Commentary

Malignant pleural mesothelioma: beyond the mathematical models

Giovanni Leuzzi[1], Leonardo Duranti[1], Filippo Lococo[2]

[1]Thoracic Surgery Unit , IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy; [2]Thoracic Surgery Unit, Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia, Italy

Correspondence to: Giovanni Leuzzi. Thoracic Surgery Unit, IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy.
Email: giovanni.leuzzi@istitutotumori.mi.it.

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Nowadays, the question on whether performing surgical resection in malignant pleural mesothelioma (MPM) patients is an open and endless debate. The treatment of MPM is still surrounded by controversies based on the results of retrospective studies, institutional and personal experiences, empirical observations, clinical judgments and habits. The most significant "dogma" frightening most clinicians is that MPM has an unfavorable prognosis, even in those cases receiving surgery. This is particularly true if considering that only a few surgically-treated patients experience a prolonged survival, ranging from 18% to 20% at 3 years in favorable cases (1,2). As a result, it is inevitable wondering which factors really influence long-term survival and if this "lucky" subset represent a distinct category of MPM patients. To answer these questions, some prognostic scores have been proposed in Literature. In the late 90s, the European Organization for Research and Treatment of Cancer (EORTC) (3) combined five clinical variables into a scoring system through the analysis of 181 nonsurgical MPM patients, thus allowing classifying the patients into good and poor prognosis groups. Similarly, the Cancer and Leukemia Group B (4) reported a regression tree by combining seven prognostic factors and obtaining six subgroups with different outcome. As well, an eight-variable scoring system was developed by Linton *et al*. (5) by taking into account a series of 551 patients receiving either surgery or medical treatment.

In this ongoing debate, Tagawa *et al*. (6) recently reported and validated a prognostic model by analyzing a sample of 85 MPM patients (65 with blood test available) undergoing extra-pleural pneumonectomy (EPP). Specifically, this score was established using sex (female:male =0:1 point) and platelet-to-lymphocyte ratio (PLR; PLR <215:>215=0:1 point) as unique variables. The patients were then classified into three risk groups (according to the sum of the points) with progressively worse outcome. Although both the training and the validation cohort accounted a limited number of cases (85 and 32 patients respectively), the main strength of this prognostic model is its ease of use in the preoperative setting by considering two variables only (sex and PLR). Specifically, such simple score may be adequately used to select preoperatively those patients who could receive the full benefit from EPP. In this scenario, the preoperative utility of statistical models potentially complementary to pathologic stage has been evaluated by Pass *et al*. (7) who analyzed a cohort of 906 patients (from the IASLC database) and assessed the CORE variables (histology, sex, age, white blood cell count and platelets) that could be evaluated noninvasively on presentation. This is partially in line to that previously reported by ourselves (8). Specifically, our prognostic score integrated both clinical (age, asbestos exposure) and surgico-pathological variables [histotype, ratio between metastatic and resected lymph-nodes (RL)]. Differently from that reported by others (6,7), we deem that surgical variables should be taken into account as the pretreatment ones (either clinical or laboratory test variables) in the attempt to predict the outcome. The impact of pathological factors is of particular interest if considering the extreme heterogeneity of nodal spreading pattern in MPM. Unlike non-small-cell lung cancer, N2 skip metastases occur mostly in MPM patients (about 40%) as a result of drainage from diaphragmatic pleura directly

into mediastinal nodes (9). Furthermore, the present TNM staging counts N1 and N2 involvement together as stage III because of the lack of data currently available to clarify this issue. In this debate, we reported that nodal status alone did not predict survival of MPM patients undergoing EPP while RL did so. Compared with nodal status or the number of involved lymph-nodes, we deem that RL is a more reliable pathological factor to be used in prognostic model, given that it may reduce the bias of inter-patient variability of lymph-nodes number (varying for body mass index, induction therapy, previous malignancies, underlying chest diseases, and so forth).

Another matter of debate that has been scarcely explored in literature is the association between systemic inflammation and MPM occurrence and outcome. Specifically, the bi-variable model proposed by Tagawa *et al*. (6) counts a significant prognosticator (PLR), that reflects both inflammatory (high platelet count) and immunosuppressive (low lymphocyte count) status of MPM patients. It is widely accepted that inflammation is strongly associated to cancer survival (10). Similarly, immune mediators are likely to be relevant for the biological response to asbestos exposure (11). This issue is intriguing if one considers that different drugs (involved in inflammation cascade) may modulate immune hyperactivity of cancer patients. In this setting, the administration of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) for chemoprevention has been widely explored in the literature, especially for prevention of colorectal cancer (12). Interesting results have been reported also in the setting of MPM (13,14). These data may open the doors to future clinical trials exploring the role of NSAIDs in modulating inflammatory status in asbestos-related diseases as well as in MPM. As well, PLR could be easily used to select high-risk candidates and to monitor patient's immune status during such possible "tailored" therapy. Further prospective studies should be performed to better investigate this association.

In conclusion, different prognostic scores for MPM patients have been explored in Literature and should be further validated in larger cohorts. By splitting patients into good and poor prognosis groups, these statistical models may help clinicians to tailor postoperative treatment (by identifying those patients requiring a more aggressive therapy or close follow-up) and to design future trials on induction and adjuvant therapy (by homogenizing those MPM cases with heterogeneous factors). In view of these limited data, it is prudent to recommend using such prognostic models only within institutional trials. However, this work by Tagawa *et al*. (6) gives us many open questions on the possible use of lab-tests to evaluate preoperative systemic inflammation as well as immune-modulation in the setting of innovative therapeutic trials.

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