

staging (in general) and the high proportion of understaged or unstaged patient in their series; this, in our opinion, is a strong methodological bias with a high potential of hampering the subsequent multivariate analysis planned to dissect, in detail, the role of staging and surgical approach on survival. The flickering of values defining the role of pathological stage as a prognostic factor in this series would recommend a cautious approach the coherence of the clinical and pathological TNM values, in particular regarding their capacity to predict the outcome—especially in the long-term setting where curves do abate and flat—and by consequence to substantiate, and thus justify, the indication for a more extensive surgical approach. More information around this issue would add precious knowledge on the natural history of the MPM, which is indeed peculiar.⁵ We would furthermore appreciate a deeper analysis of the unstaged/understaged cases taken separately from those where data on staging where, preoperatively, complete. Anyway, if in the future only EP/D procedures will be offered to patients with MPM with “curative” or “palliative” intent (as in their conclusions Bovolato et al³ foresee) in the context of a multimodal treatment, what could be the usefulness of an extensive staging apart from excluding from surgery patients with unresectable disease or with N-positive or M-positive status?

We would conclude constructively by inviting Bovolato et al³ to go deeper into the analysis in-line with the discussed points and provide the community with further interesting details. As well, we believe that experts’ dialogue—given the level of complexity of conflicting evidences on this subject, in turn, generated by strong determinants as such as the heterogeneity of therapeutic choices—is still the best way to move on to resolve the large grey areas of knowledge for management and clinical decision in this field.

Cristiano Carbonelli, MD

Pulmonology Unit
Department of Cardiology, Thoracic
and Vascular Surgery and Critical Care
Medicine
Azienda Ospedaliera ASMN, Istituto di
Ricovero e Cura a Carattere Scientifico
Reggio Emilia, Italy

Cristian Rapicetta, MD

Thoracic Surgery Unit
Department of Cardiology, Thoracic
and Vascular Surgery and Critical Care
Medicine
Azienda Ospedaliera ASMN, Istituto di
Ricovero e Cura a Carattere Scientifico
Reggio Emilia, Italy

Alfredo Cesario, MD

Office for International Research
Activities and Systems Medicine
Scientific Direction
Azienda Ospedaliera ASMN, Istituto di
Ricovero e Cura a Carattere Scientifico
Reggio Emilia, Italy

REFERENCES

1. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011;12:763–72.
2. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg* 2015;99:472–480.
3. Bovolato P, Casadio C, Billè A, et al. Does surgery improve survival of patients with malignant pleural mesothelioma? A multicenter retrospective analysis of 1365 consecutive patients. *J Thorac Oncol* 2014;9:390–396.
4. Datta A, Smith R, Fiorentino F, et al. Surgery in the treatment of malignant pleural mesothelioma: recruitment into trials should be the default position. *Thorax* 2014; 69: 194–197.
5. Rusch VW, Giroux D, Kennedy C. Initial analysis of the international association for the study of lung cancer mesothelioma database. *J Thorac Oncol* 2012;7:1631–1639.

In Response

To the Editor:

Carbonelli et al. made a very important point, focusing on the lack of evidence regarding the best surgical treatment to manage malignant pleural mesothelioma (MPM) patients. The only prospective randomized trial published in the literature showed no

advantages for extrapleural pneumonectomy (EPP) compared with chemotherapy alone,¹ although several biases had influenced those results.² After the MARS trial was published, EPP has been abandoned in many European countries.

Recently, several series demonstrated comparable or sometime better results for pleurectomy decortication (PD) compared with EPP in terms of overall survival and quality of life.^{3,4} As showed by the paper published by Lang-Lazdunski et al., the macroscopic complete resection was an independent prognostic factor for survival and not the type of surgery, and also the group of patients underwent an incomplete resection after PD had similar results in terms of survival compared with patients underwent to EPP.³ Considering the role of surgery in mesothelioma multimodality treatment and the impact of EPP on the quality of life, PD should be favored compared with EPP as surgical treatment of choice. EPP is still performed in very highly selected patients with no evidence of nodal disease and when a complete macroscopic resection can be achieved.^{1,3}

Most of the patients included in our analysis were treated before the MARS trial results were available; at that time the decision of performing EPP versus PD was driven by the patient’s operative risk and mainly by the intraoperative assessment of the extension of the tumor to achieve aiming a complete macroscopic resection.

As we know the clinical staging is unreliable, and many patients are understaged, making difficult the comparison of different groups.^{5,6} In our study, clinical staging was missing in 854 out of 1365 patients (62.6%); in patients not treated surgically the impact of missing data was higher (634 of 862 [73.5%] patients). Due to lack of data and accuracy of the clinical staging, we did not include the clinical stage in the univariate and multivariate analysis. We do not believe that this a methodological bias, but excluding this factor from the analysis had improved the quality of the comparison between the nonsurgical and the surgical groups. The clinical staging would have represented a confounding factor.

Address for correspondence: Andrea Billè, MD,
Guy's Hospital, London, United Kingdom.
E-mail:andrea_bille@hotmail.it
DOI: 10.1097/JTO.0000000000000614
Copyright © 2015 by the International Association
for the Study of Lung Cancer
ISSN: 1556-0864/15/1009-0e93

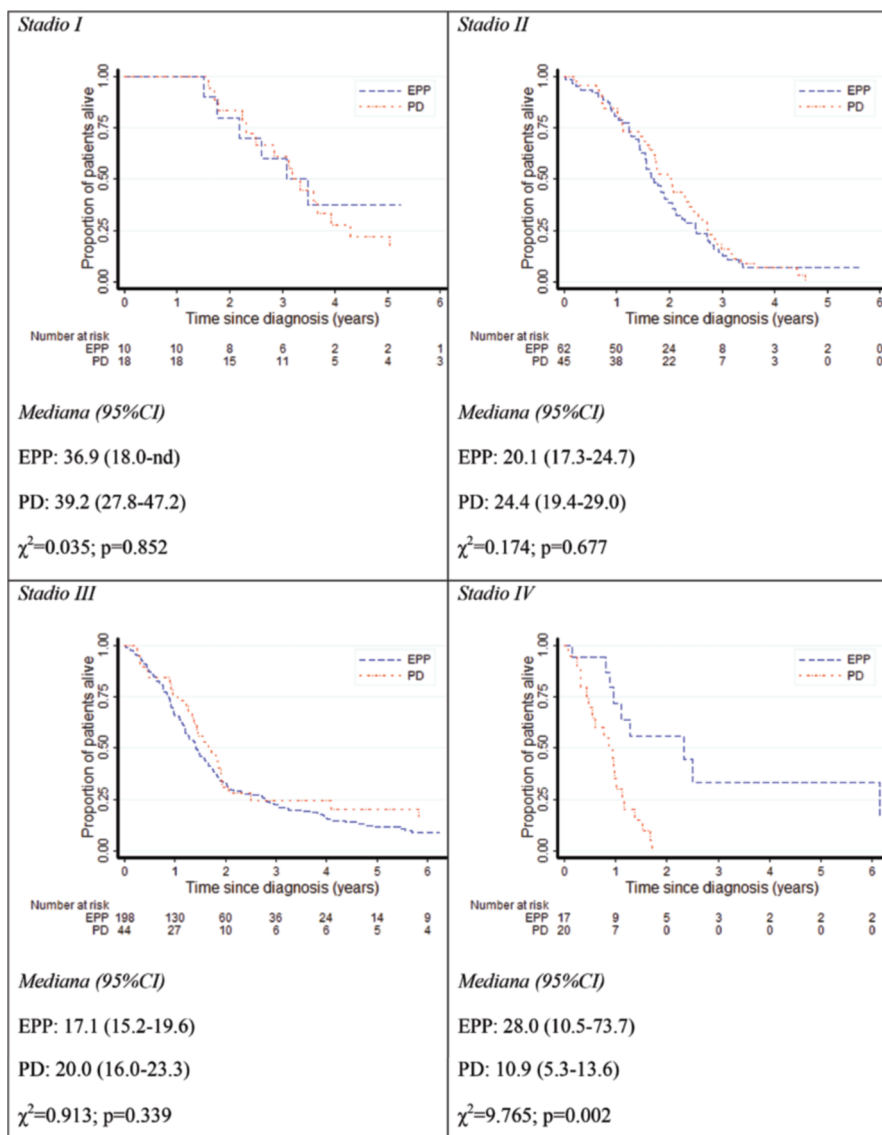


FIGURE 1. Kaplan Meier overall survival curves for patients underwent EPP vs PD analyzed by stage.

We addressed the understaged patients, when we reported the survival rates stage by stage as part of the descriptive results of our populations, and not surprisingly there were no correlations between clinical staging and overall survival. In nonstaged patients, the only reliable characteristics as showed by our article in the multivariate analysis were age, histology, and chemotherapy treatment.

Pathological staging was more reliable and in our study it was less affected by missing values (75 of 503 [14.9%]); as shown in Figure 1, the

relative risk of death between the surgical approaches is qualitatively (survival curve PD over survival curve EPP) and quantitatively (HR estimated as ratio of median overall survival under assumption of exponential distribution) similar for stages I, II, and III. This behavior is drastically different for stage IV. We pointed out that the results regarding stage IV should be considered very carefully due to the missing data and the small sample size of stage IV patients, before considering EPP a better surgical option for advanced stage MPM.

We strongly believe that a presurgical staging with computed tomography and positron emission tomography is still necessary to exclude patients with extensive N2 disease or M disease or obvious T4 disease from surgery and avoid unnecessary surgical exploration, but we still need to improve the accuracy of the clinical staging in MPM. We do not recommend routinely preoperative mediastinal staging or staging laparoscopy, even though they could be necessary to rule out the resectability in selected patients.

We agree that discussion is fundamental in such a complex disease to manage, as mesothelioma, but what we really need is prospective trials comparing different treatments. MARS2 trial in United Kingdom and PASS trial in Italy can help to assess the role of PD compared with chemotherapy alone in the management of MPM.

Andrea Billè, MD
Luca Porcu, PhD
 Department of Thoracic Surgery
 Guy's Hospital
 London, United Kingdom

REFERENCES

1. Treasure T, Lang-Lazdunski L, Waller D et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: Clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol* 2011;12:763–72.
2. Weder W, Stahel RA, Baas P, et al. The MARS feasibility trial: Conclusions not supported by data. *Lancet Oncol* 2011;12:1093–4; author reply 1094.
3. Lang-Lazdunski L, Bille A, Lal R, et al. Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. *J Thorac Oncol* 2012;7:737–743.
4. Rena O, Casadio C. Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: A harmful procedure. *Lung Cancer* 2012;77:151–155.
5. Frauenfelder T, Kestenholz P, Hunziker R, et al. Use of computed tomography and positron emission tomography/computed tomography for staging of local extent in patients with malignant pleural mesothelioma. *J Comput Assist Tomogr* 2015;39:160–165.
6. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. *J Thorac Oncol* 2012;7:1631–1639.