International Prognostic Modeling: A Platform for Collaborative Approach for Patients With Mesothelioma

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Introduction

Staging and prognostication for diffuse pleural mesothelioma (PM) are limited by the low incidence, inconsistent patient presentation, and variability in treatment approaches. The International Association for the Study of Lung Cancer (IASLC) developed the Mesothelioma Domain to evaluate prognostic factors with the goal of improving staging of this rare disease. Accurate prognostication is critical to help with treatment planning and counseling of patients; yet, achieving this goal is difficult owing to the low incidence. Therefore, this international consortium was created to maximize the number of patients and the variables collected. In addition, the robustness and generalizability of the data set enable identification and analysis of significant prognostic factors for patients across many countries and institutions. International collaboration can be leveraged to develop better treatment strategies and ultimately improve patient outcomes.

Research Summary

The focus of this manuscript is to evaluate whether the IASLC model could be improved compared with its prior model in addition to comparing it with the European Organization for Research and Treatment of Cancer (EORTC) model.[1] The EORTC model was calculated on the basis of data from five EORTC phase 2 trials that enrolled patients from 1984 to 1993. For the IASLC data set, patient data were analyzed in three different clinical scenarios that include all available variables, clinical variables without the surgically resected pathologic variables, and only baseline variables that are available at patient presentation. The training set included 3101 patients from 1995 to 2009 and a validation set of 1733 patients enrolled from 2009 to 2019. Once the model was constructed, the C-index for the training set was 0.650 and for the validation set was 0.652. In contrast, the EORTC model yielded a C-index of 0.550. On the basis of the presentation model, the IASLC C-index was 0.668 whereas the EORTC model was 0.577. The independent variables associated with survival include pathologic stage, histological type and grade, sex, adjuvant therapy, and platelet count. Adding anemia with updated cutoffs that reflected sex-based differences in normal ranges improved this model.

This research highlights the ability to create and analyze a data set to overcome the limitations with PM. The ability to identify prognosticators required leveraging data from multiple mesothelioma treatment centers around the world. With this strategy, the study reveals that the IASLC model performs well in identification of prognostic variables and outperforms the EORTC model. The article emphasizes the importance of international collaboration in generating the data set and its importance to improve outcomes for this rare disease. In addition, by including a larger proportion of nonsurgical patients in the data set, the analysis increases the generalizability of the results to patients who do not undergo surgery. The study also discusses the relevance of prognostic factors in the context of evolving treatment options, such as immunotherapy, and the need to understand the relationships between prognostic factors, predictive factors, and outcomes. Overall, this study

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provides valuable insights into prognostication that will help treatment decisions for patients with PM.

Relevance and Potential Impact

The research focuses on improving prognostication for patients with PM. The research builds on previous studies that have assessed prognostic factors in the development of the staging systems for PM. It expands the knowledge by including a larger data set of patients including those who were not treated surgically. This report specifically evaluates the performance of the IASLC models compared with the EORTC model in an attempt to externally validate the data. By identifying significant prognostic factors and evaluating existing models, the study contributes to developing more accurate prognostic tools and potentially leading to better treatment decisions and improved outcomes for patients with PM. Importantly, the data set was generated from multiple institutions around the world with the goal to increase the generalizability of the prognostic models to patients regardless of location.

Patient outcomes have increased in the past two decades. For example, cisplatin and pemetrexed were approved by the U.S. Food and Drug Administration on the basis of a median overall survival (OS) benefit from 9.3 to 12.1 months in 2004.[2] More recently, in the MAPS trial, the addition of bevacizumab to cisplatin and pemetrexed increased OS from 16.1 to 18.8 months.[3] The control arm of the MAPS trial with cisplatin and pemetrexed was the same as the prior experimental arm that added pemetrexed to the regimen. Yet, the median OS was 4 months longer with an identical treatment. Other trials, such as CheckMate 743, also have a longer survival with the same chemotherapy regimen.[4] These changes in OS reveal that regardless of whether improvements are based on more accurate staging or better symptom management, evaluating updated prognostic factors is critical to potentially identify changes over time. As an example in the validation cohort, age, treatment intent, and white blood cell count were not significant, which differed from the training set.

Both the retrospective and prospective enrolment is critical to these findings. Originally, the TNM system for PM was derived by applying the lung cancer lymph node maps to mesothelioma.[5,6] This system was not data driven, but to the authors' credit, data to develop an independent staging system did not exist; therefore, lung cancer provided the best alternative. By continuing to include patients treated during the era of the prior staging systems, the IASLC model was applied to that data which enables evaluation of the strengths and weakness of this approach. For example, the N1 and N2 lung cancer staging of intrapulmonary and ipsilateral mediastinum, respectively, did not reveal a difference with PM; therefore, these stations were combined as N1.[7] In contrast, the prospective enrolment enables protocol-based data capture that focuses on the most relevant data with a greater ability to thoroughly collect the data.

Evaluation of different clinical scenarios provides a practical approach to the data. For the most thorough data collection, surgical resection with all nodal diseases provides the most information. Nevertheless, that level of data is available for the minority of patients. In addition, the decision to proceed with surgery predates the collection of these data. In this report, the baseline variables which are the data points that are available at patient presentation were analyzed. This analysis is critical for assessment of patients who may not proceed to additional staging procedures or surgical resection. In fact, staging procedures in which nodal stations are assessed are usually limited to patients who are potentially operative candidates. With this approach, treatment decisions may be easier without performing excessive testing.

Strengths and Limitations

The strengths of this research are that the study used a large data set from multiple institutions. Patients were enrolled both retrospectively and prospectively which enabled a comprehensive analysis over a significant time. In addition, the analysis used advanced statistical methodologies with Cox proportional hazards regression with bidirectional stepwise selection to assess the association between prognostic factors and OS. Both the number of patients and the multiple international centers increase the generalizability of the results so that the findings are applicable to patients throughout the world.

The limitations of this study are the bias toward a surgical population, slight inconsistencies with the prognostic variables, and potential bias owing to the small number of palliative-intent cases. The study acknowledges that most of the patients included were treated surgically, limiting the generalizability of the findings for nonsurgical patients. Patients referred to centers for surgery may not be generalizable to a broader group of patients. In contrast, although pathologic variables were present in the surgical population, a selection bias toward not operating on patients with advanced T and N disease on the basis of image findings limited the pathologic data on these patients who may have been included in prior decades. Some variables that were significant in the initial analysis, such as age, treatment intent, and white blood cell count, were not associated with survival in the updated data set which raises questions regarding the consistency of these variables as prognostic of survival. In addition, the study acknowledges that the small number of patients treated

with only palliative intent may have limited the identification of significant effects for that covariate. This bias may result in overestimates of OS given that the patients with the worst disease are not well represented in the data set. In contrast to surgical patients and patients enrolled on trials, patients with the most limited performance status practically cannot travel to mesothelioma centers and require management near home in which they are probably not be included in the data sets.

Conclusion

The development of the IASLC model provides the most robust data set for prognostication of patients with PM. The IASLC model identified several variables independently associated with survival. As molecular data collection becomes more common for all tumor types, the collection of additional variables may improve the prognostic ability of this model in the future. Moreover, larger sample sizes, especially with intraoperative data collection and imaging data at patient presentation, may further improve the model. This international consortium stresses the importance of collaboration among centers and integration of data. This model provides a mechanism to not only refine prognostication for patients with PM but also build the foundation for treatment approaches that may refine predictive modeling as well.

CRediT Authorship Contribution Statement

Cristian G. Medina: Conceptualization, Data curation, Format analysis, Methodology, Writing.

Yuan Xu: Conceptualization, Format analysis, Writing.

R. Taylor Ripley: Conceptualization, Format analysis, Investigation, Methodology, Writing, Final approval.

References

1. Wolf AS, Rosenthal A, Giroux DJ, et al. The International association for the study of lung cancer pleural mesothelioma staging project: updated modeling of prognostic factors in pleural mesothelioma. *J Thorac Oncol*. 2023;18:1689–1702.
2. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol*. 2003;21:2636–2644.
3. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2016;387:1405–1414.
4. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2021;397:375–386.
5. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. *Chest*. 1995;108:1122–1128.
6. Euhus CJ, Ripley RT. The staging of malignant pleural mesothelioma. *Thorac Surg Clin*. 2020;30:425–433.
7. Rice D, Chansky K, Nowak A, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming eighth edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11:2100–2111.