9–14.0) months for the Clive et al. cohort. Consequently, since a significant number of nonepithelial mesothelioma patients were a part of our cohort (14 patients), the usual "0" in the "T" domain of the LENT score should be arbitrarily substituted with "2". By doing this, the median LENT score for nonepithelial mesothelioma patients becomes 2^{2-5} and they belong to the medium-risk category. Various nonanatomical prognostic parameters have been used to design a therapeutic strategy for mesothelioma patients including ECOG performance status, weight loss, chest pain, and biological findings leading to scoring systems.[16–18] Mesothelioma patients are usually included in an entire cohort of patients with unselected malignant pleural effusion. The recent "PROMISE" score is a prospectively validated prognostic model for malignant pleural effusion that combines biological and clinical parameters to estimate three-month mortality, and as with the LENT score, includes mesothelioma patients with score "0" citation for this histological tumor.[6] Scoring systems dedicated to mesothelioma patients are scarce. However a clinical model has been proposed which evaluates a patient's prognosis based on their weight loss, hemoglobin and serum albumin levels, and sarcomatoid histological subtype.[19] This score defined four categories with significant different

outcomes of patients with the best survival (risk group 1) at 18 months (median survival of 34 months) and the worst outcome (risk group 4) at 7.5 months (median survival of 7.5 months). This routine score is encouraged by the ERS/ESTS/EACTS/ESTRO task force for future clinical trials.[2] However, one of the major drawbacks of the LENT score is the lack of consideration for the local extent of the disease which can be a strong prognostic parameter for malignant pleural effusion, in particular for mesotheliomas. Studies in the future have to create a tool aimed an optimal evaluation of mesothelioma pleural tumor burden and create "pleuro- or thoracoscore" for the best therapeutic decision-making.

In conclusion, the LENT scoring system has been built to create a robust and prognostic score to facilitate decision-making for the management of malignant pleural effusion. Although this scoring system is easy to use and fairly relevant as a prognostic parameter for malignant pleural mesothelioma, it underestimates patient survival for various reasons, mainly the quotation of mesothelioma subtype and the lack of consideration for the pleural tumoral extent. Further studies are therefore necessary in this field.

CONFLICT OF INTEREST
None declared.

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