Review

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Re-Evaluating Breast Malignant Pleural Effusion: Toward Evidence-Based, Precision-Aligned Care with Organoids

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Review

Re-Evaluating Breast Malignant Pleural Effusion: Toward Evidence-Based, Precision-Aligned Care with Organoids

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Abstract

Breast cancer–associated malignant pleural effusion (MPE) is a common and debilitating manifestation of advanced disease, yet current management is largely limited to indwelling pleural catheters and chemical pleurodesis and offers only transient palliation without addressing the underlying tumor biology. We propose that integrating patient-derived organoid modeling of pleural tumor cells with characterization via technologies like next-generation sequencing could shift MPE care from symptom management toward precision intervention. Organoid-based drug testing enables ex vivo evaluation of local therapeutic agents, including intrapleural chemotherapy, immune modulators, and bispecific antibodies, while paired genomic profiling may reveal actionable resistance pathways unique to pleural metastases. Together, these approaches could identify rational, localized combination therapies that improve local control, reduce effusion recurrence, and ultimately extend survival. By coupling functional and molecular analyses directly to the pleural compartment, we envision a translational framework that redefines breast MPE from a purely palliative condition to one amenable to mechanism-driven, patient-tailored therapy.

Keywords: malignant pleural effusion; organoid; indwelling pleural catheter; pleurodesis; standard-of-care; next-generation sequencing

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women and the most fatal. Worldwide, approximately 2.3 million women per year are diagnosed with this biologically unique and frequently aggressive malignancy and approximately 670,000 succumb annually [1]. While the risk of breast cancer increases with age and the peak age of diagnosis in Western countries is 60, those affected may also be premenopausal [2] with significantly reduced quality of life [3]. Despite advances in treatment, metastatic disease is generally considered incurable [4].

It is estimated that 7-23% of patients with breast cancer will develop a malignant pleural effusion (MPE) [5)] with subsets of metastatic breast cancer patients having an organ specific predilection for the pleural space [6]. Malignant pleural effusion results from metastasizing cancer cells, extravasating the bloodstream or lymphatic system and invading the pleural space leading to fluid accumulation. As many as 1 million individuals per year are estimated to be affected by MPE worldwide [7] and breast cancer is superseded only by lung cancer as the underlying etiology [5]. Patient quality of life is poor and median survival time is 6-18 months for breast-derived MPE [8–10]. Clinical presentation of MPE most frequently involves dyspnea, impaired chest wall movement and dysfunction of the diaphragm [11]. These frequently debilitating symptoms add further to the discomfort and psychological suffering of an already mentally and physically burdensome disease [12,13]. The tumor spread underlying MPE pathogenesis is in part promoted by the dysregulated formation of leaky

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tumor neo-vasculature that is part of metastatic cancer pathogenesis [14,15]. Tumor-driven vascular growth factors [15] and a purported cancer promoting pleural immune environment [16] are driving factors for malignant progression and often voluminous fluid accumulation.

1.1. Standard-of-Care

In the Western world, MPE is regarded as a resulting from the end stage of an incurable malignancy. Driven by a belief in the inevitability of finality and by healthcare directives frequently concerned with the optimal economics of care, treatment is in many instances is directed predominantly to symptomatic, mechanical palliation [17]. While the ultimate goal is to reduce physical symptoms, economics are a central consideration, with efforts made to minimize hospital stays and treatment costs [11,18,19]. Palliative strategy education efforts seek to inform oncologists of the best effusion management strategies as developed by the American Thoracic Society (ATS) the Society for Thoracic Surgeons (STS) and the European Association for Cardio-Thoracic Surgery (EACTS) among others [20]. While post-treatment quality-of-life measures have been considered and integrated within treatment strategies, attempts to measure psychosocial impacts of mechanical treatments have been inconsistent [21]. Furthermore, patients are predisposed to multiple complications including discomfort or infections that have been historically under-recognized but cause physical and psychological implications that negatively impact quality-of-life [22].

Despite clearly formulated guidelines [20], palliative treatments can be applied inconsistently depending on location, local expertise or a physician's experience [23,24]. The lack of effective or perceived effective systemic therapy strategies for MPE leaves the management of these suffering patients most often to surgical services or interventional radiology, which can be superb in centers of excellence and potentially deficient in "safety-net" hospitals [25,26]. While some advances have occurred in recent years, these mechanical treatments remain frequently painful, body image altering and potentially morbid [11,27]. Although well-trained thoracic surgeons are skilled in palliative mechanical solutions for MPE, enhanced systemic or regional therapies may offer the possibility of MPE control while better addressing underlying disease and would therefore be welcomed [26]. Amongst cancer patients and care providers there has been long-standing recognition that treatment should be personalized to the patient and consider wide-ranging individual factors [26,28].

A primary mechanical treatment approach which has recently gained traction is the placement of an indwelling pleural catheter (IPC), which is selectively applied based on lung expansibility and characteristics of the patient or effusion [29,30]. Here, a catheter is tunneled under the skin and into the intrapleural space. This allows individuals to undergo continuous or intermittent drainage in an ambulatory home environment [26,31]. The use of IPC has been shown to be successful at reducing symptoms and is often touted as patient-centric [32] but despite the apparent convenience of ambulatory repeat drainage-on-demand, multiple undesirable side effects have been reported. These include IPC-related infections, IPC-site metastasis, pain, itching, pleural fluid loculation, and issues with the IPC itself including catheter blockage and IPC fracture leading to a catheter fragment being retained [22,33]. Furthermore, patients report negative impacts on their wellbeing and quality-of-life that include anxiety and altered relationships [21,34].

A commonly employed alternative approach recommended by expert organizations is pleurodesis. This amounts to a physical obliteration of the intrapleural space by surgically administered, abrasive or inflammation-inducing agents such as dry talc or talc slurry between the pleura [28,35]. First described by Norman Bethune in 1935 [11,26] chemical pleurodesis remains a common course of treatment in the modern era. One recent study reported that 22.7% of MPE patients were treated by pleurodesis while 77.3% received IPC, usually significantly longer after cancer diagnosis [36]. While literature has been dedicated to the overall safety of pleurodesis [37], it is nonetheless associated with a range of undesirable side-effects that include pain, fever, dyspnea, pneumothorax and pneumonia at incidences ranging from 4-20%, as well as rare events such as respiratory failure and acute respiratory distress syndrome [38].

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It is prudent to reiterate the mechanical palliative nature of these mainstay treatments. Beyond the physically destructive elements of pleurodesis, or the physical and psychosocial ill-effects of IPC, neither attempt to address the underlying malignancy nor are expected to extend the lifespan of the patient. However, a striking disparity in treatment patterns exists worldwide. While Western recommendations appear to focus on mechanical palliative solutions, international practices include novel regional approaches [39,40].

1.1. Alternatives to Standard-of-Care

Beyond the West, in an era of personalized medicine and targeted tumor treatments, modernized approaches to treat breast MPE are routinely employed or under active investigation. International clinical trials involving MPE patients routinely describe treatment approaches that involve pharmaceutical agents administered intrapleurally and designed to physically target the tumor or the neovascular network responsible for the effusion. Many studies describe treatment of breast or lung cancer-driven MPE using an anti-vascular agent based on a modified Rh-endostatin (Endostar), frequently combined alongside intrapleural chemotherapy [41–43]. Endostar was approved by the China State Food and Drug Administration for the treatment of non-small cell lung cancer as the first-line therapy in 2005 [43]. Despite widespread reports of successful combined cancer treatment and management of MPE symptoms, we are aware of no studies that directly compare the efficacy of these Endostar-based treatments to Western mechanical palliative approaches.

While intrapleural Endostar and combined chemotherapy appear to be unique as a commonly adopted first line alternative, the concept of intrapleural tumor or vascular targeting treatments is not unique and has wide and long-standing precedent. Examples in animal models and human clinical trials exist of intrapleural administration of bevacizumab, bispecific antibodies, immunotherapeutics and other wide-ranging approaches [44,45]. In fact, intrapleural administration of the bispecific antibody catumaxomab was tested in an phase 1/2 trial in MPE patients and 5 of 7 evaluable breast cancer patients showed positive response to the treatment at day 60 post infusion [46]. One patient had complete response, defined as relief of symptoms related to the effusion with absence of fluid reaccumulation. The remaining four patients had partial response, defined as diminution of dyspnea, with partial reaccumulation of fluid and no further therapeutic thoracenteses required [47]. In a separate Phase I study [48] a breast MPE patient treated with gene-mediated cytotoxic immunotherapy achieved stable disease and the treatment was safe and well tolerated in a cohort of MPEs arising from various primary cancers. Another phase I study (RIOT-2) is currently underway to assess the use of intrapleural or intraperitoneal tocilizumab in patients with MPE secondary to any metastatic cancer [49]. The case for intrapleural administration of immunotherapies to treat MPE has been extensively reasoned by others [50], and intrapleurally administered anti-PD1 antibody controlled malignant pleural effusion and the growth of cancer when tested in murine models of lung MPE [51]. De-platinum-based pleural perfusion bevacizumab was shown to be efficacious in managing MPE in lung cancer patients [52]. Other agents tested intrapleurally in lung cancer include bispecific antibodies [53,54], bevacizumab, anti-angiogenic tyrosine kinase inhibitors, cytokine-based immunotherapy, tumor necrosis factor-α treatment, intrapleural immunogene therapy, tumor infiltrating lymphocyte treatment and more [55]. A recent review states that bevacizumab and Endostar have been approved for MPE treatment, although we have been unable to verify this independently [40]. Nonetheless, much of the prior work described has been conducted in very limited cohorts or is preliminary, indicating a need for more extensive, robust and disease specific future studies.

While encouraging preliminary reports of efficacy have been described and reviewed in other works [56,57], it is our opinion that these modernized pharmaceutical approaches to MPE treatment have been significantly understudied. There appears to be a dearth of Western studies investigating these alternative regional treatment modalities [55]. We believe this is partially due to the widely recommended approach from medical societies to apply mechanical treatment as first line [11,17,20], but is also influenced by unavailability of Endostar [58] and local recommendations against routine

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use of intrapleural treatment by official bodies, despite the recognition that early evidence may support improved effusion control and quality of life through intrapleural combination therapies [17]. The lack of research in this area is potentially exacerbated by challenges in clinical trial recruitment due to MPE patients' frequently poor performance scores not meeting inclusion criteria [59]. Furthermore, understanding of the processes underlying metastasis to the pleural space and effusion development are incomplete [59] and assessment of new cancer treatments is in general impeded by the challenges in human testing and a lack of readily employed or representative models of tumors and their microenvironment [60]. Animal models have existed for some time but are laborious and slow to test. Further, these may be inadequately representative of the patient tumor, and are increasingly falling out of favor [61] as concerns about ethical treatment of animals grow, to the extent that the NIH have stated they will no longer directly support animal model-only research [62].

1.2. New Models and Approaches

For some time, the field has been transitioning toward powerful alternative models that could facilitate testing of novel treatment methods utilizing patient-derived systems that represent the individual's tumor more closely and readily than any traditional approach. Several early studies in recent years have described success in establishing patient-specific organoids from MPE underlying breast cancer [63]. Organoids have been reported to retain the histological features, receptor status and the hotspot mutations of the parent cancer [64]. Immune cell subtypes have also been shown to be similar between breast primary tumor and breast MPEs in pilot studies [65]. Furthermore, dose response testing has been shown to mirror the drug sensitivity profile of the patient [66,67]. Collectively this preliminary work suggests potential applications for functional precision medicine in advancing care of breast MPE. The promise of organoid technology has been further evidenced and bolstered by the recent establishment of the NIH Standardized Organoid Modeling (SOM) Center with the goal of developing standardized organoids and protocols for biological and medicinal research, with $87 million in contracts to awarded in its first three years [68].

Next-generation sequencing (NGS) approaches have also been promoted as high value in MPE profiling and offer diagnostic, prognostic and theranostic value. Concordance of mutations between lung cancer MPE and primary tumor samples using NGS has been high and it is reported that studies in breast and other cancers have also shown promising results [69]. The versatile applications of NGS open avenues to ready assessment of tumor content, genome-wide mutation profiling, neoantigen detection and more. Via these methodologies, assessments of the MPE compartment's genomic landscape versus that of a primary tumor can be assessed to ensure adequate tumor cell presence and genetic similarity. While treatments can sometimes be targeted to known genes or mutations individually, combination with a functional assay is imperative prior to taking on potentially risky or expensive regional therapies [70]. NGS likely represents a high-value partner assay to functional readouts that directly monitor drug responsiveness, including organoids or similar platforms.

Utilizing a proprietary microfluidic 3-dimensional organoid technique [71], we have observed promising early results suggesting the feasibility of up-scaling functional precision medicine in the context of solid and liquid tumors including breast cancer. We have been able to successfully establish models from solid and liquid tumors with success rates that compare favorably to published data [67]. Generated models reflect the original sample cell composition including tumor cells and CD45+ immune cells. Furthermore, we have observed retention of key immune components including helper and cytotoxic T-cells, as well as a non-T cell niche. We have recorded preservation of relative cell proportions across a period of 7 days. Our past successes in other disease areas and the ability to retain immune components in consistently produced tumor models make us confident that future efforts will enable us to expand upon the promising organoid work reported by others at a new level of scale and automation (Figure 1). Our prior work has demonstrated turnaround times compatible with clinical treatment selection, as well as correlation between patient-derived organoid drug

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responses and clinical response in retrospective studies [71,72]. Collectively these findings add confidence in our ability to successfully deploy clinically valuable predictive assays in breast MPE.

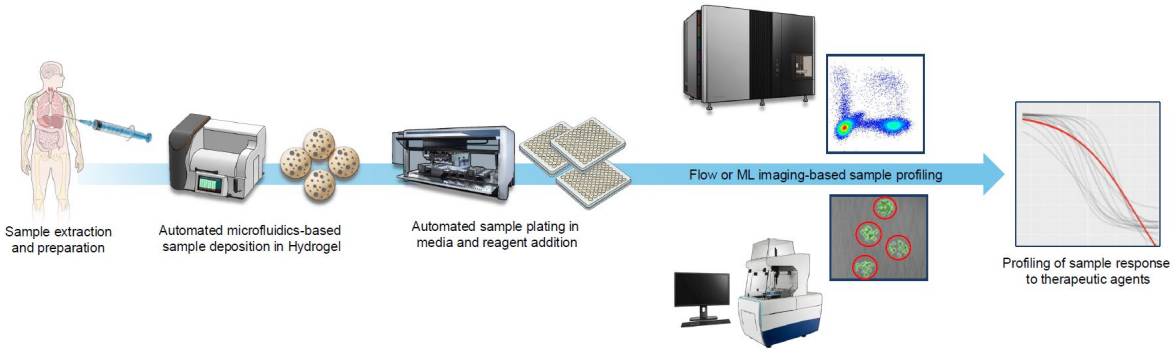

Figure 1. Schematic of our workflow. Breast MPE samples are acquired from a patient and deposited in uniform, microfluidics-created, spherical hydrogel scaffolds with proprietary technology. Automated processing enables deposition of these in reaction plates with media where they can be maintained, profiled and drug treated. Cell populations are assessed by spectral flow cytometry and cytometry-based cell counts can be utilized in determining cellular response to drug addition. Widefield microscopy combined with machine-learning based analysis can image, identify and measure signals of cell viability to determine drug-sensitivity based on markers of interest, while simultaneously identifying morphological characteristics of cells and heterogeneity of response.

1.3. Discussion

For some time now, the field of oncology has benefited from an era of personalized treatment based on predictive precision medicine approaches. Functional precision medicine technologies such as organoids increasingly offer the added possibility of treatment based on actual observed drug effects in model systems representative of patient tumor genetics and biology. To date, the standard-of-care for breast MPE has not meaningfully benefited from these modern paradigms, but several characteristics of the disease make it an excellent candidate for increased study. MPE yields relatively large numbers of tumor cells, in contrast to solid metastases, where cell numbers are fewer and biopsy is frequently risky. Since MPE fluids are removed for palliative care, no additional intervention is required and risk to the patient is reduced. This large volume of tumor cells from MPE enables direct interrogation of drug response without the need to expand small amounts of tumor cells and increase risk of clonal selection. This also increases speed of processing so that a treating physician may render a decision quickly, and limit drift in the populations of cells beyond the tumor cells alone.

As we have described, generic organoid studies have shown significant initial promise in the profiling and treatment of breast MPE, but the approach is inherently limited. The tumor microenvironment is increasingly appreciated as a key player in the tumorigenesis and disease progression [73]. Furthermore its role in regulating treatment response is progressively being understood, particularly with regard to adaptive cell responses and the part they play in immune checkpoint blockade response and resistance [74,75]. Despite some success, a central hurdle to successful clinical implementation of traditional organoid technologies has been the lack of a representative tumor microenvironment [76,77]. A solution that maintains both tumor cells and key functional components of the tumor microenvironment has the potential to more closely mimic cancer biology, replicate treatment effects ex vivo and open new avenues of clinical utility.

We believe that we currently possess unique technology and techniques that enable large-scale testing of breast MPE models with unparalleled accuracy in the replication of tumor phenotype and microenvironment. Furthermore, the platform introduces automated and microfluidic-controlled deposition of a primary cellular tumor sample in uniform 3D hydrogel spheres, reducing processing times from weeks or months [78,79] to days. Ultimately this offers the potential for *ex vivo* testing at

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new levels of scale and translatability. Our approach involves all the components necessary to enable the identification of precision medicine targets in the application of existing agents, and to enable discovery and development of entirely novel therapeutics. While breast MPE represents just one disease suited to application of our technology, it is our goal to imminently expand study in this area to drive clinical benefit for what we consider a patient population with significant potential for improved care.

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Conflict of Interest: GRO and CCB and WRS are employees of Xilis Inc.

References

1. Filho AM, Laversanne M, Ferlay J, Colombet M, Piñeros M, Znaor A, et al. The GLOBOCAN 2022 cancer estimates: Data sources, methods, and a snapshot of the cancer burden worldwide. Int J Cancer. 2025 Apr 1;156(7):1336–46.
2. Winters S, Martin C, Murphy D, Shokar NK. Breast cancer epidemiology, prevention, and screening. Prog Mol Biol Transl Sci. 2017 Oct 10;151:1–32.
3. Vrancken Peeters NJMC, Kerklaan R, Vlooswijk C, Bijlsma RM, Kaal SEJ, Tromp JM, et al. Long-term health-related quality of life among adolescent and young adult breast cancer survivors. Qual Life Res. 2025 May;34(5):1483–500.
4. Cohn JG, Locke SC, Herring KW, Dent SF, LeBlanc TW. Palliative care use and end-of-life care quality in HR+/HER2- metastatic breast cancer. Breast Cancer Res Treat [Internet]. 2025 Aug 16; Available from: http://dx.doi.org/10.1007/s10549-025-07805-4
5. Han Y-M, Yan-Dong, Wang H-L, Li X-M, Zhang X-, Wei X-Y, et al. Prognostic significance of malignant pleural effusions in patients with advanced luminal B breast cancer. BMC Womens Health. 2024 Oct 14;24(1):562.
6. Soni A, Ren Z, Hameed O, Chanda D, Morgan CJ, Siegal GP, et al. Breast cancer subtypes predispose the site of distant metastases. Am J Clin Pathol. 2015 Apr;143(4):471–8.
7. Piggott LM, Hayes C, Greene J, Fitzgerald D. Malignant pleural disease. Breathe (Sheff) [Internet]. 2023 Dec 1;19. Available from: http://dx.doi.org/10.1183/20734735.0145-2023
8. Zamboni MM, da Silva CT Jr, Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulm Med. 2015 Mar 28;15(1):29.
9. Fentiman IS, Millis R, Sexton S, Hayward JL. Pleural effusion in breast cancer: a review of 105 cases. Cancer. 1981 Apr 15;47(8):2087–92.
10. Wang Y, Zhou T, Zhao S, Li N, Sun S, Li M. A novel clinical prognostic model for breast cancer patients with malignant pleural effusion: Avoiding chemotherapy in low-risk groups? Cancer Manag Res. 2023 May 11;15:409–22.
11. Munavvar M, Bodtger U, Carus A, Cordovilla R, Naik S, Salud A, et al. Current trends in treating malignant pleural effusion: Evidence, guidelines, and best practice recommendations. JCO Oncol Pract. 2025 June;21(6):759–65.
12. Zaza C, Baine N. Cancer pain and psychosocial factors: a critical review of the literature. J Pain Symptom Manage. 2002 Nov;24(5):526–42.
13. Guo Y-Q, Ju Q-M, You M, Liu Y, Yusuf A, Soon LK. Depression, anxiety and stress among metastatic breast

 doi:10.20944/preprints202511.1952.v1

cancer patients on chemotherapy in China. BMC Nurs. 2023 Feb 6;22(1):33.

14. Economidou F, Margaritopoulos G, Antoniou KM, Siafakas NM. The angiogenetic pathway in malignant pleural effusions: Pathogenetic and therapeutic implications. Exp Ther Med. 2010 Jan;1(1):3–7.
15. Jovanovic D. Etiopathogenesis of malignant pleural effusion. AME Med J. 2021 Sept;6(0):28–28.
16. Donnenberg VS, Luketich JD, Sultan I, Lister J, Bartlett DL, Ghosh S, et al. A maladaptive pleural environment suppresses preexisting anti-tumor activity of pleural infiltrating T cells. Front Immunol. 2023 Mar 30;14:1157697.
17. Sivabalah K, Balata H, Craig C, Alsaaty A, Conroy K, Ong WH, et al. The 2023 British Thoracic Society guideline for pleural disease update on malignant pleural effusion. JoR. 2024 Nov 26;4(4):210–22.
18. Shafiq M, Frick KD, Lee H, Yarmus L, Feller-Kopman DJ. Management of malignant pleural effusion. J Bronchology Interv Pulmonol. 2015 July;22(3):215–25.
19. Siefen A-C, Eilers L, Baltin CT, Kron F. Cost comparison of treatment alternatives for pleural effusion and ascites from a payer perspective: Are there cost savings from indwelling catheters? J Palliat Med. 2023 Nov;26(11):1510–20.
20. Duong V, Hargreaves B, Muruganandan S. Management of malignant pleural effusion in 2024: A definitive and unified global approach. JCO Oncol Pract. 2025 June;21(6):739–41.
21. Peel AM, Mishra EK. The psychosocial impact of Indwelling Pleural Catheters: A scoping review. Cureus. 2023 July;15(7):e41689.
22. Iqbal B, Bedawi E, Rahman NM. Pro: indwelling pleural catheters cause harm to patients. Breathe (Sheff). 2024 Oct;20(3):240034.
23. Sidhu C, Wright G, Peddle-McIntyre CJ, Tan AL, Lee YCG. Management of malignant pleural effusion and trapped lung: a survey of respiratory physicians and thoracic surgeons in Australasia. Intern Med J. 2024 July;54(7):1119–25.
24. Mei F, Tamburrini M, Gonnelli F, Morandi L, Bonifazi M, Sediari M, et al. Management of malignant pleural effusion in Italian clinical practice: a nationwide survey. BMC Pulm Med. 2023 July 10;23(1):252.
25. Sarkar RR, Courtney PT, Bachand K, Sheridan PE, Riviere PJ, Guss ZD, et al. Quality of care at safety-net hospitals and the impact on pay-for-performance reimbursement. Cancer. 2020 Oct 15;126(20):4584–92.
26. Thomas R, Francis R, Davies HE, Lee YCG. Interventional therapies for malignant pleural effusions: the present and the future: Interventions for MPE. Respirology. 2014 Aug;19(6):809–22.
27. Gonnelli F, Hassan W, Bonifazi M, Pinelli V, Bedawi EO, Porcel JM, et al. Malignant pleural effusion: current understanding and therapeutic approach. Respir Res. 2024 Jan 19;25(1):47.
28. Orlandi R, Cara A, Cassina EM, Degiovanni S, Libretti L, Pirondini E, et al. Malignant pleural effusion: Diagnosis and treatment-up-to-date perspective. Curr Oncol. 2024 Nov 2;31(11):6867–78.
29. Boshuizen RC, Thomas R, Lee YCG. Advantages of indwelling pleural catheters for management of malignant pleural effusions. Curr Respir Care Rep. 2013 June;2(2):93–9.
30. Bhatnagar R, Kahan BC, Morley AJ, Keenan EK, Miller RF, Rahman NM, et al. The efficacy of indwelling pleural catheter placement versus placement plus talc sclerosant in patients with malignant pleural effusions managed exclusively as outpatients (IPC-PLUS): study protocol for a randomised controlled trial. Trials. 2015 Feb 12;16:48.
31. Semenova Y, Burkitbayev Z, Kalibekov N, Digay A, Zhaxybayev B, Shatkovskaya O, et al. The evolving role of chemotherapy in the management of pleural malignancies: Current evidence and future directions. Cancers (Basel) [Internet]. 2025 June 25; Available from: http://dx.doi.org/10.3390/cancers17132143
32. Mitchell MA, Deschner E, Dhaliwal I, Robinson M, Li P, Kwok C, et al. Patient perspectives on the use of indwelling pleural catheters in malignant pleural effusions. Thorax. 2023 Nov;78(11):1111–7.

 doi:10.20944/preprints202511.1952.v1

33. Wang S, Zhang R, Wan C, Qin J, Hu X, Shen Y, et al. Incidence of complications from indwelling pleural catheter for pleural effusion: A meta-analysis. Clin Transl Sci. 2023 Jan;16(1):104–17.
34. Zhang J, Liang J, Kadwani O, Agoramoorthy L, Montalvo S, Radcliffe G, et al. S138 Malignant pleural effusions: evaluating the psychosocial impact of indwelling pleural catheters on patients (MY-IPC) – an interim analysis. In: 'Bridge over troubled waters' – Managing the exudative effusion [Internet]. BMJ Publishing Group Ltd and British Thoracic Society; 2023. Available from: http://dx.doi.org/10.1136/thorax-2023-btsabstracts.144
35. Kathamuthu V, Balakrishnan R, Rajendran S, Rathinam P. The safety and efficacy of chemical pleurodesis agents in patients with malignant pleural effusion admitted in tertiary care hospital. Journal of Association of Pulmonologist of Tamil Nadu. 2025 Jan;8(1):17–22.
36. Kwok C, Thavorn K, Amjadi K, Aaron SD, Kendzerska T. Mortality after treatment of malignant pleural effusions with indwelling pleural catheters versus chemical pleurodesis: a population-based study. Respir Res. 2024 Nov 13;25(1):409.
37. Baiu I, Yevudza E, Shrager JB. Talc pleurodesis: A medical, medicolegal, and socioeconomic review. Ann Thorac Surg. 2020 Apr;109(4):1294–301.
38. Zhang W, Zhao Y-L, Li S-J, Zhao Y-N, Guo N-N, Liu B. Complications of thoracoscopic talc insufflation for the treatment of malignant pleural effusions: a meta-analysis. J Cardiothorac Surg. 2021 May 4;16(1):125.
39. Chinese Thoracic Society, Chinese Medical Association. Chinese expert consensus on treatment of malignant pleural effusion (2023 Edition). Zhonghua Jie He He Hu Xi Za Zhi. 2023 Dec 12;46(12):1189–203.
40. Xu Y, Cui Y, Jiang L, Yu Y, Si W, Zhu X. Thoracic perfusion of antiangiogenic agents combined with chemotherapy for treating malignant pleural effusion in non-small cell lung cancer: a network meta-analysis. BMJ Open. 2024 Dec 20;14(12):e080703.
41. Wang C-Q, Huang X-R, He M, Zheng X-T, Jiang H, Chen Q, et al. Intrapleural administration with Rh-endostatin and chemical irritants in the control of malignant pleural effusion: A systematic review and meta-analysis. Front Oncol. 2021 Aug 3;11:649999.
42. Fan Y, Zou Q, Li X, Qi X, Dong J, Liu J, et al. Analysis of the Efficacy of Endostar Thoracic Perfusion and DDP Intravenous Chemotherapy for Malignant Pleural Effusion of Breast Cancer. Pract J Cancer. 2018;33(7):1175–7.
43. Biaoxue R, Xiguang C, Hua L, Wenlong G, Shuanying Y. Thoracic perfusion of recombinant human endostatin (Endostar) combined with chemotherapeutic agents versus chemotherapeutic agents alone for treating malignant pleural effusions: a systematic evaluation and meta-analysis. BMC Cancer. 2016 Nov 14;16(1):888.
44. Hao Y, Gkasti A, Managh AJ, Dagher J, Sifis A, Tiron L, et al. Hyperthermic intrathoracic chemotherapy modulates the immune microenvironment of pleural mesothelioma and improves the impact of dual immune checkpoint inhibition. Cancer Immunol Res. 2025 Feb 3;13(2):185–99.
45. Khosrawipour C, Nicpoń J, Kiełbowicz Z, Prządka P, Liszka B, Zielinski K, et al. First in vivo applicational data of foam-based intrathoracic chemotherapy (FBiTC) in a swine model. Pharmaceuticals (Basel) [Internet]. 2023 Dec 27;17(1). Available from: http://dx.doi.org/10.3390/ph17010045
46. Sebastian M, Kiewe P, Schuette W, Brust D, Peschel C, Schneller F, et al. Treatment of malignant pleural effusion with the trifunctional antibody catumaxomab (Removab) (anti-EpCAM x Anti-CD3): results of a phase 1/2 study. J Immunother. 2009 Feb;32(2):195–202.
47. Ammouri L, Prommer EE. Palliative treatment of malignant ascites: profile of catumaxomab. Biologics. 2010 May 25;4:103–10.
48. Aggarwal C, Haas AR, Metzger S, Aguilar LK, Aguilar-Cordova E, Manzanera AG, et al. Phase I study of

 doi:10.20944/preprints202511.1952.v1

intrapleural gene-mediated cytotoxic immunotherapy in patients with malignant pleural effusion. Mol Ther. 2018 May 2;26(5):1198–205.

49. Park H, Lewis C, Dadgar N, Sherry C, Evans S, Ziobert S, et al. Intra-pleural and intra-peritoneal tocilizumab therapy for managing malignant pleural effusions and ascites: The Regional Immuno-Oncology Trial (RIOT)−2 study protocol. Surg Oncol Insight. 2024 June;1(2):100045.
50. Donnenberg AD, Luketich JD, Dhupar R, Donnenberg VS. Treatment of malignant pleural effusions: the case for localized immunotherapy. J Immunother Cancer. 2019 Apr 18;7(1):110.
51. Li X, Wu G, Chen C, Zhao Y, Zhu S, Song X, et al. Intrapleural injection of anti-PD1 antibody: A novel management of malignant pleural effusion. Front Immunol. 2021 Dec 13;12:760683.
52. Wang P, Zhang C, Hao P, Wang S, Zhu R, Li J, et al. The Observation of Clinical Efficacy and Safety of De-Platinum-Based Pleural Perfusion in the Treatment of Malignant Pleural Effusion and Its Correlation with the Expression of VEGF in Pleural Fluid. Journal of Cancer Therapy. 2024;15(12):432–45.
53. Kroesen BJ, Nieken J, Sleijfer DT, Molema G, de Vries EG, Groen HJ, et al. Approaches to lung cancer treatment using the CD3 x EGP-2-directed bispecific monoclonal antibody BIS-1. Cancer Immunol Immunother. 1997 Nov;45(3–4):203–6.
54. Cai J, Zhang F, Song Z, Jin J, Lv D, Pang W, et al. 1371P An anti-EpCAM x CD3 bispecific antibody, M701, for the treatment of malignant pleural effusion in NSCLC patients: Intermediate results of a prospective multicenter phase Ib trial. Ann Oncol. 2024 Sept;35:S862.
55. He D, Ding R, Wen Q, Chen L. Novel therapies for malignant pleural effusion: Anti-angiogenic therapy and immunotherapy (Review). Int J Oncol. 2021 Mar;58(3):359–70.
56. Murthy V, Katzman D, Sterman DH. Intrapleural immunotherapy: An update on emerging treatment strategies for pleural malignancy. Clin Respir J. 2019 May;13(5):272–9.
57. Wong T, Fuld AD, Feller-Kopman DJ. Malignant pleural effusions in the era of immunotherapy and antiangiogenic therapy. Semin Respir Crit Care Med. 2023 Aug;44(4):447–53.
58. Wang D-X, Zhu M, Guo D-H, Gu J, Xia L, Huang X-W, et al. Safety of Endostar in combination with chemotherapy in patients with cancer. Indian J Cancer. 2024 Oct 1;61(4):694–702.
59. Penz E, Watt KN, Hergott CA, Rahman NM, Psallidas I. Management of malignant pleural effusion: challenges and solutions. Cancer Manag Res. 2017 June 23;9:229–41.
60. Honkala A, Malhotra SV, Kummar S, Junttila MR. Harnessing the predictive power of preclinical models for oncology drug development. Nat Rev Drug Discov. 2022 Feb;21(2):99–114.
61. Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. Am J Transl Res. 2014 Jan 15;6(2):114–8.
62. NIH animal model funding. https://grants.nih.gov/news-events/nih-extramural-nexus-news/2025/07/nih-funding-announcements-to-align-with-nih-initiative-to-prioritize-human-based-research.
63. Brugge J, Chang K-C, Silvestri F, Olipant M, Martinez-Gakidis MA, Orgill D, et al. Breast organoid suspension cultures maintain long-term estrogen receptor expression and responsiveness [Internet]. Res. Sq. 2024. Available from: https://www.researchsquare.com/article/rs-4463390/v1
64. Önder CE, Ziegler T, Becker R, Brucker S, Hartkopf A, Engler T, et al. Advancing cancer therapy predictions with patient-derived organoid models of metastatic breast cancer. Cancers (Basel) [Internet]. 2023 July 1;15. Available from: http://dx.doi.org/10.3390/cancers15143602
65. Laberiano-Fernandez C, Gan Q, Wang SM, Tamegnon A, Wistuba I, Yoon E, et al. Exploratory pilot study to characterize the immune landscapes of malignant pleural effusions and their corresponding primary tumors from patients with breast carcinoma and lung adenocarcinoma. J Am Soc Cytopathol. 2024 May;13(3):161–73.

 doi:10.20944/preprints202511.1952.v1

66. Pan B, Zhao D, Liu Y, Li N, Song C, Li N, et al. Breast cancer organoids from malignant pleural effusion-derived tumor cells as an individualized medicine platform. In Vitro Cell Dev Biol Anim. 2021 May;57(5):510–8.
67. Choi W, Kim YH, Woo SM, Yu Y, Lee MR, Lee WJ, et al. Establishment of patient-derived organoids using ascitic or pleural fluid from cancer patients. Cancer Research and Treatment: Official Journal of Korean Cancer Association. 2023;55(4):1077–86.
68. NIH establishes nation's first dedicated organoid development center to reduce reliance on animal modeling [Internet]. National Institutes of Health (NIH). [cited 2025 Oct 8]. Available from: https://www.nih.gov/news-events/news-releases/nih-establishes-nations-first-dedicated-organoid-development-center-reduce-reliance-animal-modeling
69. Yang S-R, Mooney KL, Libiran P, Jones CD, Joshi R, Lau HD, et al. Targeted deep sequencing of cell-free DNA in serous body cavity fluids with malignant, suspicious, and benign cytology. Cancer Cytopathol. 2020 Jan;128(1):43–56.
70. Liu Y, Gan Y, AiErken N, Chen W, Zhang S, Ouyang J, et al. Combining organoid models with next-generation sequencing to reveal tumor heterogeneity and predict therapeutic response in breast cancer. J Oncol. 2022 Aug 22;2022:9390912.
71. Ding S, Hsu C, Wang Z, Natesh NR, Millen R, Negrete M, et al. Patient-derived micro-organospheres enable clinical precision oncology. Cell Stem Cell. 2022 June 2;29(6):905-917.e6.
72. Xi R, Wang X, Moseley R, Raman R, Zhang R, Jaibbar S, et al. Abstract 3412: Patient-derived MicroOrganoSpheres (MOS) enable precision clinical decision-making for multiple myeloma patients. Cancer Res. 2023 Apr 4;83(7_Supplement):3412–3412.
73. Hanahan D. Hallmarks of cancer: New dimensions. Cancer Discov. 2022 Jan;12(1):31–46.
74. Aliazis K, Christofides A, Shah R, Yeo YY, Jiang S, Charest A, et al. The tumor microenvironment's role in the response to immune checkpoint blockade. Nat Cancer. 2025 June;6(6):924–37.
75. Wang Q, Shao X, Zhang Y, Zhu M, Wang FXC, Mu J, et al. Role of tumor microenvironment in cancer progression and therapeutic strategy. Cancer Med. 2023 May;12(10):11149–65.
76. Thorel L, Perréard M, Florent R, Divoux J, Coffy S, Vincent A, et al. Patient-derived tumor organoids: a new avenue for preclinical research and precision medicine in oncology. Exp Mol Med. 2024 July;56(7):1531–51.
77. Zhou C, Wu Y, Wang Z, Liu Y, Yu J, Wang W, et al. Standardization of organoid culture in cancer research. Cancer Med. 2023 July;12(13):14375–86.
78. Huang S, Mei Z, Wan A, Zhao M, Qi X. Application and prospect of organoid technology in breast cancer. Front Immunol. 2024 Aug 26;15:1413858.
79. Tzeng Y-DT, Hsiao J-H, Tseng L-M, Hou M-F, Li C-J. Breast cancer organoids derived from patients: A platform for tailored drug screening. Biochem Pharmacol. 2023 Nov;217(115803):115803.