J Bras Pneumol. 2022;48(5):e20220064
https://dx.doi.org/10.36416/1806-3756/e20220064

Mesothelioma in a developing country: a retrospective analysis of the diagnostic process

Paulo Henrique Peitl Gregório[1], Ricardo Mingarini Terra[2], Leonardo Pontual Lima[2], Paulo Manuel Pêgo-Fernandes[1]

1. Instituto do Cancer do Estado de Sao Paulo, Hospital das Clinicas, Faculdade de Medicina, Universidade de São Paulo, Sao Paulo (SP) Brasil.
2. Instituto do Coracao, Hospital das Clinicas, Faculdade de Medicina, Universidade de São Paulo, Sao Paulo (SP) Brasil.

Submitted: 16 February 2022.
Accepted: 12 June 2022.

Study carried out at the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate the process of diagnosing patients with malignant pleural mesothelioma (MPM) at a tertiary care hospital. **Methods:** This was a retrospective study involving patients referred to a tertiary-care cancer center in Brazil between 2009 and 2020. The diagnostic process was divided into four steps: onset of symptoms, referral to a specialist visit, histopathological diagnosis, and beginning of treatment. The intervals between each phase and the factors for delays were evaluated. Data including clinical status, radiological examinations, staging, treatment modalities, and survival outcomes were collected. **Results:** During the study period, 66 patients (mean age = 64 years) were diagnosed with MPM and underwent treatment. Only 27 (41%) of the patients had knowledge of prior exposure to asbestos. The median number of months (IQR) between the onset of symptoms and the first specialist visit, between the specialist visit and histopathological characterization, and between definite diagnosis and beginning of treatment was, respectively, 6.5 (2.0-11.4), 1.5 (0.6-2.1), and 1.7 (1.2-3.4). The knowledge of prior asbestos exposure was associated with a shorter time to referral to a specialist (median: 214 vs. 120 days; p = 0.04). A substantial number of nondiagnostic procedures and false-negative biopsy results (the majority of which involved the use of Cope needle biopsy) were found to be decisive factors for the length of waiting time. The mean overall survival was 11.9 months. **Conclusions:** The unfamiliarity of health professionals with MPM and the patient's lack of knowledge of prior asbestos exposure were the major factors to cause a long time interval between the onset of symptoms and beginning of treatment. An overall survival shorter than 1 year is likely to have been due to the aforementioned delays.

Keywords: Mesothelioma; Mesothelioma, malignant; Pleural effusion, malignant; Pleural diseases.

INTRODUCTION

Malignant pleural mesothelioma (MPM) has a proven association with prior asbestos exposure. Despite this correlation, most countries in Latin America (LA) have yet to adopt broad restrictions on asbestos mining and processing industries.[1] For decades, Brazil was the third largest asbestos producer in the world, accounting for 15.1% of global asbestos production in 2015.[2] Nevertheless, between 1980 and 2010, only 3,718 deaths caused by asbestos exposure were reported to the Brazilian National Mortality Information System, and such deaths were reported to have been caused by some type of pleural cancer, including but not limited to mesothelioma. In contrast, 2,497 deaths caused by asbestos exposure were reported in the United States in 2013 alone, where asbestos mining has been banned since 2002.[3]

Studies of mesothelioma in LA are scarce and usually limited to case reports, case series, or brief epidemiological studies.[4,5] In addition, despite the historically critical position regarding asbestos production, Brazil was only responsible for 22 of the 6,907 articles on asbestos and mesothelioma that were published between 1988 and 2011.[4]

The lack of data hinders a more effective and targeted intervention for the general population and health professionals who still have difficulties in identifying the disease, causing the current underdiagnosis and underreporting.[1] As descriptive studies are pivotal for the development of improved health care policies and progress of research, the objective of the present study was to evaluate the process of diagnosing patients referred to a public, tertiary-care cancer center in Brazil.

METHODS

This was a retrospective study conducted at a cancer center located in the city of São Paulo, Brazil. All patients diagnosed with MPM and treated between July of 2009 and December of 2020 had their medical records reviewed. Only

Correspondence to:
Paulo Henrique Peitl Gregório. Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Avenida Dr. Enéas de Carvalho Aguiar, 44, Bloco II, Sala 9, Cerqueira César. CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5248 or 55 11 2661-5000. E-mail: paulo.gregorio@hc.fm.usp.br
Financial support: None.

patients with a histopathological diagnosis of MPM were included. Data including demographic characteristics, past medical history, diagnostic procedures, radiological examinations (including CT and 18F-FDG PET/CT), histopathological reports, disease staging, treatment modalities, and mortality were collected.

To evaluate the diagnostic process of MPM for each patient, the medical records were specifically reviewed for the following four events: onset of symptoms; first specialist visit (with a pulmonologist, a thoracic surgeon, or an oncologist); adequate histopathological characterization; and beginning of treatment, including chemotherapy, radiotherapy, or surgery—extended pleural decortication (EPD) or extended pleuropneumonectomy (EPP).

Performance status was classified using the ECOG scale.[6] Since this study involves a time interval when two different TNM editions (7th and 8th) were in use, each medical record based on the 7th edition was reviewed and reclassified in accordance with the 8th edition.

Data were assessed for normality of distribution using the Shapiro-Wilk test and described as means and standard deviations or as medians and interquartile ranges, respectively, when distribution was normal or non-normal. The association between categorical and continuous variables with non-normal distribution was analyzed using the Mann-Whitney U test. The correlation between non-normal continuous variables was tested with Spearman's correlation coefficient. The Kaplan-Meier estimator and the log-rank test were adopted for survival analysis.

All statistical analyses were conducted using the R software, version 4.1.1, and R Studio, version 3 (R studio, Boston, MA, USA). A significance level of $p < 0.05$ was adopted.

The local institutional review board approved this study (Protocol no. 02213612.8.0000.0068). Individual patient consent was waived due to the retrospective nature of the research and the fact that all data were managed anonymously.

RESULTS

Between 2009 and 2020, a total of 66 patients were treated. The medical records of all these patients were reviewed, and some of the characteristics evaluated are summarized in Table 1. The male-to-female ratio was 3.7:1.0, and the subjects had a mean age of 64.3 ± 11.3 years at diagnosis. Twenty-six patients had an ECOG score of 2 or higher. Remarkably, 30 (45%) and 11 (17%) of the subjects were smokers and former smokers, respectively. Also, less than a half of the patients (41%) had knowledge of prior exposure to asbestos.

Epithelioid mesothelioma was the main histopathological subtype, accounting for 88% of the cases, and predominated on the right side (in 56%). The mean standardized uptake value (SUV) for half of the patients who underwent 18F-FDG PET/CT was 8.60 ± 4.05.

Table 1. Characteristics of patients (N = 66) and disease at diagnosis.[a]

Characteristic	Result
Age, years	64.3 ± 11.3
Gender	
Male	52 (78)
Female	14 (22)
BMI, kg/m^2	24.3 ± 4.8
ECOG at first medical visit	
0	14 (21)
1	35 (53)
2	10 (15)
3	4 (6)
4	3 (5)
Smoking status	
Current smoker	30 (45)
Former smoker	11 (17)
Never smoker	25 (38)
Asbestos exposure	
Yes	27 (41)
No	39 (59)
Histological subtype	
Epithelioid	58 (88)
Sarcomatoid	4 (6)
Biphasic	4 (6)
TNM staging	
I	15 (22.7)
II	5 (7.6)
III	25 (37.9)
IV	21 (31.8)
PET-CT	33 (50)
PET-CT, SUV	8.60 ± 4.05
Laterality	
Right	37 (56)
Left	29 (44)

SUV: standardized uptake value. [a]Values expressed as n (%) or mean ± SD.

The number of months spent in each stage of the diagnostic process is outlined in Figure 1. After the onset of symptoms, a median of 6.5 months (2.0-11.4 months) lapsed before the patient had a specialist visit. Prior to undergoing pleural biopsy or being referred to our cancer center, the patients had undergone a median of 2 procedures (range, 0-5), majorly thoracentesis, with the sole purpose of relieving symptoms since oncologic cytology had rarely been requested. The Mann-Whitney U test was used in order to test the hypothesis that there was a correlation between knowledge of previous asbestos exposure and shorter time to referral. The median number of days to referral was 214 vs. 120 days (Mann-Whitney U test:: 231.5 vs. 419.5 days; $p = 0.04$) for the group with no knowledge of prior asbestos exposure and the group with that knowledge. The correlation between the number of

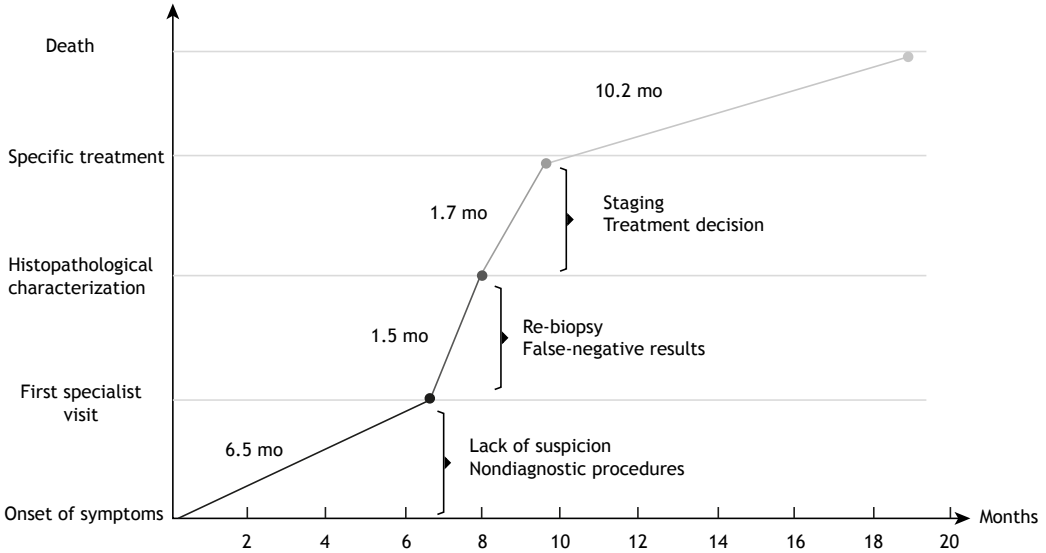

Figure 1. Timeline of the process of diagnosing patients with malignant pleural mesothelioma. mo: months.

procedures prior to a specialist visit and the number of days to referral was analyzed using the Spearman's correlation coefficient. A nonsignificant small negative relationship was found (ρ = −0.07; 95% CI: −0.39 to 0.26; p = 0.68).

The median time to adequate histopathological characterization of the neoplasm was 1.5 months (0.6-2.1). Only 27 (40.9%) of the patients had undergone pleural biopsy prior to referral, 7 (25.9%) of whom having been reported as negative for any kind of neoplastic processes. Due to inadequate histopathological examination or lack of histopathological diagnosis, 40 patients underwent pleural biopsy (surgical biopsy, in 23; Cope needle biopsy, in 14; and radiologically guided biopsy, in 3) after being referred to our cancer center. Of those, 9 had a negative biopsy result which was later diagnosed as MPM—8 who underwent Cope needle biopsy (false-negative rate of 57.1%); and 1 of those who underwent surgical biopsy (false-negative rate = 4.3%). Cytological pleural effusion analysis prior to pleural biopsy was carried out in 26 patients, 15 of whom (57.7%) had a negative result.

Disease staging and treatment decision required a median of 1.7 months (1.2-3.4) before the beginning of treatment. Only 15 patients were oncologically and/or clinically suitable for any major surgical treatment; therefore, EPP and EPD could be performed in 11 and 4 patients, respectively. In our sample, 44 patients received chemotherapy, 15 received chemotherapy and radiotherapy, and 1 was treated with immunotherapy. However, 6 patients were unable to undergo any kind of treatment and received supportive care only.

The overall survival time after diagnosis was 11.9 months (95% CI: 8.4-15.3). Survival analyses considering all subjects and according to disease staging are set forth in Figures 2 and 3, respectively. A survival analysis based on histological subtypes was not carried out due to the small number of patients with sarcomatoid and biphasic subtypes, and thus no attempt was made to compare those groups statistically.

DISCUSSION

Unfortunately, few cancer centers in LA have a reasonable number of MPM cases to allow for an optimal experience with the disease. In 2019, the largest observational study of mesothelioma in LA was published, including 302 patients from nine different countries/centers.[7] The analysis was focused on the overall response rate to first-line chemotherapy and on progression-free, survival-related factors. Although the study[7] provided pivotal information about clinical and pathological features, it compiled data from countries with distinct features, such as diverse health care systems and different types of asbestos fibers to which the populations were exposed.[5]

To date, the present study is the largest observational study in Brazil evaluating clinical and pathological features of MPM. The demographic characteristics, such as the male-to-female ratio and age, are similar to those in a report based on the WHO database concerning MPM patients.[8] In contrast, 45% of the patients in our study were smokers, which is considerably higher than the Brazilian national rate of smokers between 2008 and 2019, which decreased from 18.5% to 12.6% over that period.[9] The trend toward a stronger smoking habit among MPM patients was observed in several studies, which may be explained by a greater prevalence of smoking among asbestos workers.[10,11] Additionally, due to the high latency between asbestos exposure and development of mesothelioma, the patients treated tend to be older, and this part of the population is generally more prone to smoking.[12] The correlation between a previous environmental exposure and a pathological condition is a milestone in terms of improving the diagnostic

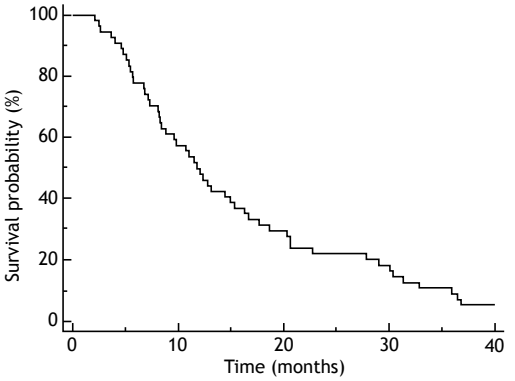

Figure 2. Survival analysis of the patients included in the study (N = 66).

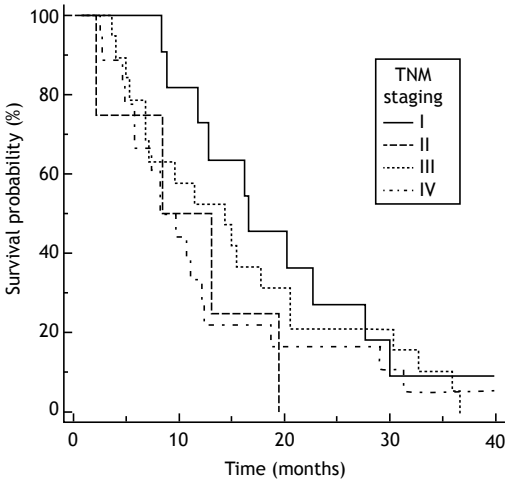

Figure 3. Survival analysis of the patients (N = 66) according to TNM staging.

process of occupational diseases.[13] Surprisingly, less than half of the patients in the present study had any knowledge of prior exposure to asbestos, according to their medical records, which contradicts current world statistics that associates 80% of the cases of MPM with exposure to asbestos.[14] The disparity can certainly be explained by the patients' unawareness of their environmental exposure that has happened throughout their lives. Unfortunately, such disparity may have consequences for the diagnosis of such patients since a significantly shorter time to referral to a specialist was observed among the patients who were aware of their prior exposure when compared with those who were unaware of such exposure.

On average, patients waited more than 6 months after the onset of symptoms to seek medical assistance. During this time, they underwent a median of two procedures before being referred to a specialist visit. A possible reason behind this delay was the use of procedures that had no clear diagnostic intention, mainly thoracentesis, performed in primary and secondary health care centers prior to referral. Moreover, despite the abovementioned delay, over 60% of the patients were referred without a definitive biopsy result/diagnosis. Although this finding may contain inaccuracies related to imprecise patient reporting their past medical history, it may provide valuable information for policy makers to develop targets for improvement of the recognition of the disease.

After the first specialist visit (with a thoracic surgeon, an oncologist, or a pulmonologist), an additional waiting time of almost 2 months was necessary to reach the diagnosis of MPM. As stated above, more than half of the subjects were referred without an established diagnosis, and therefore pleural biopsy had to be performed. However, there were an unexpected number of re-biopsies due to false-negative results. MPM has been a diagnostic challenge to pathologists even with the advances of immunohistochemistry over the last decades.[15] Two critical prospective studies have evaluated the diagnostic yield of different biopsy methods.[16,17] One prospective study analyzed 188 patients with MPM between 1973 and 1990 and showed that the diagnosis was confirmed using thoracoscopy, pleural fluid cytology, and needle biopsy in 98%, 26%, and 21% of the subjects, respectively,[16] and one randomized clinical trial compared Abram's needle biopsy and CT-guided biopsy and showed a significant superiority of the latter method regarding sensitivity (47% vs. 87%) and negative predictive value (40% vs. 80%).[17] Such findings support the fact that Cope needle biopsy had the highest false-negative rate among the pleural biopsy methods used in the present study.

Video-assisted thoracoscopy is the procedure with the highest sensitivity to diagnose MPM when compared with image-guided biopsy or Cope needle biopsy. Furthermore, it allows for the removal of a sufficient amount of tissue in order to perform all kinds of molecular analyses which are crucial for oncology today.[16,17] In the present study, although only a few cases of image-guided biopsies were analyzed, the same superiority of thoracoscopy regarding false-negative results was observed when it was compared with Cope needle biopsy. The recently released Brazilian national guidelines for the diagnosis of MPM states that there are advantages of thoracoscopy over other modalities. Therefore, thoracoscopy should be considered the mainstay method for the diagnosis of MPM as it may reduce eventual delays in terms of achieving proper histopathological characterization.[18]

Although epithelioid mesothelioma was the most frequent subtype in our sample, its proportion (88%) was higher than that reported in previous research, in which the presence of this subtype ranged from 60-75%.[19] The high frequency of epithelioid mesothelioma may have improved the overall survival rate, despite the adversities mentioned above with respect to the diagnostic process, since epithelioid morphology remains one of the dominant prognostic factors, together with TNM staging.[20,21]

To our knowledge, this is the first study to describe the mean SUV (8.6) of 18F-FDG PET/CT in MPM patients from a Latin American country. The use

of this radiological parameter as a tool to predict several outcomes and to help the differentiation of MPM from benign pleural diseases is currently under development.[22] However, in countries where infectious diseases are most of the times the main differential diagnoses of pleuropulmonary diseases, the SUV may have a different clinical implication. As such, the SUV data gathered in the present study may guide further research in those locations.

A well-known randomized feasibility study[23] that compared surgical treatment with systemic therapy alone found a lower survival rate (adjusted hazard ratio = 2.75) in patients who underwent trimodal therapy (including EPP) than in patients who received only systemic therapy. There was a great deal of criticism about that study, including the use of an underpowered sample size and poor compliance with the indication criteria for surgery.[23] On the other hand, a study[24] that included 14,228 patients with MPM found an improved survival rate (adjusted hazard ratio = 0.64) for patients who received cancer-directed surgery.

Even if we consider the uncertainty of the benefits of surgery in MPM, the current guidelines recommend surgical therapy for those who have resectable disease and are fit for surgery.[25] In the present study sample, due to advanced staging and poor performance status, less than 20% of the patients could undergo EPD or EPP. Consequently, aside from a lower overall survival rate when compared with other studies, poor baseline conditions also prevented those patients from receiving the recommended treatment modalities such as surgery, which could potentially be beneficial.[26]

The current stagnation of treatment options offered to MPM patients can be identified by a comparison between the results of the present study and those of a study carried out in Brazil 14 years ago.[27] That retrospective study, which reviewed the medical records of 17 patients treated for MPM between 2000 and 2005, found a low proportion of MPM patients who could undergo surgical treatment, and the mean overall survival was 11 months. The present study, carried out more than 10 years later, found very similar results, corroborating the lack of improvement in the management of the disease.

It is expected that mesothelioma in Brazil will reach its peak incidence by the year 2026, but health care systems are still not properly prepared to manage MPM.[28] Several factors, including the patient's lack of awareness of previous asbestos exposure and unfamiliarity of health professionals with this disease, threaten the capacity to offer the best available treatment for this type of cancer in Brazil.[18] Therefore, it is critical that progressive improvements in the abilities to recognize MPM be made in order to increase the survival rate of these patients, which today is very low.

AUTHOR CONTRIBUTIONS

PHPG: study design; data analysis; and reviewing of the manuscript. RMT: study design; and reviewing of the manuscript. LPL: data collection; and drafting of the manuscript. PMPF: study conception and design; and reviewing of the final manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Park EK, Takahashi K, Hoshuyama T, Cheng TJ, Delgermaa V, Le GV, et al. Global magnitude of reported and unreported mesothelioma. Environ Health Perspect. 2011;119(4):514-518. https://doi.org/10.1289/ehp.1002845
2. The United States Geological Survey (USGS). National Minerals Information Center [homepage on the Internet]. USGS: Reston, VA, USA; [cited 2022 Jan 2]. Minerals Yearbook - 2015 [Adobe Acrobat document, 9 p.]. Available from: https://d9-wret.s3-us-west-2.amazonaws.com/assets/palladium/production/mineral-pubs/asbestos/myb1-2015-asbes.pdf
3. Pedra F. Mortalidade por mesotelioma no Brasil de 1980 a 2010. [thesis] Rio de Janeiro: Escola Nacional de Saúde Pública Sergio Arouca; 2015. https://www.arca.fiocruz.br/handle/icict/34320
4. Ugolini D, Bonassi S, Cristaudo A, Leoncini G, Ratto GB, Neri M. Temporal trend, geographic distribution, and publication quality in asbestos research. Environ Sci Pollut Res Int. 2015;22(9):6957-6967. https://doi.org/10.1007/s11356-014-3925-1
5. Algranti E, Ramos-Bonilla JP, Terracini B, Santana VS, Comba P, Pasetto R, et al. Prevention of Asbestos Exposure in Latin America within a Global Public Health Perspective. Ann Glob Health. 2019;85(1):49. https://doi.org/10.5334/aogh.2341
6. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655. https://doi.org/10.1097/00000421-198212000-00014
7. Rojas L, Cardona AF, Trejo-Rosales R, Zatarain-Barrón ZL, Ramírez-Tirado LA, Ruiz-Patiño A, et al. Characteristics and long-term outcomes of advanced pleural mesothelioma in Latin America (MeSO-CLICaP). Thorac Cancer. 2019;10(3):508-518. https://doi.org/10.1111/1759-7714.12967
8. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. Bull World Health Organ. 2011;89(10):716-724C. https://doi.org/10.2471/BLT.11.086678
9. Brasil. Ministério da Saúde. Instituto Nacional do Câncer (INCA). Observatório da Política Nacional de Controle do Tabaco; c2021 [homepage on the Internet]. Rio de Janeiro: INCA; [updated 2022 May 13; cited 2021 Oct 2]. Dados e números da prevalência do tabagismo; [about 32 screens]. Available from: https://www.inca.gov.br/observatorio-da-politica-nacional-de-controle-do-tabaco/dados-e-numeros-prevalencia-tabagismo
10. Algranti E. Tabagismo e ocupação: elo de exposições pouco explorado como estratégia de combate ao tabagismo. J Pneumologia. 2001;27(4):07. https://doi.org/10.1590/S0102-35862001000400001 https://doi.org/10.1590/S0102-35862001000400001
11. Osinubi OY, Afilaka AA, Doucette J, Golden A, Soriano T, Rovner E, et al. Study of smoking behavior in asbestos workers. Am J Ind Med. 2002;41(1):62-69. https://doi.org/10.1002/ajim.10031
12. Malta DC, Flor LS, Machado ÍE, Felisbino-Mendes MS, Brant LCC, Ribeiro ALP, et al. Trends in prevalence and mortality burden attributable to smoking, Brazil and federated units, 1990 and 2017. Popul Health Metr. 2020;18(Suppl 1):24. https://doi.org/10.1186/s12963-020-00215-2
13. Landrigan PJ, Baker DB. The recognition and control of occupational disease. JAMA. 1991;266(5):676-680. https://doi.org/10.1001/jama.1991.03470050076026

14. McDonald JC, McDonald AD. The epidemiology of mesothelioma in historical context. Eur Respir J. 1996;9(9):1932-1942. https://doi.org/10.1183/09031936.96.09091932
15. Fels Elliott DR, Jones KD. Diagnosis of Mesothelioma. Surg Pathol Clin. 2020;13(1):73-89. https://doi.org/10.1016/j.path.2019.10.001
16. Boutin C, Rey F. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 1: Diagnosis. Cancer. 1993;72(2):389-393. https://doi.org/10.1002/1097-0142(19930715)72:2<389::AID-CNCR2820720213>3.0.CO;2-V
17. Maskell NA, Gleeson FV, Davies RJ. Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: a randomised controlled trial. Lancet. 2003;361(9366):1326-1330. https://doi.org/10.1016/S0140-6736(03)13079-6
18. Brasil. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no SUS. Diretrizes Brasileiras para Diagnóstico do Mesotelioma Maligno de Pleura; Brasília: Ministério da Saúde; 2020.
19. Antman K, Hassan R, Eisner M, Ries LA, Edwards BK. Update on malignant mesothelioma. Oncology (Williston Park). 2005;19(10):1301-1316.
20. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. J Thorac Oncol. 2012;7(11):1631-1639. https://doi.org/10.1097/JTO.0b013e31826915f1
21. Meyerhoff RR, Yang CF, Speicher PJ, Gulack BC, Hartwig MG, D'Amico TA, et al. Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database. J Surg Res. 2015;196(1):23-32. https://doi.org/10.1016/j.jss.2015.01.043
22. Basu S, Saboury B, Torigian DA, Alavi A. Current evidence base of FDG-PET/CT imaging in the clinical management of malignant pleural mesothelioma: emerging significance of image segmentation and global disease assessment. Mol Imaging Biol. 2011;13(5):801-811. https://doi.org/10.1007/s11307-010-0426-6
23. Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, 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(8):763-772. https://doi.org/10.1016/S1470-2045(11)70149-8
24. Taioli E, Wolf AS, Camacho-Rivera M, Kaufman A, Lee DS, Nicastri D, et al. Determinants of Survival in Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients. PLoS One. 2015;10(12):e0145039. https://doi.org/10.1371/journal.pone.0145039
25. Popat S, Baas P, Faivre-Finn C, Girard N, Nicholson AG, Nowak AK, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(2):129-142. https://doi.org/10.1016/j.annonc.2021.11.005
26. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial [published correction appears in Lancet. 2021 Feb 20;397(10275):670]. Lancet. 2021;397(10272):375-386. https://doi.org/10.1016/S0140-6736(20)32714-8
27. Terra RM, Teixeira LR, Beyruti R, Takagaki TY, Vargas FS, Jatene FB. Malignant pleural mesothelioma: multidisciplinary experience in a public tertiary hospital [Article in Portuguese]. J Bras Pneumol. 2008;34(1):13-20. https://doi.org/10.1590/S1806-37132008000100004
28. Algranti E, Saito CA, Carneiro AP, Moreira B, Mendonça EM, Bussacos MA. The next mesothelioma wave: mortality trends and forecast to 2030 in Brazil. Cancer Epidemiol. 2015;39(5):687-692. https://doi.org/10.1016/j.canep.2015.08.007