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 generally have a 20-40-year latency with no or few symptoms. Such has been the case in the Piedmont and Lombardy regions of Italy where industrial production of materials laden with asbestos, mainly cements, has created a large number of patients. The fibers from this production did not only pose a substantial risk to the workers breathing the fibers, but also to the relatives and the surrounding community. Since 1992, the use of asbestos has been illegal in Italy, but such a long latency means that our center in the university town of Pavia, which is quite close to two former asbestos factories, is currently receiving a large number of patients.

Methods. Since 2017 in Pavia, a multidisciplinary team has been collecting data on over 100 patients with MPM, including presentation, pathology type and the diagnostic method used. In addition, imaging data has also been analyzed in 49 patients who underwent CT with contrast prior to treatment. In this study, we bring together the abundant epidemiologic, histologic, radiologic, and other patient data to compare it with similar studies and draw correlations with predictive and prognostic significance. The basic descriptive statistical analysis was conducted through the Excel “Data Analysis” addon package.

Results. Overall, the median survival (OS) was of 13.7 months. It was statistically influenced by the detection of pleural effusion at baseline ($p<0.0001$) and by histology (survival was higher in epidermoid forms ($p<0.0001$), irrespective of TNM disease stage.

Conclusions. Quite unexpectedly, no statistically significant association could be demonstrated between OS and TNM disease stage at diagnosis. This result confirms that the TNM staging system is probably not adequate to manage MPM alone. Multidisciplinary approach to MPM has allowed us to create robust databases that will help guide radiomic projects, treatment research and thus improved patient management

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 [,,]. Malignant mesothelioma (MM) was first linked to exposure to the industrial fiber, asbestos in 1935 [,]. It is well documented that at least 80% of mesothelioma cases are caused by exposure to asbestos [4,]. The versatility of this material made it extremely popular in the 1970s and 80 s for the production of cements, tiles, yarn, toys, jewelry, pipelining and more [5,] In addition, its temperature-resistant properties made it particularly appealing for

insulation and heating trades []. Unfortunately, these resistant properties have rendered the disposal of the carcinogenic asbestos-laden materials nearly impossible (fittingly, the word asbestos comes from the Greek word for “inextinguishable”), posing formidable epidemiological challenges [8]. In developed countries like Italy, roughly 1.15 per 100,000 cases are diagnosed annually. The Piedmont and Lombardy regions of Italy are most affected, due to industrial production, particularly by two main companies: Eternit, located in a small town called Casale Monferrato in Piedmont and Fibronit, located in the town of Broni, in Lombardy []. In fact, every year for the last decade, more than 300 new cases have been diagnosed in Lombardy alone. Laws against asbestos have led to the closure of Fibronit plant in Broni, in the year 2000 but when they were active, they employed more than 3,400 workers in a large factory located in a populous area of town where they primarily made asbestos cement. Our center in the University town of Pavia, just 55 km from Broni and 105 km from Casale Monferrato is thus conveniently located to receive, diagnose and manage numerous new patients with suspected or confirmed cases of mesothelioma. In 2018, different branches of the public Italian health system published a report on the incidence and mortality of MM in Pavia between 1980 and 2015. They found that during this time period, 778 inhabitants died of pleural and peritoneal MM (6.08 cases / 100,000 inhabitants). Of these, 447 were men (8.48 cases / 100,000 male inhabitants) and 331 were women (4.38 cases / 100,000 female inhabitants) []. Since 2017, our institution has been dedicated to organizing an integrated path to malignant pleural mesothelioma (MPM) diagnose, coupled with optimal patient treatment. Pavia’s location and size has provided a unique opportunity to analyze the clinical data of the patients with a multidisciplinary approach. More specifically, we aimed to match the clinical and pathological disease features to the imaging ones 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 by using easily accessible data at diagnosis. Ultimately, this work will provide preliminary findings to develop future radiomics assays and analysis 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 and shared in 2014 within the Provincial Oncology Intercompany Department (DIPO) of Pavia. It 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 (Fig. 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 []. The structures then 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. Thus, they can guarantee a high standard of diagnosis and treatment for such a complex disease as MPM by maintaining a widespread link with the territorial management. This benefits the patient by providing care and follow-up close to home.

Patients identification and selection

Since 2017 we have been retrospectively collecting data on all the patients with mesothelioma managed through the PDTA. The number of patients was then narrowed by several criteria in order to be included in the study (Fig. 1). The information collected includes the tumor histotype, diagnostic method, treatment received and radiologic information. Data were collected from the anamnestic records, outpatient reports and discharge letters of the interdivisional outpatient clinic of the asbestos – related diseases level at the IRCCS Policlinico San Matteo. 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 Spreadsheets. The basic statistical analysis was conducted through the Excel “Data Analysis” addon package. Advanced statistical analysis was made using a dedicated software (Stata 16, StataCorp, Texas, USA). A hypothesis test was performed to validate the findings and evaluate if deviation of the observed frequencies was statistically significant. This was done through a chi-squared test.

Results

Epidemiology and demographics

This study followed 49 patients for 4 years (2017 to today) at the Pavia University Hospital. Of these 49 patients, 19 (39%) were females and 30 (61%) were males. The ratio of males to females was 1.6:1. Our 49 patients received their diagnosis of MPM between the ages of 47 and 85. More patients were 71 years old at diagnosis than any other age. The median age was also 71 years and the average age was 69 years (standard deviation: 9.4). The more common range of age at diagnosis for men was the 70-74-year-old whereas in women, it was equally as common as the older age ranges: 75–79 and 80–85. No women were diagnosed before the age of 58, indicating that women in our cohort were diagnosed later than men. Further evidence for this is that most of the diagnosis in women occurred after age 71, while the opposite is true for the men (Fig. 2, panel A). The vast majority (46/49 or 94%) of patients reside in the province of Pavia. Just 3 (6%) reside outside Pavia. Notably, 6 of the 49 patients reside in the actual town of Broni (12.2%)

Out of the 49 total patients, 20 (41%) claimed to have never smoked, while 4 (8%) were active smokers and 20 (41%) were ex-smokers. Thus, the sum of active and past smokers was 49% of our total cohort (Fig. 2, panel B). A total of 5 (10%) of our patients did not provide any smoking history. The majority of the patients observed had a significant exposure to asbestos as part of their employment/family/social

history. Just one of the 49 patients followed (2%) had a certain professional exposure; as in, the patient was an employee of Fibronit or Eternit plants. Instead, 7 (14%) of the observed patients had a probable professional exposure because of their work as a builder, mechanic, or in other fields known to be high-risk for exposure to asbestos particles. One patient (2%) was the family member of an asbestos worker and thus at risk due to interaction with the worker and the belongings (clothing, bags, etc) of that worker. The patients living in towns that had large asbestos factories, and thus high levels of asbestos in the air, made up 37% (18 patients) of our total cohort. No relevant exposure history was reported for 22 (45%) of the patients in our cohort (Fig. 2, panel C).

Diagnostic algorithm

The method by which histological samples were obtained to analyze the 49 patients. Three main approaches were utilized: thoracoscopic, percutaneous and surgical, of which thoracoscopic was the most common (28 patients or 57%). Percutaneous biopsies were used on 11 patients (23%) and surgical resections were used on 10 patients (20%). Biopsy results showed that most of our patients received a diagnosis of an epithelioid-type MPM (38 patients or 78%) (Fig. 3, panel A). The diagnosis of a sarcomatoid lesion was found in just one patient (2%) and the biphasic type was found in 5 patients (9%). Non-specific histotypes were reported for 5 patients (10%) (Fig. 18). Thus only 10 (20%) were of the non-epithelioid type (Fig. 3, panel B).

Thoracentesis/drainage

Of all 49 patients followed, we wanted to identify key radiological features in patients who had not received any treatment, and thus their lesions had not been altered yet. 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 8 patients (16%) had evidence of a previous evacuation of pleural fluid via drain or thoracentesis on radiologic reports or CT images.

Radiological and clinical staging

Of the 49 patients we observed, 18 were stage IA, which means that their tumor involvement was limited to the ipsilateral parietal pleura and that no lymph node nor metastatic sites were found. 5 patients were stage IB, indicating that their tumor was somewhat invasive, with invasion of the visceral pleura, diaphragmatic muscle, pericardial fat, or other nearby structures. 14 patients were stage II, indicating some proximal lymph node involvement. 5 patients were classified as IIIA, which means more distant lymph node involvement and more invasive disease. Finally, 3 patients were classified as stage IV, indicating that distant metastasis was found (Fig. 3, panel C and D).

Pleural effusion

Most patients presented with some level of pleural effusion, even if minimal. Of the 49 patients we observed, just 2 (4%) of them had a bilateral pleural effusion and 2 (4%) of them had no pleural effusion at all, the other 45 (92%) had a unilateral pleural effusion (Fig. 4, panel A and B).

Bilateral disease

In our study, 19 (39%) patients showed bilateral alterations disease before chemotherapy treatment. Bilateral involvement meant pleural effusion, pleural plaques or contralateral lymph node or chest wall involvement visible on CT or mentioned in the documentation of the CT analysis by the radiologist. Interestingly, most patients with bilateral disease also have disease progression to the mediastinum and diaphragm.

Mediastinum involvement

Out of the 49 patients in our cohort, 36 (73%) showed mediastinal involvement before treatment. Mediastinal involvement meant that the disease invaded the pericardial sack, caused pericardial effusion, invaded mediastinal structures or caused enlarged, pathologic-looking mediastinal lymph nodes. This information was obtained from CT analysis and patient documentation. core

Diaphragm involvement

Roughly half of our patients (25 patients or 51%) had some sort of involvement of the diaphragm before receiving chemotherapeutic treatment. This means that the diaphragm contained pathological calcifications, pleural plaques or gross invasion/distortion by the tumor.

Treatments

Surgery

More than half of the 49 patients in our study received some form of surgery as a treatment for MPM (30 patients or 61%). Of these 30 patients, 17 (35%) received pleurectomy/decortication surgery. Another 13 (26%) received various other surgeries. Overall, 19 patients (39%) were not treated surgically in any way (Fig. 5, panel A).

Chemotherapy

Out of the 49 patients, we are certain 33 (67%) underwent chemotherapy; we are uncertain about 16 (33%) because patients were lost to follow-up or their records contained insufficient information. Just one (2%) patient did not receive treatment. Of the 34 who underwent treatment, 3 (6%) of them received neoadjuvant treatment, another 9 (18%) underwent adjuvant treatment and 20 (41%) received the first line therapy: pemetrexed and cisplatin (Fig. 5, panel B)

Radiotherapy

Out of the 49 patients we followed, 47 (96%) did not receive radiotherapy. Just 2 patients (4%) received radiotherapy, of which one patient (2%) received as a debulking procedure while another patient (2%),

received radiotherapy for palliation

Outcome

Disease-Free Months (DFMs)

The number of months that a patient was “disease-free” was reported for 22 patients (27 had no information or did not have any disease-free months). Of these, the range of disease-free months was between 3 and 45 months. The median amount of time was 8.5 months, the average amount of time was 12.8 months and the standard deviation from the mean was 11.0 months (Fig. 5, panel C).

Overall survival

The overall median survival (OS) was 13.7 months. Within the limit of this cohort, OS is statistically influenced by the detection of pleural effusion at baseline ($p < 0.0001$) and by histology. Specifically, survival is higher in epidermoid forms ($p < 0.0001$). Quite unexpectedly, no clear association can be identified between OS and TNM disease stage.

Discussion

Demography

The total number of patients referred to our Territorial Diagnostic, Therapeutic and Assistance Planning was 88. From there, the total number of patients that did not fit our inclusion criteria was 39. In our raw data, we looked at more than 30 parameters in 49 patients between 2017 and 2020. The male-to-female ratio we report is roughly 1.6, which is significantly lower than the national one as reported in the 6th edition of the ReNaM report (M:F ratio of 2.5) [7]. This male predominance was expected as exposure to asbestos often occurred in and around industrial factories where most employees were men. Our ratio may have been lower though because our observational period was later than theirs and women increased longevity in comparison to men. The average age at diagnosis supports this concept: it was of 69 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. No cases of diagnosis under the age of 47 were found in our study, confirming what is contained in the ReNaM report "Up to 45 years the disease is very rare (only 2% of the total cases recorded)". Interestingly, the older patients were mostly women. Indeed, the youngest woman in our study was diagnosed at 58 (in comparison to 47 for men), and most of the diagnoses in women were after the age of 71. The advanced age makes sense due to the significant latency associated with the disease, but the even older age of women may have to do with the decreased concentration of exposure and increased longevity. Indeed, all 9 of the patients who reported workplace exposure (either directly from the factory or indirectly through various blue-collar work), were men. If the higher exposure led to an earlier disease, and the lower, environmental exposure led to a longer latency, then this would help explain why women seemed to be diagnosed later than men.

Studies have shown that cigarette smoking is associated with an increased risk of developing all types of lung cancer. Though smoking is not strictly causative of MPM, it shows some important synergistic activity with asbestos as both have a common pathogenesis which includes provoking inflammation and directly damaging DNA []. Even with equal asbestos exposure, smoking has been correlated with increased risk of developing MPM [5]. In the cohort analyzed, almost half of the patients were smokers or ex-smokers; this data is likely underestimated since about 10% of the patients observed had an uncertain smoking history.

The vast majority of patients were residents in the province of Pavia. However, the fact that we received patients from Italian provinces distant from Pavia shows how the organization of the interdisciplinary diagnostic-therapeutic pathway form MPM defined in the PDTA makes our institution attractive for a non-local population as well. A considerable rate of the initial, 88-patient cohort (14%) was found to be a resident of Broni (within a 10 km radius). This is explained by the fact that the vast majority of the Fibronit workers lived in the municipality of Broni and the neighboring towns. The significant environmental pollution and massive exposure during the company's peak activity period (1970s and 1980s) created this high incidence, as previously mentioned. Interestingly, our cohort showed a lower occupational exposure with just one patient having a certain exposure, as he worked for Fibronit. On the other hand, 7 patients had a probable professional exposure, as they were builders, mechanics, or working in some other field that deals with materials like cement and insulation that is laden with asbestos. This means our (certain/probable/possible) occupational exposure rate was around just 16%. Environmental exposure cases were significantly higher (37%) as the pollution from the factories had an effect on members of the town. There are a few reasons why our study has different occupational exposures to previous studies. The first issue may be because the cohort in the study includes diagnosis of MPM made relatively recently (i.e., in the last 5 years) compared to the observation period of the data contained in the ReNaM (1993–2015). It is possible that a large proportion of patients had occupational exposure were diagnosed in the years prior to the baseline time interval of the cohort in our study. Moreover, the area of Broni corresponds to high environmental pollution and we had a significant number of patients from the city of Broni, but also from surrounding cities.

Diagnostic And Therapeutic Approaches

In the study cohort, the majority of patients (57%) was subjected to medical thoracoscopy, while 20% were diagnosed by surgical pleural biopsy (both in VATS and thoracotomy). In our cohort, 23% of patients received a transthoracic CT-guided core-needle biopsy (CNB), while none received diagnosis through cytology on pleural fluid. The fact that 100% of the patients in the cohort have undergone diagnostic procedures approved by various guidelines enhances the quality and reliability of the information provided. In this study, the vast majority of diagnoses of MPM showed an epithelioid histotype (78% of cases); this result is in-line with the AIOM 2018 guidelines that showed a prevalence of the epithelioid histotype in 75–80% of cases, but is significantly higher than the percentage of epithelioid cases reported in the ReNaM (55% of cases). As expected, the epithelioid histotype was associated with an increased

overall survival ($p < 0.0001$). Sarcomatoid and biphasic histotypes were found in 2% and 9% of cases respectively, being less represented than the data reported in ReNaM, where the biphasic histotype accounts for 10.5% of cases. 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%. No cases of desmoid mesothelioma were found in our cohort, confirming that this histotype is the least expressed (< 2% of cases). Finally, in 10% of our cases 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).

Before a definite diagnosis was made and before a treatment regimen was established, many of our patients had a significant pleural effusion; indeed, dyspnea due to pleural effusion is a common presenting symptom. As a result, prior thoracentesis or past/current drain placement was available on roughly 16% of our radiologic reports. This number could be higher, but we believe it's still small enough that it did not distort our analysis of pleural effusion levels. In addition, patients with significant levels of pleural effusion, who merit an early drainage, are known to often require repeated drainage. In the study cohort, 76% of patients have an early stage of disease (IA-B, II) developed on clinical data (TC and PET) [] according to the TNM-8 Ed system. As a result, the majority of patients are susceptible to surgical therapy or a multimodal approach. The reliability of this data is quite robust as all patients had undergone contrast tomography with contrast media. We expected that this high number of early disease stages would correlate with an even poorer prognosis, but no statistically significant association can was identified between OS and TNM disease stage. The reason for this is not known but it's possible that limited information on overall survival and disease-free progression could have skewed these results. Furthermore, less than a quarter of the patients had an advanced staging, which may not have been enough to find a significant association.

Pleural Effusion

As previously mentioned, a very small amount of pleural fluid (roughly 10 mL) physiological, however a pathological pleural effusion is a common occurrence in mesothelioma and is a common cause of dyspnea. Support of the high prevalence is that only 4% of our patients had no pleural effusion. Our 96% pleural effusion prevalence is significantly higher than the 79% found by Dogan and colleagues in their CT analysis of 212 patients with MPM in Turkey []. The different patient population and different time-period analyzed with different environmental and epidemiological factors could account for this difference. Pleural effusion can cause the lung to poorly ventilate and can be a cause of death, especially when bilateral. Thus, patients with a bilateral pleural effusion are at a bigger risk of complications and are associated with a higher progression of disease. Indeed, just 2 of our patients had evidence of bilateral pleural effusion on pre-treatment CT scans. This correlates with the Turkish study that found that 2.3% of their patients had bilateral pleural effusion [8]. Measurements of pleural effusions on CT scan can estimate the amount of fluid the patient has in the lung(s). This estimation can be done with table 4 and is important to take into consideration when thoracentesis or drain placement is being

considered. The posterior costo-phrenic recess at the level of the apex of the emi-diaphragm was determined to be the best for estimating the fluid amount as the increased dimensions at the lower thorax mean a larger amount of fluid can be collected there. This measurement was then used when we compared the amount of pleural effusion to the TNM staging. Here we found that no obvious differences in pleural fluid level existed between TNM stages. Although expected, it was interesting to find that there appeared to be 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.

Therapy

Surgery is an important treatment option for patients with MPM. This is demonstrated in our cohort by the fact that more than half of our patients received some type of surgery. This correlates with the fact that most of our patients had low-stage tumors (TNM stage I or II), which is necessary to be eligible for surgery. More than half of the patients who underwent surgery (35% of total patients) underwent pleurectomy and decortication (P/D). As mentioned, this procedure is favored to extrapleural pneumonectomy (EPP,) due to its safety in an elderly population and better outcomes. Of the 17 patients who underwent P/D, we know that 11 of them had several months of survival without disease progression. From these 11 patients, we can say that on average, patients who underwent P/D surgery had 15 months free of disease. This is slightly higher than the average of 12.5 months free of disease and within the standard deviation (10 months). There is not enough data on the surgical procedures received to draw any statistically significant analysis about whether P/D showed superior outcomes. video-assisted thorascopic surgery was not discussed in the results because it was only used in 4 patients from our cohort and its use in comparison to more conservative measures is debatable, as mentioned in the introduction.

Chemotherapy was the most common therapeutic option for our patients. As mentioned, 67% of our patients received a chemotherapy regimen of pemetrexed and cisplatin, which is first-line therapy for mesothelioma. The timing of the treatment was not the same for all patients though: 6% of the 67% received neoadjuvant treatment and 18% underwent adjuvant treatment. Neoadjuvant treatment means that chemotherapy was given before another treatment, such as surgery (either open, or VATS) or radiotherapy, with the aim of shrinking the tumor as much as possible. This was the case for 3 of our patients. Of these three patients, one patient received surgery only while another patient received both surgery and radiotherapy. The third patient did not go on to receive any further treatment, likely because of poor tolerance to the treatment, worsening condition, or personal wishes which made surgery or radiotherapy contraindicated. Adjuvant therapy means the chemotherapy was started after another therapy, with the aim of destroying all remaining tumor cells, for example. Indeed, in every case in which adjuvant therapy was used (9/9), the patient had previously received a non- VATS pleurectomy/decortication. Of these 9 patients, we know that 7 of them had several months of disease-free progression. The average number of months free of disease in these patients was nearly a year

(11.6 months), which is close to the total average for all patients with months free of disease (12.5 months) and certainly within the standard deviation (10 months). Side effects of the chemotherapy was not monitored, but it's known that providing B12 and folate can help limit toxicity [], and thus this combination may have contributed to the nearly one year free of disease in 7 of our patients.

The main role of radiotherapy was to reduce the size of the tumor so other treatment options can be more effective or to relieve symptoms.

Conclusions

This study showed that The Pavia Experience: Territorial Diagnostic, Therapeutic and Assistance Planning has become an established reference center for mesothelioma within its first few years. Our center has had the goal of providing multidisciplinary management for MPM and acting as a reference for the territory through partnership with 1st level outpatient clinics. Being located in an area where, unfortunately there has been a significant history of asbestos pollution has allowed us to create robust databases that will help guide radiomic projects, treatment research and thus improved patient management. We therefore successfully collected data from a relatively large cohort of patients with MPM and compared its epidemiology and clinical aspects with data collected nationally by ReNaM. Preliminary findings of the present study allow us to conclude the following issues. I) Our study shows that those living longest with the disease are females, and thus the ratio of males to females may start to become more equal, despite the male predominant work environment characteristic of occupational asbestos exposure. This conclusion is coherent with the data showing that women enjoyed the largest number of disease-free months. This data was correlative and thus not statistically analyzed. II) 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. III) 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. No statistical analysis was done on this data and thus this is correlative only. IV) Adjuvant chemotherapy after pleurectomy/decortication surgery was associated with nearly a year without disease progression. Certainly, this patient group was fitter than the other patient group if they were able to undergo both surgery and chemotherapy, but this result seems to agree with other studies, though not statistically analyzed. V) Detection of pleural effusion, even in small amount, is associated with a worse prognosis ($p < 0.0001$). This result was expected as pleural effusion leads to dyspnea and can be a significant cause of death. VI). The epithelioid histotype is associated with increased overall survival ($p < 0.0001$). This was expected, based on previous research mentioned above. VII) Quite unexpectedly, no statistically significant association could be demonstrated between OS and TNM disease stage at diagnosis. Although several limitations affect the cohort analyzed, this result confirm that the TNM staging system is probably not adequate to manage MPM alone.

Further developments include an imaging-related biomarker analysis that will look to make important predictions on patient parameters without invasive measures like biopsies or VATS, treatment studies that will look to evaluate the changes in the radiologic profiles analyzed here, and the continuation of our database. Our study hopes to show how a multidisciplinary approach is vital to the correct analysis of patients with severe chronic diseases, especially related to environmental pollution. Though new diagnostic and treatment approaches provide hope to patients like the ones we followed, the best treatment is primary prevention; therefore, industries like nanotube industry should use great caution when using materials that could pose as potential risks to workers and consumers.

Abbreviations

MPM
malignant pleural mesothelioma
PDTA
Percorso Diagnostico Terapeutico e Assistenziale- Territorial Diagnostic, Therapeutic and Assistance Planning
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.** The procedure was approved by the local Ethical Commission and each enrolled patient gave written informed consent before enrolment (Comitato di Bioetica, Fondazione IRCCS Policlinico San Matteo
- **Consent for publication** Informed consent 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.
- **Competing interests:** nothing to declare
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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.
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Figures

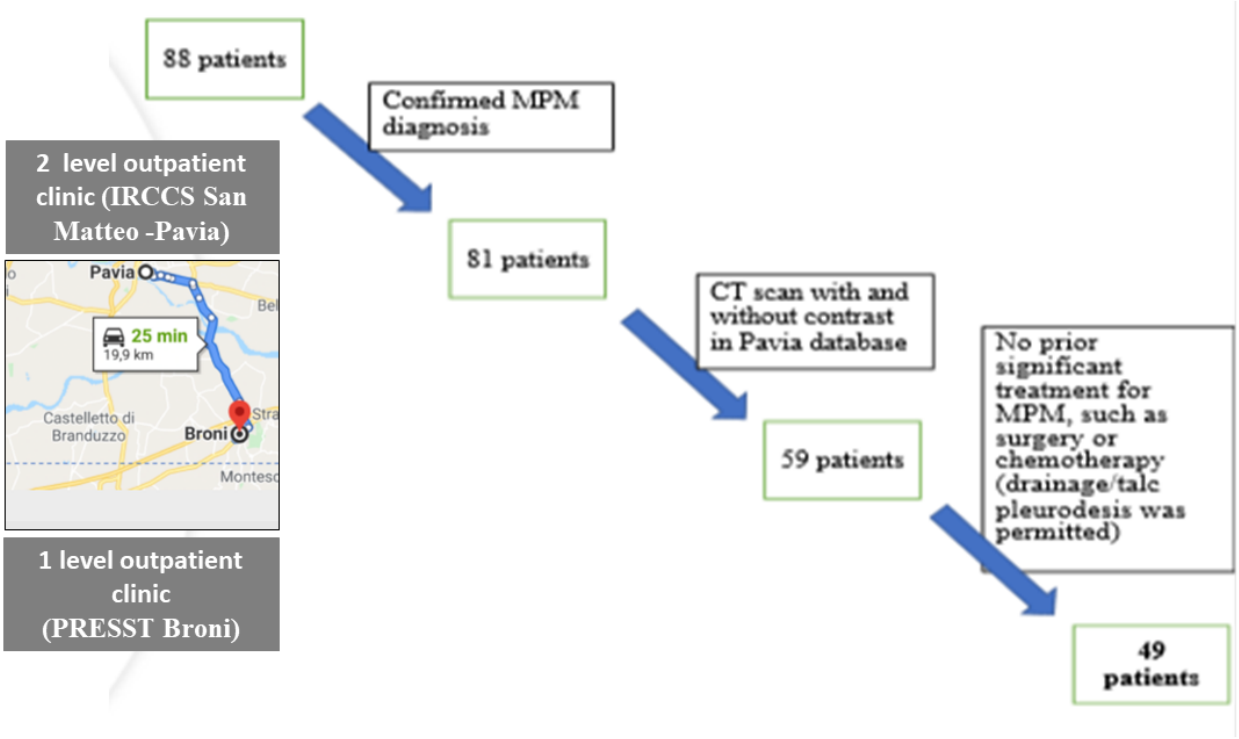


Figure 1

Flow-chart of patient exclusion. In detail the level one outpatient hospital in Broni and the level 2 multidisciplinary outpatient facility at IRCCS San Matteo Hospital.

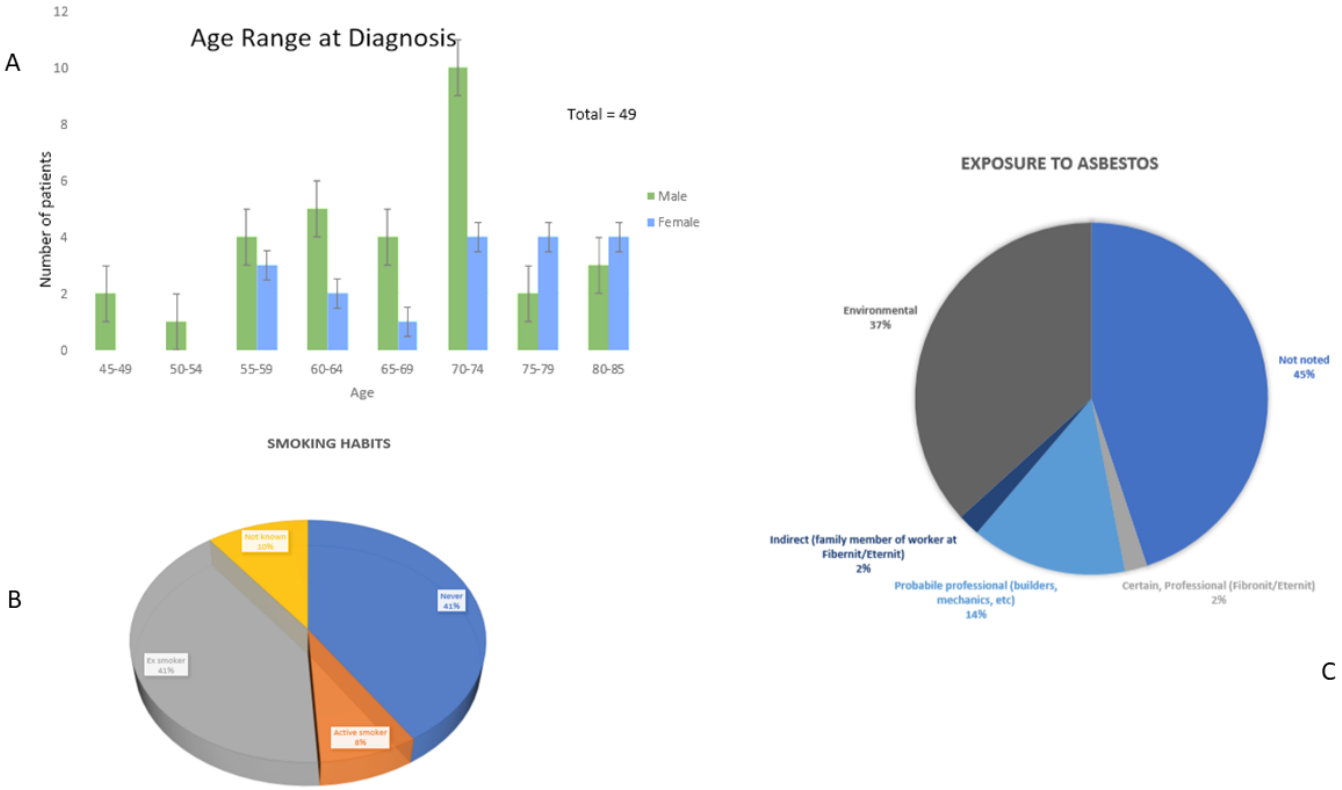
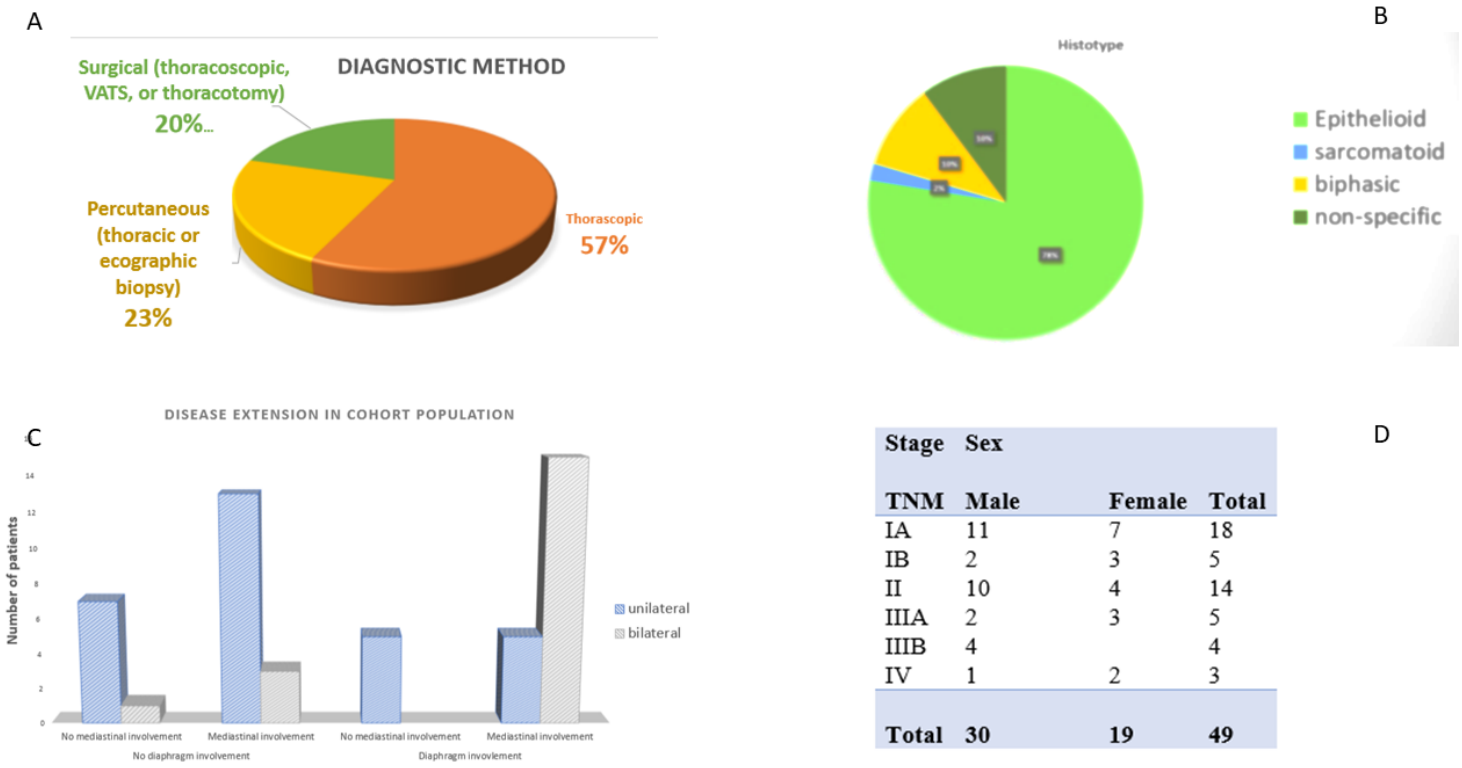


Figure 2

Epidemiology and demographics of the population evaluated. Panel A. Bar graph of the patients in this study when they received the diagnosis of MPM. Error bars were automatically generated by Excel's standard error bar function. Panel B. Graphical representation of the smoking habits of the 49 patients followed in our study. As shown, the minority (49%) had a known past or present smoking history. Panel C. Types of exposure to asbestos and corresponding percent of patients with a history of each type of exposure



Stage	Sex		
TNM	Male	Female	Total
IA	11	7	18
IB	2	3	5
II	10	4	14
IIIA	2	3	5
IIIB	4		4
IV	1	2	3
Total	**30**	**19**	**49**

Figure 3

Desease diagnosis and staging results. Panel A. Graphical representation of the methods used to obtain biopsies, and thus the histological diagnosis for the 49 cases of MPM reported in this study. Panel B. Graphical representation of the histotypes present in 49 patients. Panel C. Disease extension to the contralateral lung (bilateral), mediastinum and diaphragm. Most patients with bilateral disease involvement also had mediastinal and diaphragmatic involvement. Panel D. TNM staging based on clinical and radiological data and the number of patients corresponding to each stage, stratified by sex

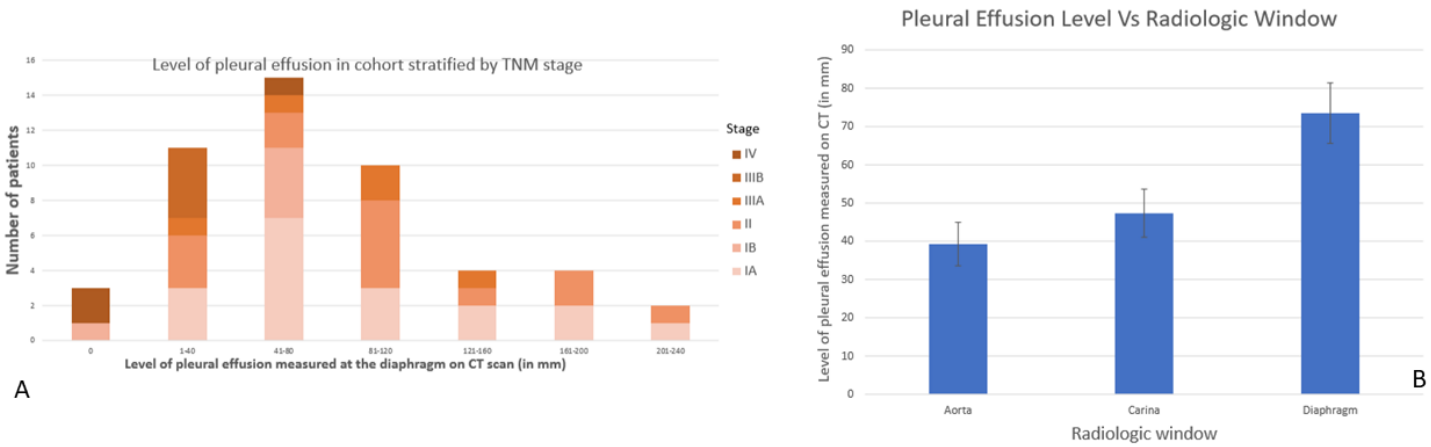


Figure 4

Imaging findings. Panel A. Pleural effusion levels in patients with different TNM stages. Massive amounts of pleural effusion seem to be associated with a lower TNM stage Panel B. Bar graph representing the average levels of pleural effusion found in our patients, measured in different radiologic windows on contrast tomography

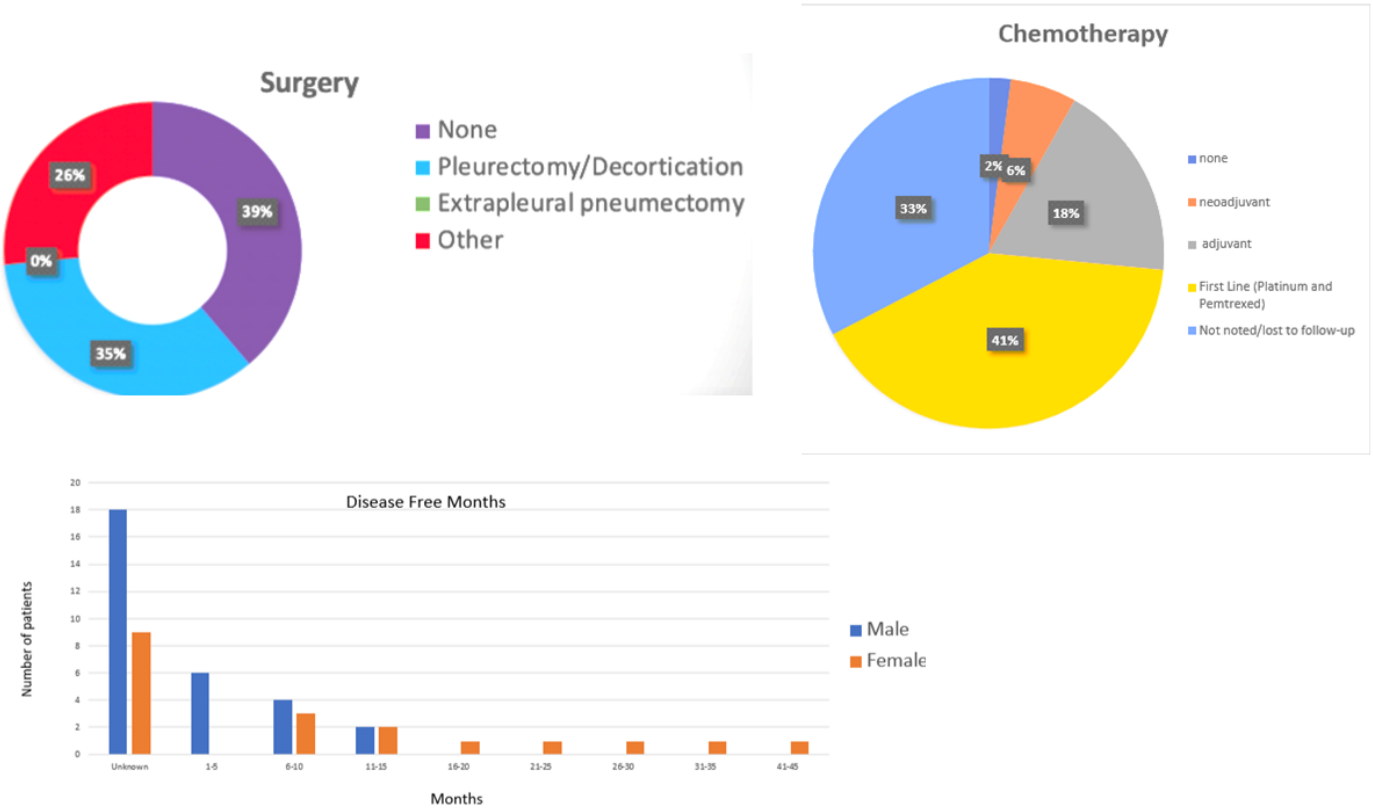


Figure 5

Therapeutic approaches and outcome of the patients evaluated. Panel A. Pie chart representing the patients who underwent surgery and the type of surgery received. Panel B. Pie-graph demonstrating the percentage of our patient population that underwent chemotherapy and the type of chemotherapy received. Panel C. Bar graph of the number of disease-free months and the number of patients that had lived without the active disease during that time span. Graph stratified by sex.