Updates in Staging and Management of Malignant Pleural Mesothelioma

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KEYWORDS

• Surgery for malignant pleural mesothelioma • Extrapleural pneumonectomy
• Pleurectomy/decortication • Perioperative mortality • Quality of life

KEY POINTS

- While without treatment, malignant pleural mesothelioma (MPM) confers poor survival, cancer-directed surgery as part of multimodality treatment has been associated with a 15% 5-year survival.
- Extrapleural pneumonectomy (EPP) and radical or extended pleurectomy/decortication (P/D) are the 2 types of resection performed in this context. Preoperative staging is critical to patient selection for surgery and, generally, P/D is recommended over EPP in most cases.
- Adjuvant therapy with intraoperative platforms, traditional chemotherapy, hemithoracic radiotherapy before or after resection, and new immunotherapy agents are instrumental in achieving durable long-term results for MPM patients. This article outlines the latest understanding of the staging of this disease and describes the current state of literature and practice for MPM.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a primary malignancy of the pleura best known for its association with asbestos exposure. A locally aggressive disease, MPM is difficult to eradicate, with progression and/or recurrence so frequent they are considered the rule, not the exception. Left untreated, the median overall survival of for MPM is 7 months.[1] Resection, chemotherapy, radiotherapy, and immunotherapy have been used in various combinations, and in the context of multimodality therapy, curative-intent surgery has been associated with improved survival.[2–5]

Surgery for MPM includes both diagnostic and therapeutic procedures to stage and treat this disease. Surgical biopsy via pleuroscopy or video-assisted thoracoscopic surgery distinguishes MPM from metastatic disease of other primaries, such as

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lung, colorectal, and breast cancers. Moreover, surgical biopsy most accurately predicts tumor histology (epithelial, sarcomatoid, biphasic, and so forth).[6] While the therapeutic benefit of surgery is the subject of ongoing discussion, cancer-directed surgery for MPM has been associated with a 5-year survival of 15%, not dissimilar to other aggressive solid cancers such as locally advanced esophageal or pancreatic carcinoma.[7–10]

STAGING IN MALIGNANT PLEURAL MESOTHELIOMA

As with any solid malignancy, patients who present with MPM require staging to determine prognosis and guide therapy. An ideal staging system stratifies patients into discrete groups (with sufficient numbers in each group) based on prognosis in which analysis results in survival curves with clear separation and reduced survival with each advancement in stage. Multiple staging systems have been developed and described for MPM, generally limited by the rarity and relative poor survival for most patients with this disease.[11]

Published staging systems that have been based on retrospective data from mostly surgical studies. Butchart and colleagues[12] described the first staging system for MPM based on their single-institution study of 29 patients undergoing extrapleural pneumonectomy (EPP) for MPM, in which 9 (31%) died in the hospital and 3 (10.3%) survived 2 or more years. The Brigham and Women's Hospital published the first iteration of the Brigham staging system based on a series of 52 patients undergoing EPP, chemotherapy, and radiotherapy.[13] This group published revised editions of this system based on updates in the original dataset.[14] Analysis of a large cohort of mostly new cases was used to derive proposed adjustments for the staging of patients with epithelial disease in 2010.[15]

Additional staging systems have incorporated clinical variables available before surgical resection (or, if none is performed, factors available as part clinical staging) as datasets became available that included large enough cohorts of patients treated operatively.[16] The International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) first proposed tumor, node, and metastasis criteria for MPM in the 4th edition of the UICC/AJCC staging system in 1992.[17,18] Modifications were proposed by the International Mesothelioma Interest Group in 1994, which have subsequently been adopted as the international standard.[19] In the 25 years since, the International Association for the Study of Lung Cancer staging committee has subsequently assembled an international database combining retrospective datasets from participating institutions with an ongoing prospective registry with continued efforts to standardize documentation of clinical, demographic, pathologic, and treatment variables.[20–22]

Clinical Staging of Malignant Pleural Mesothelioma for Preoperative Evaluation

All MPM patients are staged with PET-computed tomography to evaluate for nodal and/or distant metastases. High PET-avidity in the pleural tumor is associated with worse survival.[23] Mediastinal nodal evaluation with endobronchial ultrasound or mediastinoscopy should be considered, and certainly if there are enlarged or PET-avid mediastinal lymph nodes. Some clinicians advocate routine pathologic mediastinal staging, but the variable nodal drainage of the pleura and unpredictable patterns of nodal metastatic spread from MPM have resulted in poor sensitivity of cervical mediastinoscopy for detecting extrapleural nodal spread of disease.[24,25] Diffuse chest wall, subdiaphragmatic, and mediastinal invasion are assessed with chest MRI.[26] Laparoscopic staging to rule out intra-abdominal spread of MPM should be performed

if imaging suggests subdiaphragmatic extension of tumor and/or ascites, although some surgeons perform this in all patients. In general, cancer-directed surgical resection is not offered to patients with intra-abdominal invasion of disease.

SURGICAL RESECTION FOR MALIGNANT PLEURAL MESOTHELIOMA

Although few MPM patients undergo resection in the general population, up to 40% are offered surgery at tertiary referral centers.[27] In a study of 5937 MPM patients in the Surveillance, Epidemiology, and End Results (SEER) dataset diagnosed between 1990 and 2004, Flores and colleagues[27] found that 22% of patients underwent cancer-directed surgery. Updated, more comprehensive datasets were analyzed in more recent studies and also found that cancer-directed surgery was predictive of longer survival.[7,28] In 1 study exploring racial disparities, surgery was an independent predictor of reduced mortality (hazard ratio [HR] = 0.68; 95% CI, 0.63–0.74) and surgery was associated with a median overall survival of 11 months (compared with 7 months without, $P<.0001$), but fewer black patients were treated with resection.[28]

In MPM, surgical resection includes either EPP or radical or extended pleurectomy/decortication (P/D). EPP is the en bloc removal of the lung, parietal and visceral pleurae, diaphragm, and pericardium. Radical or extended P/D includes resection of the parietal and visceral pleurae, with or without removal of the diaphragm and/or pericardium if involved with tumor, but always preserving the underlying lung. While individual surgeon, patient, and tumor-specific factors determine which procedure is performed, most experts recommend radical or extended P/D as the procedure of choice, and all clinicians and investigators agree that surgery should be performed in the context of multimodality therapy whenever possible. Preoperative, intraoperative, and/or postoperative adjuvant treatment includes chemotherapy, intracavitary chemotherapy or photodynamic therapy, preoperative or postoperative external beam radiotherapy, and immunotherapy.[29–35]

Selecting Patients for Surgery

Historically, it was believed that resection should be considered for patients with more disease characteristics such that the possible benefit of surgery would offset its risk. Criteria for patient selection for surgery are therefore based on identifying patients with favorable clinical and demographic characteristics. Positive prognostic factors for MPM are epithelial histology, female gender, and earlier stage. In a retrospective study of 945 patients, epithelial histology, female gender, early stage, absence of tobacco or asbestos exposure, and left-sided tumors were associated with longer survival.[36–38] In a SEER analysis of 14,229 MPM patients diagnosed between 1973 and 2009, female gender was a significant predictor of longer survival, independent of age, stage, race, and treatment (adjusted HR = 0.78; 95% CI, 0.75–0.82).[4] Another study of the impact of gender on survival found that the association with positive effect on survival was only present for young women with epithelial tumors.[5] In this series evaluating patients who survived at least 3 years after EPP, women under the age of 56 years with epithelial MPM had a median survival longer than 7 years, compared with less than 4.5 years for older women.[5] For men and women, higher stage and nonepithelial histology are associated with lower survival.[2,36]

Outcomes of Extrapleural Pneumonectomy

Because EPP is generally performed in the context of multimodality therapy, studies evaluating results for EPP reflect effects of EPP and adjuvant treatment, such as

chemotherapy, radiotherapy, and/or immunotherapy. In an early series of 183 patients who underwent EPP with adjuvant chemotherapy and radiotherapy, perioperative mortality was 3.8% and morbidity was 50%.[14] Median survival for those who survived surgery was 19 months. Patients with epithelial disease, negative margins, and normal extrapleural (mediastinal) nodes had a median long-term survival of 51 months.

Heated intraoperative chemotherapy (HIOC) has been used successfully as an adjunct to surgery for MPM. In a phase I study of EPP with HIOC, a median survival of 26 moths was seen in patients who received cisplatin doses of 175 to 200 mg/m^2.[39] Median survival was 39 months for stage I/II epithelial patients, compared with 15 months for those with stage III epithelial disease. The same investigators published a larger phase II study of 121 patients, reporting an overall median survival of 12.8 months, and for patients with early-stage tumors, 21 months.[40] In a trial evaluating EPP and adjuvant chemotherapy in 302 patients in Scotland, those with stage I/II MPM had a median survival of 35 months.[41] Those who underwent EPP alone had a survival of 13 months. Batirel and colleagues[42] in Turkey analyzed results for 20 patients undergoing EPP and adjuvant radiotherapy and platinum-based chemotherapy, reporting a median survival of 17 months in this cohort. Yan and colleagues[8] reported a retrospective series of 70 patients undergoing EPP followed by chemotherapy and/or radiotherapy, resulting in a median survival of 20 months. Adjuvant radiotherapy and pemetrexed were independent predictors of longer survival.

In 1 trial of 19 patients undergoing induction chemotherapy, EPP, followed by adjuvant radiotherapy, Weder and colleagues[30] found an overall median survival of 23 months, with 13 patients completing the full regimen. In a large, multicenter prospective study of 61 patients, the same investigators reported that 58 (95%) completed induction chemotherapy, 45 (74%) underwent EPP, and 36 (59%) received at least part of planned adjuvant radiotherapy.[43] Overall median survival was 19.8 months, with 23 months for patients who underwent EPP after completing chemotherapy.

In a phase II trial of neoadjuvant chemotherapy, EPP, and hemithoracic radiotherapy, Flores and colleagues[29] reported an overall median survival of 19 months. For 8 patients who completed cisplatin-gemcitabine chemotherapy and EPP, median survival was 35 months. In a phase II multicenter trial of 77 patients, the same group treated 77 patients with cisplatin-pemetrexed, EPP, and radiotherapy, with 40 (52%) patients completing the full regimen and surviving a median of 29 months.[44] Perioperative mortality was 3.7% and local recurrence occurred in 14% of patients. The overall median survival was 16.8 months. de Perrot and colleagues[45] found similarly promising results in a retrospective analysis of 60 patients treated with cisplatin-based chemotherapy followed by EPP and adjuvant radiotherapy. Median overall survival was 14 months, but for 30 (50%) patients who completed the full regimen, those with no nodal disease on final pathologic analysis had a median survival of 59 months. The same investigators enrolled 25 patients in a phase I/II trial of induction radiotherapy with 25 Gy intensity-modulated radiotherapy 1 week before EPP, with patients with positive nodes on final pathologic analysis receiving adjuvant chemotherapy.[46] There was 1 (4%) postoperative death. With a median follow-up of 23 months, 3-year survival was 84% for patients with epithelial disease and 13% for those with biphasic disease.

Recurrence After Extrapleural Pneumonectomy

While metastasis in MPM is less common than that seen with other solid malignancies, local recurrence is the rule, rather than the exception, and represents

the most common cause of death in most patients after EPP. Whereas hematogenous spread occurs rarely, recurrence is more commonly locoregional (to the ipsilateral chest and abdomen). Baldini and colleagues[47] described a series of all patients undergoing EPP-based multimodality therapy, excluding 11 patients who died perioperatively or lacked information regarding location of recurrence. In 54 patients (72% of all recurrences), recurrence first occurred in the ipsilateral hemithorax or mediastinum. The remaining recurrences occurred in the abdomen (53%), contralateral chest (38%), and distant sites (7%), with many patients recurring in multiple concurrent sites. The authors concluded that treatment failure most commonly occurred in the ipsilateral chest. Flores and colleagues[48,49] published a retrospective study of 663 patients treated with various surgery-based multimodality protocols. Of 385 patients undergoing EPP, 57% recurred, with 33% of first recurrences occurring in the ipsilateral chest or pericardium. Other sites were abdomen (31%), contralateral chest (22%), abdomen and chest (8%), and bone (3%).

Outcomes of Pleurectomy/Decortication

Over the decades, increasing evidence and experience has suggested that the high mortality and morbidity of EPP was not met with obvious benefit in long-term mortality.[50] Most clinicians now agree that P/D, the lung-sparing resection for MPM, is recommended for cancer-directed surgery in this disease.[51]

As in EPP, patients undergoing P/D are treated with adjuvant therapy in an effort to decrease the likelihood of local recurrence. In 1 prospective phase I/II trial, 44 patients underwent P/D with HIOC, with a median survival of 14 months seen in patients who were resectable. The subset of patients who received high-dose intraoperative cisplatin (175–450 mg/m^2) had a median survival of 18 months.[31] Postoperative hemithoracic radiotherapy has been used successfully as adjuvant therapy, but the presence of the remaining underlying lung parenchyma makes this a complex and highly specialized technique. In the largest retrospective series, 123 patients treated with a median of 42.5 Gy hemithoracic radiotherapy after P/D experienced a local control rate of 42% and median survival of 13.5 months.[52,53] The same investigators used 46.8 Gy intensity-modulated radiotherapy in another series and found 1- and 2-year survival of 75% and 53%, respectively, with grade 3/4 pneumonitis occurring in 20% of patients.

Recurrence After Pleurectomy/Decortication

Despite best attempts at intraoperative and postoperative adjunctive therapy, most patients who undergo P/D recur, with the most common site of treatment failure in the ipsilateral chest. The ipsilateral hemithorax and/or mediastinum were the site(s) of more frequent first recurrence in 95% of 59 patients undergoing P/D in 1 large series evaluating this issue.[54] Flores's series comparing EPP to P/D had similar findings, with 65% of first relapse presenting as local recurrence.[48]

DATA COMPARING EXTRAPLEURAL PNEUMONECTOMY WITH PLEURECTOMY/DECORTICATION

As P/D became the procedure of choice for most surgeons treating MPM, many studies evaluated outcomes for the 2 operations. P/D is associated with better perioperative morbidity and mortality. One Society of Thoracic Surgeons Database study found higher rates of acute respiratory distress syndrome, reintubation, unexpected reoperation, sepsis, and mortality after EPP compared with P/D.[55]

In the largest retrospective study comparing EPP to P/D, Flores and colleagues[48] found higher cumulative survival for curative-intent P/D than EPP for patients with early-stage disease. For patients with later-stage disease, EPP was associated with better survival. One meta-analysis of a small portion of the literature comparing the 2 operations found significantly lower mortality and a trend toward higher cumulative survival with P/D.[56] Another meta-analysis of 24 independent datasets from all English-language observational studies published from 1990 to 2014 compared 1391 patients who underwent EPP with 1512 patients who underwent P/D.[57,58] The proportion of patients with epithelial histology varied widely among the studies. There was significantly higher 30-day mortality associated with EPP (4.5% versus 1.7%, $P<.05$) with little heterogeneity between studies. For the 17 studies including data on median survival, 53% demonstrated higher median survival with EPP (and 47% with P/D). Of 7 studies reporting at least 2-year survival, there was no significant survival difference, but there was significant heterogeneity among studies.[57]

Given an association with higher risk and lack of clear survival benefit over P/D, EPP has been the subject of controversy, with some practitioners advocating against it.[59] The Mesothelioma and Radical Surgery (MARS) trial, which failed to complete successful randomization, was an attempt to compare EPP with no surgery for MPM. Post-hoc analyses explored long-term outcomes, but these studies lacked adequate power to draw meaningful conclusions. A phase III randomized control trial of P/D versus no surgery for patients undergoing platinum-pemetrexed chemotherapy for MPM, MARS2 (NCT02040272), is currently ongoing.[60]

IMMUNOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

The observation of longer-than-expected survival for MPM patients with chronic inflammatory states from smoldering postoperative infection combined with successful use of checkpoint inhibitors in other solid thoracic malignancies[61] has led to optimism that the tumor microenvironment in MPM may be modulated to promote antitumor response. In fact, although sarcomatoid histology and high tumor-infiltrating lymphocyte are considered poor prognosticators,[62] patients with these features have demonstrated clinical responsiveness in small trials of programmed cell death protein-1 (PD-1) blockade.[63] Immunotherapy alone has been tested as second- and third-line treatment options for MPM, with response rates of 20% to 30%.[64] Success with the additive and/or synergistic impact of chemotherapy combined with PD-1 blockade in non-small cell lung cancer[65,66] has led many investigators to recruit for trials of chemo-immunotherapy in MPM and also led many clinicians to use these combinations off-label in practice. Novel therapeutics in the form of oncolytic viruses, vaccines, chimeric antigen receptor T cell, checkpoint inhibition, and antibody-drug conjugates are the subject of ongoing investigation as components of multimodality therapy for MPM.[35]

SUMMARY

Despite its reputation as an aggressive and fatal disease, MPM has multiple treatment options, specifically in the context of surgery-based multimodality therapy, which is associated with a 15% 5-year survival. Staging patients preoperatively and selecting the appropriate type of resection for the appropriate patient is critical. Generally, P/D is better tolerated and evidence suggests that survival is not worse than that associated with EPP. Locoregional recurrence is common after both procedures but patients who have undergone P/D have avoided the morbidity of EPP and are generally better positioned to tolerate adjuvant therapy and treatment of recurrent disease. Traditional adjuvant therapy before or after surgery with chemotherapy and/or radiotherapy is

currently part of the standard protocols, although there are no data to support one order of treatment over another. Combination with immunotherapy represents the newest horizon with initial studies suggesting we may be able to harness individual patients' immune systems to fight this challenging disease.

CONFLICTS OF INTEREST

No conflicts of interest to disclose.

REFERENCES

1. Sugarbaker DJ, Jaklitsch MT, Bueno R, et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. J Thorac Cardiovasc Surg 2004;128:138–46.
2. Wolf AS, Richards WG, Tilleman TR, et al. Characteristics of malignant pleural mesothelioma in women. Ann Thorac Surg 2010;90:949–56 [discussion: 56].
3. Sugarbaker DJ, Wolf AS. Surgery for malignant pleural mesothelioma. Expert Rev Respir Med 2010;4:363–72.
4. Taioli E, Wolf AS, Camacho-Rivera M, et al. Women with malignant pleural mesothelioma have a threefold better survival rate than men. Ann Thorac Surg 2014; 98:1020–4.
5. Sugarbaker DJ, Wolf AS, Chirieac LR, et al. Clinical and pathological features of three-year survivors of malignant pleural mesothelioma following extrapleural pneumonectomy. Eur J Cardiothorac Surg 2011;40:298–303.
6. Chirieac LR, Hung YP, Foo WC, et al. Diagnostic value of biopsy sampling in predicting histology in patients with diffuse malignant pleural mesothelioma. Cancer 2019;125:4164–71.
7. Taioli E, Wolf AS, Camacho-Rivera M, 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:e0145039.
8. Yan TD, Boyer M, Tin MM, et al. Extrapleural pneumonectomy for malignant pleural mesothelioma: outcomes of treatment and prognostic factors. J Thorac Cardiovasc Surg 2009;138:619–24.
9. Taioli E, Wolf AS, Camacho-Rivera M, et al. Racial disparities in esophageal cancer survival after surgery. J Surg Oncol 2016;113:659–64.
10. Mayo SC, Nathan H, Cameron JL, et al. Conditional survival in patients with pancreatic ductal adenocarcinoma resected with curative intent. Cancer 2012; 118:2674–81.
11. Richards WG. Recent advances in mesothelioma staging. Semin Thorac Cardiovasc Surg 2009;21:105–10.
12. Butchart EG, Ashcroft T, Barnsley WC, et al. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 29 patients. Thorax 1976;31:15–24.
13. Sugarbaker DJ, Strauss GM, Lynch TJ, et al. Node status has prognostic significance in the multimodality therapy of diffuse, malignant mesothelioma. J Clin Oncol 1993;11:1172–8.
14. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999;117:54–63 [discussion: 5].

15. Richards WG, Godleski JJ, Yeap BY, et al. Proposed adjustments to pathologic staging of epithelial malignant pleural mesothelioma based on analysis of 354 cases. Cancer 2010;116:1510–7.
16. Brims FJ, Meniawy TM, Duffus I, et al. A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis. J Thorac Oncol 2016;11:573–82.
17. (UICC) IUAC. TNM atlas. 4th edition. Berlin: Springer; 1992.
18. Bears OH, Henson DE. Fourth edition of the AJCC manual for staging of cancer. Philadelphia: J. B. Lippincott; 1992.
19. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. Chest 1995;108:1122–8.
20. Pass H, Giroux D, Kennedy C, et al. The IASLC mesothelioma staging project: improving staging of a rare disease through international participation. J Thorac Oncol 2016;11:2082–8.
21. Pass HI, Giroux D, Kennedy C, et al. Supplementary prognostic variables for pleural mesothelioma: a report from the IASLC staging committee. J Thorac Oncol 2014;9:856–64.
22. Friedberg JS, Culligan MJ, Tsao AS, et al. A proposed system toward standardizing surgical-based treatments for malignant pleural mesothelioma, from the Joint National Cancer Institute-International Association for the Study of Lung Cancer-Mesothelioma Applied Research Foundation Taskforce. J Thorac Oncol 2019;14:1343–53.
23. Flores RM. The role of PET in the surgical management of malignant pleural mesothelioma. Lung Cancer 2005;49(Suppl 1):S27–32.
24. Flores RM, Routledge T, Seshan VE, et al. The impact of lymph node station on survival in 348 patients with surgically resected malignant pleural mesothelioma: implications for revision of the American Joint Committee on Cancer staging system. J Thorac Cardiovasc Surg 2008;136:605–10.
25. Sugarbaker DJ, Richards WG, Bueno R. Extrapleural pneumonectomy in the treatment of epithelioid malignant pleural mesothelioma: novel prognostic implications of combined N1 and N2 nodal involvement based on experience in 529 patients. Ann Surg 2014;260:577–80 [discussion: 80–2].
26. Patz EF Jr, Shaffer K, Piwnica-Worms DR, et al. Malignant pleural mesothelioma: value of CT and MR imaging in predicting resectability. AJR Am J Roentgenol 1992;159:961–6.
27. Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. J Thorac Oncol 2010;5:1649–54.
28. Taioli E, Wolf AS, Moline JM, et al. Frequency of surgery in black patients with malignant pleural mesothelioma. Dis Markers 2015;2015:282145.
29. Flores RM, Krug LM, Rosenzweig KE, et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. J Thorac Oncol 2006;1:289–95.
30. Weder W, Kestenholz P, Taverna C, et al. Neoadjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. J Clin Oncol 2004;22:3451–7.
31. Richards WG, Zellos L, Bueno R, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. J Clin Oncol 2006;24:1561–7.

32. Pass HI, Temeck BK, Kranda K, et al. Phase III randomized trial of surgery with or without intraoperative photodynamic therapy and postoperative immunochemotherapy for malignant pleural mesothelioma. Ann Surg Oncol 1997;4:628–33.
33. de Perrot M, Feld R, Leighl NB, et al. Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2016;151(2):468–73.
34. Kindler HL, Karrison TG, Gandara DR, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol 2012;30:2509–15.
35. Tano ZE, Chintala NK, Li X, et al. Novel immunotherapy clinical trials in malignant pleural mesothelioma. Ann Transl Med 2017;5(11):245.
36. Flores RM, Zakowski M, Venkatraman E, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. J Thorac Oncol 2007;2:957–65.
37. Wolf AS, Daniel J, Sugarbaker DJ. Surgical techniques for multimodality treatment of malignant pleural mesothelioma: extrapleural pneumonectomy and pleurectomy/decortication. Semin Thorac Cardiovasc Surg 2009;21:132–48.
38. Sarot IA. Extrapleural pneumonectomy and pleurectomy in pulmonary tuberculosis. Thorax 1949;4:173–223.
39. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955–63.
40. Tilleman TR, Richards WG, Zellos L, et al. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg 2009;138:405–11.
41. Aziz T, Jilaihawi A, Prakash D. The management of malignant pleural mesothelioma; single centre experience in 10 years. Eur J Cardiothorac Surg 2002;22:298–305.
42. Batirel HF, Metintas M, Caglar HB, et al. Trimodality treatment of malignant pleural mesothelioma. J Thorac Oncol 2008;3:499–504.
43. Weder W, Stahel RA, Bernhard J, et al. Multicenter trial of neo-adjuvant chemotherapy followed by extrapleural pneumonectomy in malignant pleural mesothelioma. Ann Oncol 2007;18:1196–202.
44. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. J Clin Oncol 2009;27:3007–13.
45. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Clin Oncol 2009;27:1413–8.
46. Cho BC, Feld R, Leighl N, et al. A feasibility study evaluating surgery for mesothelioma after radiation therapy: the "SMART" approach for resectable malignant pleural mesothelioma. J Thorac Oncol 2014;9:397–402.
47. Baldini EH, Richards WG, Gill RR, et al. Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2015;149:1374–81.
48. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008;135:620–6, 626.e1–3.

49. Flores RM. Surgical options in malignant pleural mesothelioma: extrapleural pneumonectomy or pleurectomy/decortication. Semin Thorac Cardiovasc Surg 2009;21:149–53.
50. McCormack PM, Nagasaki F, Hilaris BS, et al. Surgical treatment of pleural mesothelioma. J Thorac Cardiovasc Surg 1982;84:834–42.
51. Flores RM. Pleurectomy decortication for mesothelioma: the procedure of choice when possible. J Thorac Cardiovasc Surg 2016;151(2):310–2.
52. Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2005;63:1045–52.
53. Rosenzweig KE, Zauderer MG, Laser B, et al. Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2012;83:1278–83.
54. Wolf AS, Gill RR, Baldini EH, et al. Patterns of recurrence following pleurectomy/decortication for malignant pleural mesothelioma. 11th International Conference of the International Mesothelioma Interest Group:Boston, MA, USA;Sept. 12, 2012.
55. Burt BM, Cameron RB, Mollberg NM, et al. Malignant pleural mesothelioma and the Society of Thoracic Surgeons Database: an analysis of surgical morbidity and mortality. J Thorac Cardiovasc Surg 2014;148:30–5.
56. Cao C, Tian D, Park J, et al. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. Lung Cancer 2014;83:240–5.
57. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. Ann Thorac Surg 2015;99:472–80.
58. Wolf AS, Jacobson FL, Tilleman TR, et al. Managing the pneumonectomy space after extrapleural pneumonectomy: postoperative intrathoracic pressure monitoring. Eur J Cardiothorac Surg 2010;37:770–5.
59. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763–72.
60. Waller DA, Dawson AG. Randomized controlled trials in malignant pleural mesothelioma surgery—mistakes made and lessons learned. Ann Transl Med 2017;5(11):240.
61. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28.
62. Inahuma S, Lasota J, Czapiewski P, et al. CD70 expression correlates with a worse prognosis in malignant pleural mesothelioma patients via immune evasion and enhanced invasiveness. J Pathol 2020;250(2):205–2016.
63. Desai A, Karrison T, Rose B, et al. Phase II trial of pembrolizumab (NCT02399371) in previously-treated malignant mesothelioma (MM): final analysis. J Thorac Oncol 2018;13(10 Suppl).10.1016/j.jtho.2018.08.277.
64. Desai A, Nakano T, Okada M, et al. Long-term efficacy and safety of nivolumab in second-or third-line japanese malignant pleural mesothelioma patients (phase II: MERIT study). J Thorac Oncol 2018;13(10 Suppl). 10.1016/j.jtho.2018.08.275.
65. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–19298.
66. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17(11):1497–508.