Integrating Data from Multidisciplinary Management of Malignant Pleural Mesothelioma: A Cohort Study

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Abstract

Background. Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy that most commonly affects the pleural lining of the lungs. MPM has a strong association with asbestos being at least 80% of cases caused by exposure to its biopersistent fibers. Individuals with a chronic exposure to asbestos might refer a 20-40-year latency with no or few symptoms. Such has been the case of Piedmont and Lombardy regions of Italy where industrial production of materials laden with asbestos, mainly cements, has created a large epidemic. Since 2018 in Pavia San Matteo hospital, a multidisciplinary team has been collecting data on over 100 patients with MPM. The main goal of this project is to define and describe an integrated profile for each MPM case at diagnosis by using data mining and partition analysis.

Methods. Here we bring together exhaustive epidemiologic, histologic, radiologic data of 88 MPM patients that came to our observation to draw correlations with predictive and prognostic significance.

Results. Overall, the median survival (OS) was of 15.6 months. Most patients presented with pleural effusion, irrespective of disease stage. Quite unexpectedly, no statistically significant association had been demonstrated between OS and TNM disease stage at diagnosis. Although average OS is similar in male and female patients, partition analysis of data underlined a significant differential hierarchy of predictor categories based on patient gender. In never smoker female patients, full chemotherapeutic regimens are associated to better outcomes. Moreover, within respect to second line treatments, vinorelbine emerged as the most advantageous choice but only in females, whereas in the male subgroup no statistically significant differences resulted between gemcitabine and vinorelbine.

Conclusions. Multidisciplinary approach to MPM is thus mandatory to define better therapeutic approaches, personalize the management and improve patient outcomes.

Background

Mesothelioma is a rare and aggressive malignant tumor arising from mesothelial linings, most frequently affecting the pleura (90%), but also the peritoneum, the pericardium, and the tunica vaginalis. Although molecular steps leading to MPM are partially known, the disease is still lacking effective therapies. Novel biological molecules (from small molecules and checkpoint inhibitors) although successfully used for the treatment of different epithelial tumors, are not effective against MPM [1,2,3,4,5]. It is well documented that at least 80% of mesothelioma cases are caused by exposure to asbestos [6,7,8]. In developed countries like Italy, roughly 1.15 per 100,000 cases are diagnosed annually [9,10]. The Piedmont and Lombardy regions are most affected, due to industrial production. Every year for the last decade, more than 300 new cases have been diagnosed in Lombardy alone. In 2018, the incidence of MM in Italy was 6.08 cases/100,000 inhabitants, 8.48 cases/100,000 males and 4.38 cases/100,000 females. Since 2018, our Institution has been dedicated at organizing an integrated path to malignant pleural mesothelioma (MPM) diagnose, coupled with personalized patient treatment. This approach has provided a unique

opportunity to analyze the clinical data of the patients with a multidisciplinary perspective. More specifically, we here aimed at matching the clinical, pathological and imaging features of the disease to define specific patterns predictive of patient outcomes. The main goal of this project is to define and describe an integrated profile for each MPM case at diagnosis by using data mining and partition analysis. Ultimately, this work will provide preliminary findings to develop future omic-centered projects in MPM population.

Methods

The Pavia Experience: Territorial Diagnostic, Therapeutic and Assistance Planning. The PDTA (Percorso Diagnostico Terapeutico e Assistenziale- Territorial Diagnostic, Therapeutic and Assistance Planning) for MPM was firstly defined in 2014 within the Provincial Oncology Intercompany Department (DIPO) of Pavia. In 2018, the PDTA definitively established two territorial outpatient facilities in view of local epidemiological data on asbestos-related diseases: a first-level clinic, located at the PRESST in Broni, and a second-level clinic managed by the Pneumology Unit and Medical Oncology Unit at the IRCCS Policlinico San Matteo (supplementary Figure 1). The two structures cooperate to provide care for patients with suspected asbestos-related pathology. They perform first-level diagnostic investigations as well as those of greater complexity to allow diagnosis and tumor staging. Moreover, they cooperate to provide an individualized therapeutic pathway and psycho-social care plan for the patients. In addition, the PDTA manages the chemotherapy treatments available at our territorial facilities (PRESST Broni, Broni-Stradella Hospital), centralizing at the IRCCS San Matteo when high complexity investigations are needed.

Patients identification and selection. Since November 2018, we have been collecting data on all the patients with mesothelioma managed through the PDTA. The number of patients was then narrowed by several criteria to be included in the study (supplementary Figure 1), including the tumor histotype, diagnostic method, treatment received and radiologic information. Data were obtained from the anamnestic records, outpatient reports and hospital discharge letters. Informed consent of each patients was collected routinely at hospital admission according to Institutional procedures.

Statistical analysis. The collection of data was made in the form of Excel Spreadshets. The basic statistical analysis was conducted through the Excel “Data Analysis” add-on package. Advanced statistical analysis of data has been performed by using the JMP partition algorithm (JMP-Statistical Discoveries. From SAS, website at www.jmp.com) which is able to search all possible splits of best response predictors. These splits (or partitions) of the data are done recursively to form a tree of decision rules. The partition algorithm chooses optimum splits from many possible trees, making it a powerful modelling, and data discovery tool. The technique is often considered as a data mining approach since it can explore relationships in absence of a good prior model. Moreover, it can reduce big problems to easier interpretable results. A useful application of partitioning is to create a diagnostic heuristic for a disease. Given symptoms and outcomes for a population, partitioning can be used to generate a hierarchy of questions to help diagnose new patients. Predictors can be either continuous or categorical (nominal or

ordinal). If a predictor is continuous, then the splits are created by a cutting value. The sample is divided into values below and above the cutting one. If a predictor is categorical, then the sample is divided into two groups of levels. The response can also be either continuous or categorical (nominal or ordinal). If the response is continuous, then the platform fits the means of the response values. If the response is categorical, then the fitted value is a probability for the levels of the response. To properly estimate the residual uncertainty of classification, several numerical indexes are used. Among them the Gini heterogeneity index (I_G) which is calculable from relative frequencies (p_i) of each of the M total classes [11]. Another one is entropy (H) which is associated to the concept of quantity of uncertainty [12]. By using one of the above-mentioned indexes the algorithm is able to take a decision on which partition make at each step of tree construction

Ethics statement

The study entered a main project that was approved by local Ethical Commission and each enrolled patient gave written informed consent before enrolment (Comitato di Bioetica, Fondazione IRCCS Policlinico San Matteo, approval numbers: protocol #20090002344; procedure # 20090019080; date of approval: June 3rd, 2009)

Results

Data description and screening

Epidemiology and demographics

The total number of patients referred to our *Territorial Diagnostic, Therapeutic and Assistance Planning* was 105. From there, 17 patients did not fit our inclusion criteria. In our raw data, we looked at more than 30 parameters in 88 MPM patients between November 2018 and May 2020. Patients enrolled in clinical trials were excluded from the analysis. Exhaustive clinical data are summarized in Table 1. Of them, 26 (29.5%) were females and 62 (70.5%) were males. The male-to-female ratio we report is roughly 2.3, which is near that reported in the 6th edition of the ReNaM report (M:F = 2.5) [6]. The male predominance was expected as exposure to asbestos often occurred in and around industrial factories where most employees were men. The average age at diagnosis supports this concept: it was of 68.9 years (from 47 to 85 years), with a median age of 71. This data is broadly in line with that of the 6th ReNaM report, which shows an average age at diagnosis of 70 years [6]. No cases of diagnosis under the age of 47 were found in our study, confirming what is contained in the ReNaM report where only 2% of total cases recorded occurred in patients younger than 45 years and coherently to the significant latency associated with the disease onset after exposure to asbestos. The majority of the patients observed had a significant exposure to asbestos as part of their employment/family/social history. Indeed, 24 out of the 88 patients reported certain or highly probable workplace exposure (either directly from the factory or indirectly through various blue-collar work). Environmental and indirect exposure (patients were relatives of workers in asbestos industrial plants) cases were significantly higher (30 cases, 34%) as the pollution from the

factories had an effect on members of the town. The significant environmental pollution and massive exposure during the company's peak activity period (1970s and 1980s) created this high incidence, as previously mentioned. No relevant exposure history was reported for 30 (34 %) of the patients in our cohort. Out of the 88 total patients, 36 (40%) claimed to have never smoked, while 15 (17 %) were active smokers and 37 (42 %) were ex-smokers. Thus, 59% of the analyzed population referred a smoking history coherently to previous studies showing important synergistic tumorigenic activity of smoke and asbestos, related in both cases to induction of inflammation and directly damaging DNA [13,14]. Indeed, even with equal asbestos exposure, cigarette smoke has been correlated with increased risk of developing MPM [15].

Radiological and clinical diagnosis and staging algorithms

Of all 88 patients followed, we aimed at identifying key radiological features at baseline (Table 1). However, a history of thoracentesis or drain placement was permitted, as this would not alter plaque/tumor size. Despite the fact that most of our patients had a significant pleural effusion, most had not received thoracentesis or drainage before the “indicative” or “diagnostic” CT scan was taken. Indeed, just 14 patients (16%) had evidence of a previous evacuation of pleural fluid via drain or thoracentesis on radiologic reports or CT images. On the other hand, only 4.5% (4 cases) of patients had no pleural effusion. Four patients had evidence of bilateral pleural effusion on pre-treatment CT scans. Thus, the 96% pleural effusion prevalence reported in the population of study was higher than already published data [16,17] among which the 79% found by Dogan *et al*. in a CT analysis of 212 patients with MPM in Turkey [18] although some different features in terms of patient population, time-period analyzed, environmental and epidemiological factors define the two cohorts. In our study, 34 (39%) patients showed bilateral alterations (pleural effusion, pleural plaques or chest wall infiltration) whereas 64 (73%) showed mediastinal involvement at time of diagnosis. Roughly half of our patients (45 patients or 51%) had some sort of involvement of the diaphragm before receiving chemotherapeutic treatment.

MPM diagnosis confirmation has been reached through three main approaches, namely medical thoracoscopic, percutaneous and surgical biopsy (Table 1). Of them, medical thoracoscopy was the most common (50 patients or 56.8 %). Percutaneous biopsies and surgical procedures (VATS) were used in 19 patients (21,5 %) respectively, while no patient received diagnosis through cytology on pleural fluid. Biopsy results showed that most of our patients received a diagnosis of epithelioid-type MPM (66 patients or 75 %). This result is in-line with the reports from AIOM 2018 guidelines that showed a prevalence of the epithelioid histotype in 75-80% of cases [website at https://www.aiom.it/wp-content/uploads/2019/10/2019_LG_AIOM_Mesotelioma.pdf], but is significantly higher than the percentage of epithelioid cases reported in the ReNaM (55% of cases) [6]. Coherently to already reported data, the epithelioid histotype was associated with an increased overall survival (15.72 months *vs* 13.2 months in sarcomatoid cases and 11.8 in biphasic ones). The diagnosis of a sarcomatous/desmoplastic lesion was found in 6 patients (6,8 %) and the biphasic type in 7 patients (7,9%) respectively, being less represented than the data reported in ReNaM, where the biphasic histotype accounts for 10.5% of cases [6]. These percentages are also slightly different from those reported in the AIOM guidelines, where the

biphasic histotype is attested to 10-25% of cases and the sarcomatoid about 10%. In nine patients (10.22%) it was not possible to define a precise histotype even in the presence of certain MPM (defined as unspecified mesothelioma). This data is broadly in line with the ReNaM, where 12% of MPM are not otherwise specified (NOS).

Of the 88 patients observed, 23 were stage IA, 14 patients were stage IB, 30 patients were stage II, 5 patients were classified as IIIA and 9 as stage IIIB. Finally, seven patients were classified as stage IV, indicating that distant metastasis was found (Table 1). Overall, the 76% of patients have an early stage of disease (IA-B, II) according to the TNM-8 Ed system [19]. As a result, the majority of patients were susceptible to surgical therapy and/or multimodal approach.

Treatments

More than half of the 88 patients in our study received some form of surgery as a treatment for MPM (52 patients or 59,1%). Of these 46 patients received pleurectomy/decortication surgery. Six patients received various other palliative surgical approaches. These data correlate with the fact that most of the evaluated patients had low-stage tumors (TNM stage I or II), thus eligible to surgery. In all cases, P/D was followed by conventional chemotherapy and 21 patients had a progression free survival higher than 10 months. Chemotherapy was the most common therapeutic option and 67 out of the 88 patients received the standard first line chemotherapy regimen made of pemetrexed and cisplatin; 18 patients underwent mono-chemotherapy (carboplatin) due to the low performance status and comorbidities. The timing of the treatment was not the same for all patients though: 4 (6%) of the 67 patients received neoadjuvant treatment and remaining underwent adjuvant chemotherapy. Side effects of the chemotherapy were not specifically monitored, but we did not report severe toxicities. Second line treatments were performed in 52 patients: 30 of them were treated with gemcitabine, 19 with vinorelbine and three underwent first line chemotherapy re-challenge.

Out of the 88 patients we followed, just 7 patients (8 %) received radiotherapy (RT). In three cases RT was a part of multimodal treatment, while 4 patients received radiotherapy for palliation.

Data are detailed in Table 1.

Outcome

The number of months that a patient was “disease-free” was reported for all and the range was extremely heterogeneous between 3 and 45 months with an average value of 9,8 months. The average time to progression after second line chemotherapy was 4.6 months. The overall average survival (OS) was 15.6 months irrespective of tumor histotype whereas higher values are observed in female patients (mean 18.23 months vs 14.55 months in women and men, respectively)

Statistical analysis and data mining

We then moved to analyze the records through partition analysis to explore combination of factors that impact essentially on clinical outcome to identify and select and the most relevant predictive and prognostic variables. Differences emerged by subdividing the cohort based on patient gender. We thus focused on the most relevant outcome parameter, namely overall. We expected that the high number of early stage diseases in the population in study would correlate with a relatively better prognosis if compared to advanced ones, but, quite surprisingly, no statistically significant association could be identified between OS and TNM stage at diagnosis (Fig.1, panel I). The most relevant variable associated to OS in women was determined by access to second line treatment since those patients who did not underwent to it displayed a significantly lower OS (12.5 months *vs* 22.4 months). Among patients who received second line therapy, the subsequent split underlined that exposure to cigarette smoke (past and /or current) significantly affected mortality (average OS 18.7 months). Although, performance status (PS) should be a limitation in defining therapeutic strategies, these data suggested that at least in in never smoker female patients, comprehensive chemotherapeutic regimens can assure better outcomes (mean OS 25.6 months). Within respect to male patients, it should be noted that no significant splits could be found when patients were stratified by age. When removing this variable from the analysis, chemotherapy schedule significantly impacted on OS and treatment with platinum and pemetrexed was associated to OS rates (15.4 months) higher than platinum alone (11.4 months). Coherently, concomitant advanced disease stage was associated to worse prognosis (mean OS 5 months). Again, although PS and comorbidities might drive decision on treatment schedules, these findings confirmed that doublets should be the preferable conventional chemotherapeutic regimen. Results are available in Fig1, panel II. It should be noted that these findings impacted on long term overall outcome and no significant differences can be found by evaluating chemotherapy regimen and progression free survival in both men and female patients (Fig.1, panel III). Since no clear data are available in literature on the most beneficial conventional chemotherapy agent [20,21], we proceeded to analyze data regarding II line treatments. Specifically, we compared the efficacy of gemcitabine (30 patients) *vs* vinorelbine (19 patients). We excluded from the analysis the three patients who underwent first line chemotherapy re-challenge. Within the limit of the cohort analyzed, vinorelbine emerged as the most advantageous choice but only in female patients whereas in male subgroup the Student’t test comparing the pair did not reach a statistical significance (Fig1, panel IV).

Discussion

Malignant pleural mesothelioma is manmade cancer problem with increasing death rates at least in those areas at higher asbestos exposure, as in Northern Italy. In the present study we evaluated the data from a relevant cohort of MPM that entered the PDTA dedicated to MPM in our Institution with the ultimate goal to detect and identify predictive and prognostic variables for routine management of the disease. Preliminary findings of this work allow us to conclude the following issues. The first is that despite the male predominant occupational exposure to asbestos and the subsequent increased M:F ratio, no significant differences emerge between men and women within respect to the median age at diagnosis. This result suggests that susceptibility to asbestos fibers is independent from gender and

confirms the absence of a dose limiting cancerogenicity since the outcome is similar in case of higher (work) and lower (environmental/indirect) rates of exposure. Another relevant point regards the stage of disease at diagnosis, which was, for the vast majority of cases, lower than TNM III. Quite unexpectedly, no significant correlations emerge between disease stage and OS. Although several limitations affect the cohort analyzed, this result confirm that the TNM staging system is probably not adequate to manage MPM alone. Coherently, our data suggest that differing amounts of pleural effusion did not significantly correlate with the disease state. One would expect that a more advanced disease would have more pleural effusion, but this did not seem to be the case, and to a small, likely insignificant extent, the opposite seemed true. Moreover, although expected, it was interesting to find that there was a correlation between patients with a bilateral disease and patients with involvement of the mediastinum and diaphragm. This indicates that a sign, such as bilateral thickening of the parietal pleura on chest x-ray warrants further and thorough investigation.

Within the limit of the MPM population evaluated, and the exclusion from the analysis of patients treated with immunotherapy within clinical trials, patient gender seemed to impact on patient outcome and OS since females displayed better average OS, mainly when fully treated and in absence of exposure to cigarette smoke. As opposite the worse prognosis was observed in male patients who underwent mono-chemotherapy and displayed advanced disease at diagnosis. No significant impact on OS was associated to surgery whereas no conclusions could be drawn within respect to radiotherapy due to the small number of patients treated.

Conclusion

In conclusion, the preliminary results of this study suggest that, at least in routine settings and in case of acceptable PS and limited disease stage, an extensive chemotherapeutic program should be chosen to assure better outcomes. Moreover, our data, showed a slight advantage of vinorelbine *vs* gemcitabine as second line standard chemotherapy, at least in female patients. In this perspective a multidisciplinary management of a MPM is, should be of help to identify those patients who can really benefit from a more aggressive pharmacological approach. Overall, these results point out on one hand, the high complexity of the disease and the substantial inadequacy of conventional diagnostic and therapeutic approaches but on the other contribute to clarify the bottom line from which start to design more personalized therapeutic strategies.

Abbreviations

MPM: malignant pleural mesothelioma

PDTA: Percorso Diagnostico Terapeutico e Assistenziale- Territorial Diagnostic, Therapeutic and Assistance Planning

AIOM: Associazione Italiana di Oncologia Medica

ReNaM: Registro Nazionale Mesoteliomi

CT: computed tomography

CNB: core needle biopsy

P/D: pleurectomy/decortication

EPP: extrapleura pneumonectomy

VATS: video-assisted thorascopic surgery

Declarations

Ethics approval and consent to participate. This article does not contain any studies with human participants or animals performed by any of the authors. The study entered a main project that was approved by local Ethical Commission and each enrolled patient gave written informed consent before enrolment (Comitato di Bioetica, Fondazione IRCCS Policlinico San Matteo, approval numbers: protocol #20090002344; procedure # 20090019080; date of approval: June 3rd, 2009)

Consent for publication No specific informed consent needed. Informed consent for data management of each patients was collected routinely at hospital admission according to Institutional procedures.

Availability of data and material Exhaustive excel database is available from the corresponding author on reasonable request.

Conflict of interest: authors have nothing to disclose

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Author contribution: **DMA, CV, CB, ARF, GMS:** Conceptualization, Methodology; **ST, LS,FA; EP, PR, CP, DE:** case selection and clinical evaluation, **DMA, CV, CB, ARF, GMS**: Data curation, Writing- Original draft preparation. All authors have read and approved the manuscript

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Tables

Table 1

Features	Patients
Gender	
Males	62
Females	26
Asbestos exposure	
Work	26
Environmental	30
None	30
Smoking habit	
Never	36
Active smokers	15
Past smokers	37
Radiologic findings	
Pleural effusion	84
Bilateral alterations	34
Mediastinal involvment	34
Diaphragm involvement	45
Diagnostic approach	
Medical thoracoscopy	50
VATS	19
CT-guided biopsy	19
Histology	
Epitheliod	66
Sarcomatoid	6
Biphasic	7
NOS	9
Disease stage (TNM)	
I	37

Features	Patients
II	30
IIIA	5
IIIB	9
IV	7
Therapy	
Surgery	
P/D	46
Palliative surgery	6
Chemotherapy	
I line	
Platinum-pemetrexed	67
Monochemotherapy	18
II line	52
Gemcitabine	30
Vinorelbine	19
Re-challenge	3
Radiotherapy	
Debulking	3
Palliative	4
Outcome	**Months**
PFS	9.8
OS	15.6

Figures

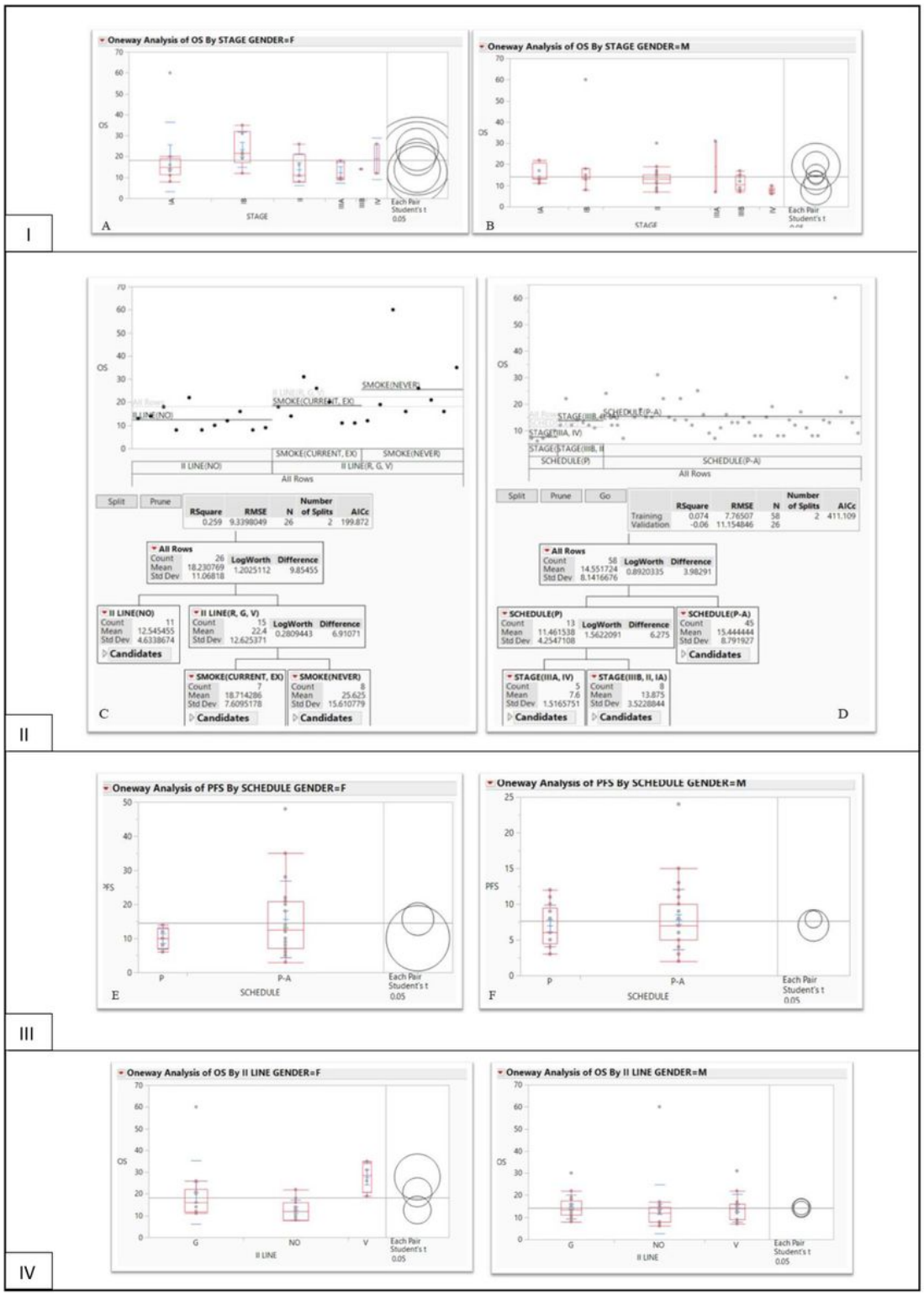

Figure 1

Statistical and partitioning analysis of MPM patient data. Panel I. Comparison of overall surviuval and TMN. Distribution of OS showed no statistically significant difference if compared to TNM disease stage, with the exception of a very slight difference related to stage IB MPM in females (A) vs males (B). Positive values show pairs of means that are significantly different. Standard deviation error bars are shown as well. Panel II. Partition analysis for overall survival of whole data. Results are represented in

female (C) and male (D) subgroups, respectively. Count: number of training observation; G2: Gini index. Lower values indicate better fit. Panel III. Comparison of progression free survival and chemotherapy schedule. Distribution of PFS showed no statistically significant difference if compared to first line chemotherapy both in females (E) vs males (F). Positive values show pairs of means that are significantly different. Standard deviation error bars are shown as well. Panel IV. Comparison of overall survival and second line chemotherapy schedule. Distribution of OS showed moderate significant difference in female patients treated with vinorelbine vs those treated with gemcitabine (G); no statistically significant differences can be shown in males (H). Positive values show pairs of means that are significantly different. Standard deviation error bars are shown as well. OS: overall survival, PFS: progression free survival, R: first line re-challenge chemotherapy, V: vinorelbine, G: gemcitabine, P: platinum. P-A: platinum-pe,metrexed, NO: second line chemotherapy not performed.

Supplementary Files

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- SFig1.jpg