American Association of Bronchology and Interventional Pulmonology Essential Knowledge in Interventional Pulmonology Series

Selected Topics in Malignant Pleural Disease

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Abstract: The goal of the American Association of Bronchology and Interventional Pulmonology Essential Knowledge in Interventional Pulmonology Series is to provide clinicians with concise, up-to-date reviews of important topics in the field of interventional pulmonology. This 3-year alternating rotation of primary topics will start with a focus on selected topics in malignant pleural disease. In this article, we update the reader on malignant pleural effusion in 3 parts: part 1—diagnosis, focusing on imaging and fluid biomarkers; part 2—management, with review of multimodal approaches, cost considerations, and evolving targeted therapies; and part 3—pleural mesothelioma. These reviews complement the Essential Knowledge in Interventional Pulmonology Lecture Series presented at the 2023 AABIP Annual Conference, available for viewing on the AABIP website (https://aabip.memberclicks.net/essential-knowledge-in-interventional-pulmonology-series).

Key Words: malignant pleural disease, clinical scoring systems, indwelling pleural catheters, mesothelioma

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Malignant pleural effusions (MPE) are an important contributor to morbidity and mortality in cancer patients, with ~15% developing an MPE.[1] Although some patients with MPE may be asymptomatic, most eventually experience symptoms of breathlessness, cough, and chest discomfort. MPEs have a high likelihood of recurrence and are associated with a shortened life expectancy, averaging 4 to 7 months.[2] MPE also imparts a significant financial burden, resulting in more than 125,000 related hospital admissions per year, median hospital charges per patient above $40,000, and estimated total inpatient charges up to $1.5 billion a year.[3]

Evaluation and management strategies for recurrent MPEs include imaging, watchful waiting, thoracentesis, pleurodesis, and indwelling pleural catheter (IPC) placement. To optimize clinical efficacy, safety, and cost-effectiveness, the therapeutic approach is individualized according to patient-specific factors. Patient prognosis helps determine the optimal management strategy, with preference given to palliative and less invasive approaches for those with short life expectancies. More aggressive and/or multimodal procedures can be offered to those expected to live longer. Evolving targeted therapies may soon supplement palliation by directly controlling the underlying disease.

Pleural mesothelioma (PM) is a distinct primary malignancy. Its genomic diversity and clinically problematic diagnosis and management distinguish it from MPE of secondary malignancies. The recent evolution of tumor grading, surgical techniques and their applications, and the emergence of targeted therapies have altered survival expectations and highlight the need for personalized approaches to optimize PM outcomes.

This 3-part article is an update of these selected concepts related to MPE. It complements the Essential Knowledge in Interventional Pulmonology Lecture Series presented at the 2023 AABIP Annual Conference, available for viewing on the AABIP website (https://aabip.memberclicks.net/essential-knowledge-in-interventional-pulmonology-series).

PART 1: UPDATE ON DIAGNOSTIC APPROACHES TO MPE

The approach to effective MPE diagnosis continues to evolve, with imaging, fluid sampling, and pleural biopsy all

playing a role in modern practice, depending on the clinical context.

Imaging and Pleural Sampling

Chest imaging modalities, including thoracic ultrasound (TUS), computed tomography (CT) scan, and positron emission tomography (PET) all effectively demonstrate the presence of a pleural effusion. TUS and CT scans are practical tests frequently used to detect findings suggestive of malignant pleural involvement. In one study, TUS distinguished benign from MPE with a sensitivity of 73% and specificity of 100% when pleural nodularity and pleural and diaphragmatic thickening were present.[4] Another study incorporated CT pleural abnormalities with various extrapleural and extrathoracic findings to derive a prediction score for MPE with a sensitivity of 88% and specificity of 94%.[5] PET/CT has both a high sensitivity and specificity for MPE. A recent systematic review and meta-analysis found that a visual/qualitative image analysis was superior to semiquantitative assessment, with a positive and negative likelihood ratio of 9.9 and 0.1, respectively.[6] Nevertheless, studies examining the utility of chest imaging to diagnose MPE are heterogeneous in design, data reporting, and patient population,[6–8] and the performance of TUS and CT remain inconsistent. For example, in one recent cohort study, the negative predictive value of using CT as a suggestive tool was only 64.9%.[9] Therefore, at present, chest imaging primarily serves a supplementary role in enhancing the suspicion of malignant pleural disease, which may be useful when more definitive diagnostic means are not possible. Future areas of investigation could focus on TUS assessment of tissue movement and strain and various CT machine learning algorithms, both of which have shown promise in evaluating nonmalignant pleural effusion (NMPE).[10–12]

Chest imaging does, however, play a central role in establishing MPE by guiding pleural sampling. US-directed thoracentesis with cytologic examination of pleural fluid remains the recommended first step in evaluating MPE.[13,14] Overall yield is ~50%[15,16] and varies due to many factors. Tumor type appears to be an important variable, with MPE cytologic yields highest from adenocarcinomas of various organs and lowest from mesothelioma.[16,17] Submitting fluid samples >50 to 100 mL or repeating thoracentesis more than once is unlikely to significantly enhance yield on an initial cytology-negative pleural effusion.[7,14,18–20] Depending on patient factors and local resource availabilities, transthoracic pleural biopsy may then be pursued for diagnosis. Chest imaging can successfully direct the clinician in this context.

TUS- and CT scan-guided pleural biopsy substantially improve MPE diagnosis, as "blind" transthoracic needle approaches often have yields that are similar or inferior to thoracentesis.[21–23] In one study, TUS-guided pleural biopsy increased yield over fluid cytology obtained by TUS-thoracentesis from 31% to 89%.[24] Similarly, in 2 separate studies, CT-guided pleural biopsy enhanced diagnosis over both "blind" biopsy[25] and TUS-guided biopsy.[26] In properly selected patients such as those with suggestive pleural abnormalities, an algorithmic approach incorporating TUS and CT-guided transthoracic pleural biopsy can achieve diagnostic sensitivity and accuracy of over 90% and help avoid more invasive sampling.[27]

Even though using PET/CT to target FDG-avid pleural disease is intuitive, its diagnostic role in this context is not clear. In the TARGET randomized controlled trial (RCT), PET/CT-guided pleural sampling was not superior to CT sampling in patients with a previously inconclusive pleural biopsy but with ongoing clinical suspicion for malignant pleural disease.[28] Repeating CT-guided sampling or a more invasive approach may be appropriate in these cases.

Pleural Fluid (PF) Biomarkers

Biomarkers are measurable substances that may assist in the prognostication, diagnosis, management, and monitoring of a disease. PF biomarkers can have diagnostic value within the setting of cytology-negative MPE and are the focus of substantial research. They may be used individually or in combination with other biomarkers and/or clinical variables. However, for biomarkers to be useful, they need to be accurate, reproducible, widely available, cost-effective, and have a short turnaround testing time. Unfortunately, to date, most PF biomarkers lack many of these attributes, and their application remains unstandardized, thus limiting their clinical use. While a comprehensive review of all candidate PF biomarkers is beyond the scope of this update, below is a brief summary of several that have the potential for future clinical application.

Soluble proteins (SPs) are widely available biomarkers. SPs studied in MPE include lactate dehydrogenase (LDH), adenosine deaminase (ADA), neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), carbohydrate antigen (CA)-125, CA15-3, CA19-9, fragment of cytokeratin (CYFRA) for carcinoma, among others. Generally, overall sensitivity of individual SPs for diagnosing MPE are consistently suboptimal (~50% or lower), while specificities can approach 100%.[7] In combination, for example with CEA + CYFRA21-1 in adenocarcinomas or when integrated with clinical characteristics using artificial intelligence and machine learning algorithms, performance improves but remains inconsistent, particularly diagnostic sensitivity.[29–32] In a meta-analysis, the serum LDH to PF ADA "cancer ratio" was found to have high diagnostic accuracy for MPE (97% sensitivity, 89% specificity).[33] However, this study was limited by using different threshold values and patient selection bias. In a separate analysis neither serum to PF-CEA ratio or serum to PF-CEA delta value added any diagnostic benefit to PF-CEA.[34] Pleural mesothelioma (PM)-specific SPs are discussed in Part 3.

Another important class of emerging biomarkers is cell-free (cf) molecules, such as DNA, mRNA, microRNA, and long-coding RNA. Malignant cells release these tumor-derived products which tend to be present in higher concentrations in the local visceral compartment compared with plasma. Consequently, assessing the presence and relative concentration of these molecules in fluid ("liquid biopsy") can be useful for diagnosing cytology-negative MPE and also assist in profiling the tumor genome for potential therapeutic targeting.[35,36] While immunohistochemistry (IHC) is the traditional standard for evaluating targetable genetic mutations and molecular markers in advanced malignant disease,[37,38] next-generation sequencing (NGS) has emerged as an efficient and comprehensive testing alternative for both tissue and cell-free fluid.[39,40] For example, Nong et al[39] compared the utility of IHC and an integrated NGS platform for detecting *EGFR* mutations and *ALK* and *ROS1* rearrangements within tumor tissue. NGS results were more informative and reliable than IHC staining for *EGFR* alterations, especially for the exon

19 region. NGS also increased the detection of *ALK* rearrangements and decreased false positive *ROS1* rearrangements of IHC, suggesting the need to confirm IHC-*ALK* negative and/or *ROS1* positive results with NGS.

NGS performance characteristics have also shown favorable results when applied to pleural fluid. In 2 recent studies, NGS pleural fluid cf-DNA testing was superior to plasma cf-DNA in the detection of actionable mutations in patients with lung adenocarcinoma-MPE.[36,41] In the study by Mahmood and colleagues, cf-DNA analysis was diagnostic in 90.7%, which was higher than cytology, biopsy, and plasma cf-DNA (48.4%, 88%, and 72.7%, respectively). PF cf-DNA analysis also detected unique mutations, possibly leading to a more thorough molecular profiling and clonal heterogeneity assessment. In another study, capture-based targeted sequencing of a 520 lung cancer–related genetic panel provided comprehensive profiling of cytology-negative MPE supernatant, including reliable EGFR mutational detection.[42] Nevertheless, despite the growing body of promising evidence supporting the diagnostic role of pleural fluid "liquid biopsy," as with SPs, cf-nucleic acid assays are limited by the need for standardization. They are also costly and have long turnaround times.

Finally, the tumor-immune microenvironment will likely serve as both a useful diagnostic and therapeutic landscape for MPE. The diagnostic utility of various immune-related biomarkers is under study. Family with sequence similarity 83 member A (FAM83A) is a recently discovered oncogene that is overexpressed in many cancers including non–small cell lung cancer (NSCLC). It modulates immune activity by impacting cytokine and chemokine profiles, altering the local extracellular matrix, and enhancing the recruitment of immunosuppressive cells.[43,44] A recent study by Liu et al[45] demonstrated FAM83A expression in 92.5% of MPE samples in lung adenocarcinoma patients, while 95.2% of non-neoplastic PF specimens were negative. This suggests FAM83A is a potentially useful diagnostic biomarker for MPE.

Macrophage profiling through flow cytometry also shows promise in distinguishing benign from MPE. Various tumor-associated macrophages (TAMs), such as CD14 +CD163+, can promote cancer development through immunomodulatory effects.[46] In one study CD163+CD14 + TAMs were found at a substantially higher concentration in MPE compared with NMPE.[47] Using a cutoff level of 3.65%, TAM expression as an MPE diagnostic biomarker had a sensitivity and specificity of 81.2 and 100%, respectively. The authors also commented that by estimating PF CD163+CD14+ cells, the diagnosis could be obtained one week earlier than by cytologic exam. In another study, using a 39.8% threshold the diagnostic accuracy of $CD206^{+}CD14^{+}$ TAMs for lung cancer-MPE showed an AUC of 0.98, with 88% sensitivity and 100% specificity.[48] However, the small size of these studies thus far limits further application.

In summary, chest imaging may assist in distinguishing benign from malignant pathology. However, performance remains inconsistent across modalities in definitively establishing MPE based on radiographic features alone, and cytohistologic confirmation remains the diagnostic gold standard. Therefore, for suspected MPE patients in whom the main goal is tumor diagnosis and characterization, the primary role of chest imaging remains as an adjunct to guiding thoracentesis or pleural biopsy (Fig. 1). The accessory role for PF biomarkers is rapidly evolving but remains limited due to suboptimal diagnostic sensitivity of individual tests and lack of clinical utility analysis, validation and standardization of various approaches. At present, PF biomarkers may supplement more definitive diagnostic methods but should not be used solely to exclude malignancy in the setting of a pleural effusion.[7] Combining diagnosis with various therapeutic approaches in properly selected patients is discussed in Part 2.

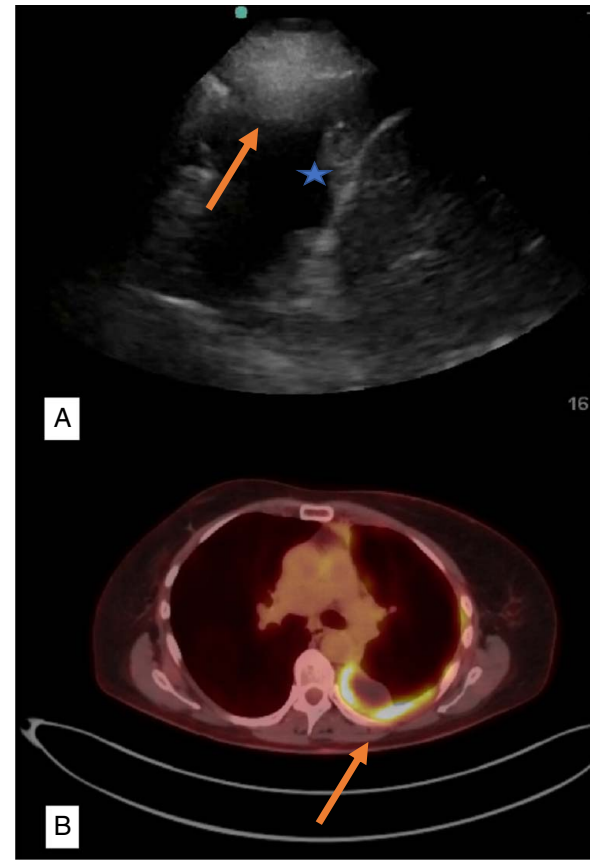

FIGURE 1. (A) Ultrasound of a patient with a malignant pleural effusion demonstrating pleural-based masses (star) and pleural thickening (arrow). (B) Corresponding PET CT confirms diffuse FDG-avid parietal pleural thickening (arrow).

PART 2: UPDATE ON THE MANAGEMENT OF MPE

The formation of MPE is governed by complex tumor-host interactions that promote robust influx and ineffective efflux of fluid, leading to large and often recurrent accumulation.[49] Therefore, while initial thoracentesis helps characterize MPEs and assess symptom response, subsequent pleural interventions are often required for more definitive palliation.[50] Furthermore, it appears that at initial diagnosis the risk of MPE recurrence is independent of tumor chemosensitivity or presence of targetable mutations.[7,51,52] Consequently, management should be efficient and definitive but also cognizant of patient-associated factors that impact important outcomes and influence the cost-effectiveness of the chosen approach. To supplement effective palliation, various targeted therapies directed at the underlying primary tumor are under

investigation to help mitigate fluid reaccumulation. This section will review aspects of the palliative approach to and emerging directed therapeutics of MPE.

Multimodal Approaches to Managing MPE

The primary definitive approaches to MPE palliation are pleurodesis, which is the fibrotic obliteration of the pleural space, and placement of an indwelling pleural catheter (IPC). Each method has its respective advantages depending on multiple factors, and both aim to palliate the patient by controlling fluid reaccumulation and reducing the need for repeat procedures and health care utilization. While there are robust data supporting the success of each strategy when applied individually, the interventions may be combined in various ways to potentially further improve outcomes.

Given the efficacy and safety of IPCs, they are commonly utilized for managing a recurrent MPE. IPCs have the advantage of being placed percutaneously under local anesthesia and in the ambulatory setting and are successful in minimizing the need for future pleural procedures ($<10\%$).[53] Furthermore, "spontaneous" pleurodesis occurs in up to 50% of patients which allows for catheter removal.[54] In comparison, the traditional means of chemical pleurodesis is the instillation of a sclerosant through a chest tube (eg, talc "slurry"). This approach requires several days' hospitalization and may fail in up to 20% to 25% of cases, necessitating additional pleural intervention.[1,3,54] However, chemical pleurodesis avoids the need for a chronic catheter and its attendant follow-up care resources, such as supplies and nursing.[55]

For patients in whom both pleurodesis and IPC removal are important and achievable treatment goals (eg, life expectancy >30 days and presence of expandable lung), these 2 approaches can be combined in an ambulatory setting to enhance the efficiency of MPE palliation.[7] This recommendation is primarily supported by the IPC-Plus RCT.[56] Bhatnagar and colleagues randomized 154 patients with MPE and expandable lung to undergo IPC placement, followed on day 10 by either talc slurry administration or placebo via IPC, all performed in an outpatient setting. The talc+IPC group had a significantly higher rate of successful pleurodesis at day 35 (43% vs. placebo 23%, $P=0.008$), which persisted at day 70 (talc 51% vs. placebo 27%, $P=0.003$). Secondary end points, including improvements in MPE-related symptoms and quality of life, also favored the talc+IPC group.

Multimodal management of MPE can also be achieved by medical thoracoscopy (MT). Also known as "pleuroscopy," MT is practiced at many centers and may be performed under moderate sedation, monitored, or general anesthesia. While talc administration by MT has not been shown to be superior for achieving pleurodesis compared to delivery via a chest tube,[1,57] MT has several potential advantages when applied in a multimodal fashion. Reliable pleural biopsy for diagnostic and molecular analysis, instillation of the pleurodesis agent (ie, "poudrage"), and IPC placement can all be performed during a single procedural setting. The success of combining pleuroscopic poudrage (PP) with concurrent IPC placement has been evaluated in 2 small observational studies. Reddy et al[58] treated 30 patients with this protocol and found that 92% achieved pleurodesis (and IPC removal) after a median of 7.54 days. The median hospitalization time was only 1.79 days. Bouajoude et al[59] compared a cohort receiving PP with IPC placement (PP + IPC; $n=29$) to a historical control group who had received PP only ($n=33$). They found high rates of pleurodesis success in both groups (PP + IPC 92% vs. PP 82% at 30 days, $P=0.431$; median IPC placement duration of 6 d) but a decreased length of hospitalization in the PP+IPC group (median 3 d vs. PP alone 7 d, $P=0.015$). Importantly, 96% of the patients in the PP + IPC group that initially achieved pleurodesis sustained this effect at 6 months, suggesting the durability of this combined approach.

Thoracoscopic inspection of the lung and pleural space can also provide valuable information that helps refine further management. For example, intraoperative histologic analysis may be used to confirm malignancy before proceeding with definitive intervention in a single anesthetic event.[60] Simple pleural adhesions and loculated areas can be mobilized with the aid of forceps or blunt instruments, which may enhance the chance of lung expansion and pleurodesis. Supporting this, Suzuki et al[61] found an increased rate of spontaneous pleurodesis in patients undergoing thoracoscopic IPC placement versus Seldinger IPC placement (53% vs. 28%, $P=0.011$). This advantage was further accentuated in the cohort with loculated effusions (67% vs. 21%, $P=0.009$). Other studies have corroborated this finding.[62] In contrast, IPC placement alone is an option if there is evidence of lung entrapment (eg, pleural rind, extensive loculations).

Despite the potential of multimodal MT, there remains a paucity of data rigorously evaluating its advantage over unimodal or less invasive techniques. A multicenter RCT (TACTIC) evaluating PP + IPC versus PP is currently underway to help address this gap.[63] Individualizing the approach by properly identifying clinical needs, understanding patient preferences and goals, and shared decision-making remains crucial for success. Multimodal MT can be considered for the following select groups with symptomatic, recurrent MPEs (Fig. 2):

- Patients without lung entrapment
- Patients with good functional status (eg, ECOG 0-2)
- Patients better suited for short-term IPC only
- Patients also requiring pleural biopsy for tumor diagnosis or characterization
- Patients amenable to postprocedure hospitalization

Cost Considerations

Cost-effectiveness of a particular approach to managing MPE requires maximizing therapeutic efficacy and safety while mitigating health care expenditure. Primary cost contributors include the procedure itself, downstream associated resource utilization (such as supplies and nursing care), and the need for both immediate and future hospitalization. Patient comorbidity and life expectancy accentuate each of these factors. Therefore, navigating the cost impact of MPE management requires insight into treatment options, their associated practical and performance characteristics, disease-related factors, as well as patient prognosis and functional status. Clinical practice guidelines endorse such an individualized management strategy based on the various advantages and disadvantages of each approach, as detailed above.[3,7]

Puri et al[64] used decision tree analysis to investigate the relative cost-effectiveness of repeat thoracentesis (RT), IPC, bedside chemical pleurodesis (BP), and thoracoscopic pleurodesis (TP) for patients with either an expected 3-month or 12-month survival. The model design assumed an

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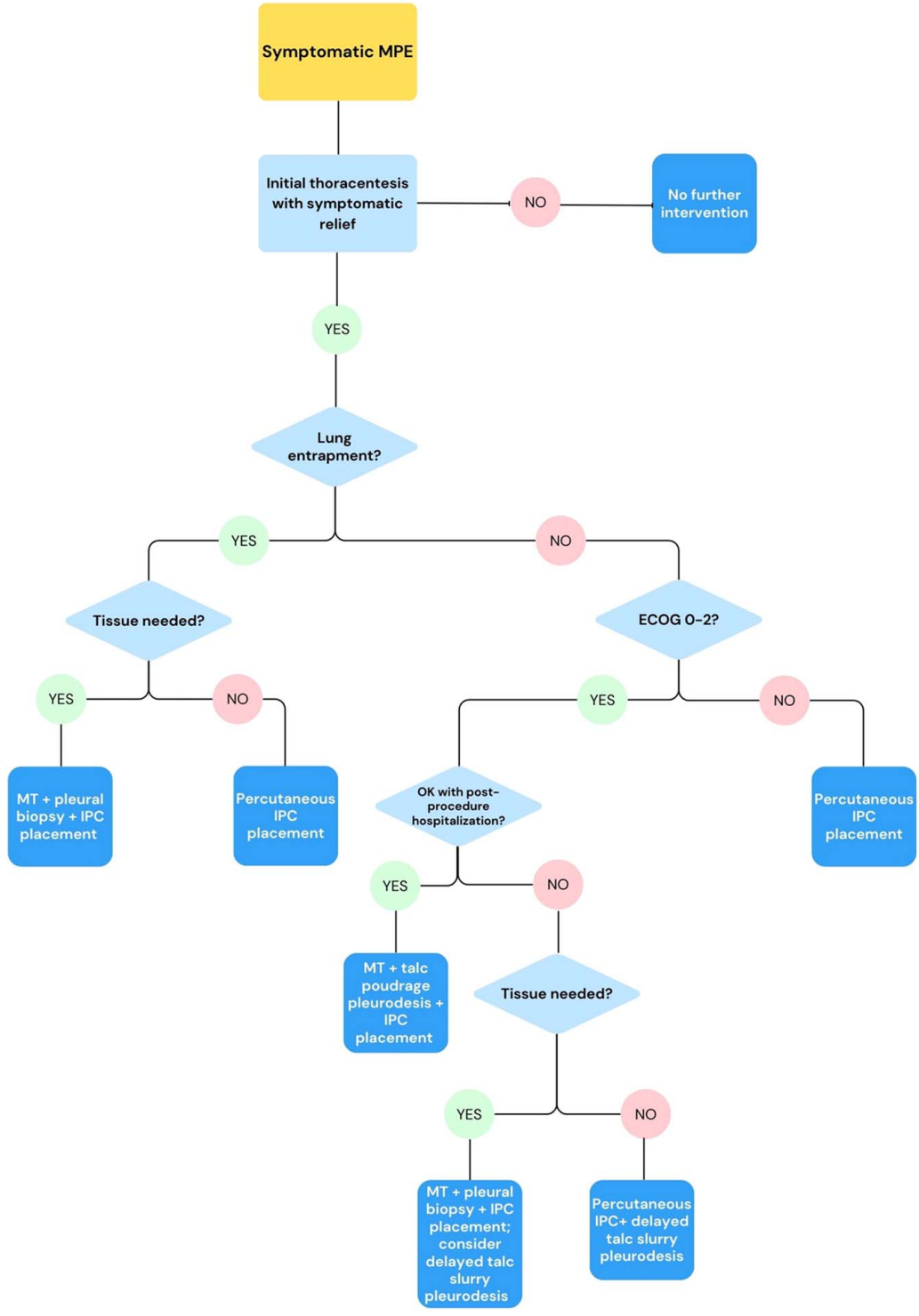

FIGURE 2. Suggested approach to the multimodal management of malignant pleural effusion. ECOG, Eastern Cooperative Oncology Group score; IPC, indwelling pleural catheter; MPE, malignant pleural effusion; MT, medical thoracoscopy

uncomplicated pleural space, expandable lung, and tolerance for anesthesia in every patient. Medicare allowable charges were used and incremental cost-effective ratio (ICER), which is the cost per quality-adjusted life years gained over the remaining lifetime for the patient, was calculated.

For an expected survival of 3 months, the investigators found RT was the least expensive treatment ($4946) but

provided the fewest (0.112) quality-adjusted life years (QALYs). This finding is intuitive since while thoracentesis provides instant symptom relief, MPE recurrence necessitates repeat procedures. Therefore, the cost-benefit ratio of thoracentesis is usually unfavorable, especially for patients with life expectancy of >30 days. Notably, IPC was more cost-effective than either pleurodesis approach (BP or TP). Reasonably varying the effectiveness and morbidity estimates for each pleurodesis option did not change the outcomes in the 3-month survival model. This suggests that in MPE patients with a fairly limited lifespan, both BP and TP approaches are associated with expenditures that do not justify the qualitative results.

In contrast, for an expected 12-month survival, the study found that BP was less expensive and more effective than both RT and IPC. The cost of each approach was BP-$13,057, IPC-$13,224, TP-$19,074, and RT-$21,377. TP was more effective than BP but ICER for TP over BP was greater than $250,000 and not sensitive to varying effectiveness and morbidity of both pleurodesis options across a clinically plausible range. In the TAPPS RCT, which demonstrated similar pleurodesis efficacy between thoracoscopic and bedside approaches, both total quality-adjusted life years and mean costs at 6 months were also similar, including after multiple imputation of missing cases.[65]

Other studies have also demonstrated the impact of prognosis on the cost-effectiveness of MPE management. Olden and Holloway[66] showed talc pleurodesis was as effective but less costly than IPC overall, though IPC became more cost-effective when life expectancy was <6 weeks. Penz and colleagues, using data from the TIME-2 trial, showed that the overall costs of IPC and talc pleurodesis were similar.[54,55] However, in patients with survival of <14 weeks, IPC was significantly less costly, with a mean cost difference of more than $1000, due to mitigation of attendant supply and home nursing-related expenditures. Collectively, the data suggest that IPC is the more cost-effective approach in MPE patients with a relatively limited life expectancy, particularly when home nursing care costs are minimized.

To evaluate cost-efficiency based on IPC management approach, Shafiq and colleagues used a decision tree model and data from the ASAP, AMPLE-2, and IPC-PLUS trials.[55,67–69] Both daily IPC drainage and combined IPC-talc pleurodesis were clinically more effective than symptom-guided drainage. However, daily drainage was not a cost-effective strategy in any scenario due to the high costs associated with home labor and supplies, resulting in an ICER of $2,474,612/QALY over symptom-guided drainage. IPC-talc was a cost-effective alternative to symptom-guided drainage, with an ICER of $59,729/QALY, but symptom-guided drainage was most cost-effective for a life expectancy of <4 months. Based on these results, when economic considerations are prioritized, the authors recommended the IPC-talc approach for candidate MPE patients with life expectancy greater than 4 months and symptom-guided drainage for all others.

As patient prognosis is a major factor dictating both practicality and cost-effectiveness of MPE management, its proper assessment is important. However, estimating life expectancy remains problematic in the MPE clinical setting. The development and implementation of prognostic scoring systems have been limited by heterogeneous cohorts, incomplete or imprecise prediction scores, and a rapidly evolving oncologic molecular and therapeutic landscape. For example, the LENT[70] and PROMISE[71] scores currently remain the only externally validated prognostic scores in MPE. However, they were developed using databases of a heterogeneous group of primary malignancies and with lung cancer *EGFR*-mutation prevalence of about 12% to 15%. In contrast, the SELECT prognostication model was developed in an Asian population with higher *EGFR*-mutation prevalence and was found to be more accurate than both LENT and PROMISE scores, although the study may have been confounded by baseline functional status.[72] In addition, a single-center observational study found that the LENT score was not prognostic for patients diagnosed with pleural mesothelioma.[73] Furthermore, LENT provides only 3 risk groups, each with defined median survivals (319, 130, and 44 d), while the PROMISE score is designed to predict 3-month survival, but not beyond. These factors may limit clinical utility in MPE patients.

Such factors were further highlighted by the Breast and Lung Survival Score (BLESS) Models, which developed a continuous-risk prediction model for breast and lung cancer-associated MPE.[74] The investigators found the disease-specific BLESS models more accurately represented survival in these groups compared with LENT and PROMISE, likely due to accounting for effect-measure modifications between predictors. As with biomarkers, the modeling for MPE-related life expectancy is likely to continue to evolve as additional prognostic variables are incorporated through a better understanding of oncobiology and the application of artificial intelligence and machine learning methods (Table 1).

Targeted Therapies

Targeted therapies (TTs) supplement palliative approaches by exploiting various oncobiological mechanisms that drive the formation and persistence of MPE. TTs for MPE include angiogenic inhibitors, which mitigate tumor-mediated vasoactivation and angiogenesis; immunomodulating agents targeting pathways that promote tumor survival and pleural carcinomatosis; and direct oncolytic agents (Table 2). As with targeted therapies in another malignant disease, this is a rapidly evolving landscape with therapies that remain either investigational or in the early phases of clinical implementation.

The vascular endothelial growth factor (VEGF) pathway is an important target for directed therapy. VEGF is a primary mediator of angiogenesis in MPE, and its levels in the pleural fluid may correlate with pleural disease progression and prognosis.[75] Bevacizumab (BEV) is a humanized monoclonal antibody that blocks the binding of circulating VEGF to its receptors. Two prospective studies evaluated intravenous BEV combined with chemotherapy (carboplatin and pemetrexed) in nonsquamous NSCLC.[76,77] They showed response rates ranging from 46% to 61%, disease control rate of 78.6% to 87.0%, and OS of 11.7 to 18.6 months. BEV efficacy as an intrapleural agent for MPE secondary to lung cancer was reviewed in a meta-analysis of 11 RCTs.[78] Compared with cisplatin alone, the combination of cisplatin and intrapleural BEV showed a significant increase in response while decreasing chest pain, dyspnea, and MPE VEGF expression. BEV did not seem to confer any significant added toxicity compared with chemotherapy alone. In a phase 2 study, administration of cediranib, an oral tyrosine kinase inhibitor (TKI) targeting the VEGF receptor, showed an increased puncture-free

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TABLE 1. Description of Scoring Systems Used for the Prognostication of Malignant Pleural Effusions

Scoring system (year published)	Malignancies included	Variables included	Survival/mortality estimates	Notes
LENT[70] (2014)	All types of malignancies	Pleural LDH, EGOG score, NLR*, tumor type	3 risk stratification groups with associated median survival (days)	Easiest to calculate Requires pleural fluid analysis
PROMISE[71] (2018)	All types of malignancies	ECOG score, tumor type, prior chemotherapy, prior radiation, hemoglobin, white blood cell count, C-reactive protein	4 risk stratification groups with associated percent risk of death within 3 mo	Only predicts 3 months survival Requires pleural fluid analysis
SELECT[72] (2020)	All types of malignancies	Sex, ECOG score, Leukocyte count, *EGFR* status, prior chemotherapy, tumor type	Estimated 90-d mortality	Asian pleuroscopy database cohort; may not be broadly applicable
BLESS[74] (2021)	Lung cancer Breast cancer	*All:* ECOG score, pleural LDH, cytology and protein *Lung:* surgery within 30 d, bilateral effusion *Breast:* NLR*	Continuous survival estimate	Only scoring system with a continuous survival estimate Requires pleural fluid analysis

ECOG indicates Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; LDH, lactate dehydrogenase; NLR, neutrophil-lymphocyte ratio.

interval and puncture-free survival after baseline therapeutic thoracentesis.[79] Whether this potential benefit extends to other TKIs or to MPE patients with actionable mutations is unclear. For example, in a recent study that evaluated 229 patients with epidermal growth factor receptor (EGFR)-positive lung cancer receiving osimertinib, of which 84 had MPE before TKI administration, the presence of MPE did not appear to impact survival.[80]

Antiangiogenic therapies independent of the VEGF pathway have also been explored. Endostatin inhibits proliferation, migration and differentiation of vascular endothelial cells through multiple mechanisms, thus promoting cancer cell apoptosis and reducing metastatic progression. A meta-analysis in 2016 evaluated 13 RCTs and demonstrated a significantly improved disease control rate (pooled odds ratio of 2.97) in patients receiving intracavitary endostatin with chemotherapy compared with chemotherapy alone.[81] Although myelotoxicity, gastrointestinal toxicity, and liver and renal injuries are commonly associated with the use of endostatin combined with chemotherapy, these were not significantly higher compared with chemotherapy alone.

Various immunotherapeutic approaches targeting the complex pleural tumor microenvironment have been investigated for MPE.[82] Interleukin-2 (IL-2) reverses cytotoxic T-cell exhaustion by several mechanisms, including reducing the expression of PD-1 and increasing interferon-gamma (IFN- γ) secretion. These effects help limit tumor-immune escape. A meta-analysis of 1279 patients receiving thoracic injection of IL-2 showed a 4.1-fold higher response rate, 7.8-fold higher disease control rate, and significantly improved quality of life compared with cisplatin-based chemotherapy alone.[83] Interleukin-based therapies appear to be safe, albeit with dose-dependent reactions including fever and flu-like syndrome.

Another emerging therapeutic strategy for MPE is gene-mediated cytotoxic immunotherapy (GMCI). An adenovirus vector is commonly used for gene transfer, and cytotoxicity is achieved through various mechanisms. One approach delivers the herpes simplex thymidine kinase gene to tumor cells (administered intrapleurally), which then selectively phosphorylates an antiherpetic prodrug (administered intravenously). This generates nucleotide analogs leading to tumor DNA damage and apoptosis. A study evaluating this method enrolled patients with NSCLC-, pleural mesothelioma (PM)-related and breast cancer–related MPE and demonstrated a disease control rate of 71% and median survival of 25.7 months post GMCI therapy.[84] In another model, the safety and feasibility of using intracavitary interferon gene transfer for immunogenic antitumor therapy was demonstrated in a phase 1 clinical trial of 10 patients with PM or MPE.[85] The study also found an antitumor immune response of 70%. GMCI and adenoviral vector therapies are associated with flu-like illness that can escalate to cytokine release syndrome and be associated with liver function abnormalities.

The utility of immune checkpoint inhibitor (ICI) therapy, which has become a mainstay of managing primary lung and other malignancies when administered systemically, remains understudied in the MPE population. There is accumulating evidence that the immunogenic effects of cytotoxic chemotherapy enhance the immunomodulatory benefits of ICIs.[86] This is supported by a recent multicenter retrospective analysis of 257 patients with driver-negative nonsquamous NSCLC-related MPE that demonstrated a

TABLE 2. Novel Targeted Therapies Evaluated for Treatment of Malignant Pleural Effusions

Type	Primary mechanism	Examples
Anti-VEGF therapy	Binds to circulating VEGF to prevent activation of VEGF-R, thus inhibiting downstream intracellular angiogenic signals	Bevacizumab
Anti-angiogenic TKI therapy	Binds to and inhibits VEGF-R, thus inhibiting downstream intracellular angiogenic signals	Cediranib
Endostatin therapy	Inhibits endothelial cell proliferation, differentiation and migration by multiple mechanisms, thus preventing angiogenesis	Recombinant Endostatin
Immunotherapy	Multiple mechanisms, including the reversal of T-cell exhaustion through reduced PD-1 expression and enhanced interferon gamma secretion	Interleukin-2
Intrapleural immunogene therapy	Various mechanisms, including selective tumor apoptosis through pro-drug activation and stimulation of immunogenic response	Thymidine kinase, Interferon genes (delivered using adenoviral vectors)
Oncolytic virotherapy	Infection of tumor cells by tumor-specific viruses leading to lysis and secondary immunogenic response	Modified HSV

PD-1 indicates programmed cell death protein-1; TKI, tyrosine kinase inhibitor; VEGF-R, vascular endothelial growth factor-receptor.

longer progression-free survival (PFS) in patients receiving combined ICI-chemotherapy compared with those receiving ICI monotherapy (11.1 vs. 3.9 mo, $P = 0.041$), regardless of PD-L1 status.[87] In this study, synergistic BEV did not appear to impact PFS. In a separate retrospective study of 323 similar patients, combined chemotherapy with either an ICI or BEV had superior PFS, OS, and MPE control compared with chemotherapy alone.[88] PD-L1 tumor proportion score dictated the better synergistic option (ICI if PD-L1 > 50%, BEV if <1%). There is little data on intrapleural anti-PD1/PDL1 therapy. In both a preclinical mouse model and a small human clinical study, intrapleural injection of an anti-PD1 monoclonal antibody appeared to favorably control NSCLC-associated MPE.[89]

Finally, oncolytic virotherapy utilizes tumor-specific viruses to infect and lyse tumor cells and consequently stimulate an antitumor immunogenic response. The clinical evidence for this model is evolving but remains scarce. Previously studied approaches include a genetically altered herpes simplex virus type 1 (HSV1) that conditionally replicates in active tumor but not in normal cells. In a phase 1 trial of 13 patients with MPM-related MPE undergoing oncolytic HSV therapy, 46% of patients had stable pleural disease at 60 days and a median survival of 15 months from treatment initiation.[90]

In summary, the mainstay for the management of MPE remains palliative intervention, and multimodal approaches in properly selected patients may improve various outcomes. Individualizing the management strategy is essential to maximizing efficacy, practicality, and cost-effectiveness. Life expectancy is an important contributor to these ends, but clinical prognostication remains imprecise and more advanced and disease-specific models are needed. In parallel, evolving therapies targeting oncogenesis and tumor propagation are a promising step toward more complete personalized treatment for MPE. However, many remain investigational or in early-phase clinical trials and are largely unincorporated into formal guideline recommendations. Better profiling of oncogenetics and host-tumor interactions will guide future therapeutic decisions and ultimately help merge directed with palliative MPE therapy.

PART 3: UPDATES IN PLEURAL MESOTHELIOMA

Pleural mesothelioma (PM) is an extremely aggressive cancer of the mesothelial lining of the pleural cavity, primarily associated with exposure to asbestos. Historically, treatment options for PM have been limited, resulting in survival between 1 and 2 years. However, recent scientific advances have offered new diagnostic tools and therapeutic options for patients with PM.

Genomics and Tumor Profiling

Recent research focusing on the genetics of PM have made it increasingly apparent that PM exhibits significant genomic heterogeneity, with most cases featuring loss of function in tumor suppressor genes due to mutations or copy-number alterations.[91] Although the overall mutational burden in PM is lower than in other solid tumors, key tumor suppressor genes such as NF2, BRCA-associated protein 1 (BAP1), and CDKN2A are frequently affected. Mutations in oncogenes, particularly EGFR and PIK3CA, are also possible.[92] The genomic diversity of PM underscores the need for personalized approaches to diagnosis and treatment.

While thoracoscopic biopsies successfully diagnose PM in up to 98% of cases, the yield of PF cytology is poor.[17,93] Therefore, PM serves as an ideal space to develop biomarkers for diagnostic purposes. BAP1 mutations have garnered significant attention in recent studies due to their critical role in various cell survival functions. BAP1 is involved in DNA repair and chromatin modulation and serves as an essential epigenetic regulator.[94] Somatic mutations in BAP1 are present in up to 60% of PM cases. Mutations can also occur in the germline and are associated with BAP1-Tumor Predisposition Syndrome (TPDS). PM patients with BAP1 mutations exhibit a worse prognosis and distinct responses to therapy, highlighting the importance of BAP1 profiling. Other markers, such as soluble mesothelin-related peptides (SMRP), osteopontin and blood fibulin-3, have only modest diagnostic performance characteristics, especially in the early stages of PM and when used in isolation.[95]

Classification, Grading, and Staging

The classification of pleural mesothelioma has evolved over the last decade, with the removal of the term "malignant" and the recognition that all histopathologic lesions are either malignant or inevitably malignant if associated with certain mutations.[96] In situ disease is so rare in mesothelioma that its existence is often debated, but the most recent guidelines allow for this diagnosis if there is identification of molecular markers BAP1, MTAP or

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CDKN2A and single cell layer disease. Cytologic diagnosis is now possible but requires the coidentification of molecular markers known to be associated with PM. The exception is sarcomatoid disease, where BAP1 is rarely mutated, and GATA3 may be a more relevant marker.

Well-differentiated papillary mesothelioma is now referred to as well-differentiated papillary mesothelial tumor (WDPMT). Although not classified as mesothelioma, these lesions progress to mesothelioma in 70% of cases, despite lacking CDKN2A or BAP1 mutations.

The 3 primary histologic subtypes (epithelioid, sarcomatoid, and biphasic) remain, with changes in their specifications. Epithelioid mesothelioma is now stratified based on histologic features as low or high grade.[97] Pleomorphic or transitional features are recognized as poor prognostic indicators, behaving more like sarcomatoid. PM exists on a spectrum from epithelioid to sarcomatoid, and the term biphasic requires an account of the relative distribution of each component.

The eighth edition of the staging system for PM, released in 2018 by the International Association for the Study of Lung Cancer (IASLC), brought several changes.[98] T1a and T1b were combined into T1, reflecting their similar prognoses. Tumor thickness, although not yet included as a determinant of T stage, is recognized as important and likely to be added in the future. Hilar and subcarinal nodal involvement is now merged into a single category (N1), emphasizing the number of nodes involved as the key prognostic factor, not the specific nodal stations.[96]

Surgical and Systemic Therapies

While pleural mesothelioma remains challenging to treat, novel surgical techniques and chemo-immunotherapeutic regimens have improved survival for select patients. Surgery remains essential in many cases for diagnosis staging and palliation, but the survival benefit of complete resection is still debated. Several retrospective studies have shown a benefit in select patients, but this has never been replicated in a prospective, randomized fashion. Resection is not beneficial in sarcomatoid disease, and pleurectomy-decortication where the lung is spared is increasingly favored over extrapleural pneumonectomy.[99] Mesothelioma and Radical Surgery 2 (MARS2) trial, a randomized-control trial comparing the addition of surgical resection to medical therapy, revealed a decrease in survival in those patients that had extended pleurectomy-decortication and chemotherapy compared with chemotherapy alone (19 vs. 24 mo, respectively). This has led many to conclude that surgical resection may no longer have any role in the treatment of PM. However, there are several study limitations that may affect its generalizability to all patients. Many of the resectable surgical patients had advanced-stage disease and many also had nonepithelioid disease, both of which are known to decrease the likelihood of success with surgery. In addition, a lower proportion of surgery patients completed adjuvant systemic therapy and less received immunotherapy compared with systemic therapy alone patients. Given the currently available evidence, surgical resection may still be considered for early-stage epithelioid PM patients with good performance status as part of multidisciplinary team in experienced centers and after extensive patient counseling.[100]

The role of radiation therapy in the management of PM is evolving, with the primary use for the palliation of pain. Prophylactic radiation at biopsy sites is no longer recommended as it has not been shown to prevent tract seeding.[99] Intensity-modulated pleural radiation therapy (IMPRINT) technique is a novel technique being explored as an adjuvant therapy.[91] Tumor treating fields (TTF), which use low-intensity, alternating electrical current to interfere with cancer cell division, show promise as a future therapy now entering phase 3 trials.[99] As new techniques continue to be identified and additional studies are conducted, it will remain critical for radiation therapy to be considered in the multimodal treatment pathway for PM patients.

Most patients diagnosed with PM have unresectable disease, therefore systemic therapy remains the standard of care. Until very recently, this therapy included platinum-pemetrexed (4 to 6 cycles) followed by maintenance BEV, as shown in the MAPS study.[101] CheckMate 743 studied 603 patients in a randomized controlled setting to assess the benefit of combination nivolumab-ipilimumab versus standard of care cisplatin-pemetrexed.[102] The critical finding of this study was an increased survival in those patients receiving immunotherapy (18.1 mo) versus those receiving chemotherapy (14.1 mo) without any increase in morbidity. Based on these results, the FDA has since given approval for the use of this therapy in the treatment of unresectable PM. This extended survival was some of the best reported to date using medical therapy alone for the treatment of PM. The survival benefit with immunotherapy was seen in both epithelioid and nonepithelioid disease, indicating one of the few therapies that have shown any benefit in the extremely treatment-resistant nonepithelioid PM. Based on the results of this study, immunotherapy is a promising new frontier for the treatment of PM. Additional studies are needed to assess the role of PD-L1 status and the generalizability of these results to potentially resectable patients. For example, nivolumab is now FDA approved for all unresectable PM patients, regardless of PD-L1 status.[103] Molecular targets like PARP inhibitors are under investigation, and immunologic therapies like CAR-T or dendritic cell, may play a role in the future.[91]

In conclusion, there has been remarkable progress in mesothelioma research and therapy. Genomic insights, updated classification, staging, and evolving treatment strategies offer renewed hope for PM patients, highlighting the importance of personalized care and a multidisciplinary approach. While challenges remain, ongoing research promises to enhance our understanding and improve outcomes for those affected by this devastating disease.

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