

Review

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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 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 have 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].

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].

1.2. 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 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 status 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].

1.3. Functional Precision Medicine in Cancer

Functional precision medicine involves direct exposure of patient-derived tissues to drugs in order to attempt prediction of clinical response [63]. The concept is not new, with a history extending more than seven decades. Perhaps the first report of using patient-derived primary tumor tissues to predict chemotherapy response *ex vivo* was the work of Dr. Jane Wright, a founding member of the American Society of Clinical Oncology, in 1957 [64]. Pioneering chemosensitivity assays appeared in the late 1970s, primarily based on clonogenic tumor properties, with numerous assays developed since and culture methods and readouts varying across time [65]. Some seminal efforts described the use of microtiter plate assays to evaluate immunological and chemical sensitivity of tumors to various agents [66]. Many methods brought initial promise but were ultimately later eliminated [67]. Editorials from the New England Journal of Medicine and American Society for Clinical Oncology cast doubt on the ability of the assays to personalize care [68]. Problems included low evaluation rates [67], variability in responses, lack of reproducibility [64], labor-intensiveness, interpretability issues, need of highly skilled operators [67], long turnaround times, poor scalability [69,70] and lack of translatability to clinical response [65]. Several commercial tests have also become available [64] but ultimately a protocol is yet to be unanimously recognized by the biomedical community or the regulatory authorities [65]. Thus, no methods are widely accepted by the medical community [67].

1.4. Modernization and Automation

It has been widely reported that traditional 2D chemosensitivity testing fails to recapitulate the *in vivo* environment in which a tumor evolves and it has been stated that an ideal model should mimic this environment as well as the tumor genomics [64]. Traditional 2D techniques have been shown to cause cytoskeletal remodeling, and altered gene and protein synthesis [71]. Studies in such cell cultures have shown cells progressively flatten and lose their differentiated phenotype [72,73], therefore lacking accurate tissues architecture, cellular interplay and personal heterogeneity aspects [74,75]. They also fail to reproduce nutrient and oxygen gradients, which impairs the ability to precisely predict drug activity [76]. 2D culture lacks natural extracellular matrix (ECM) proteins, chemokines, growth factors and sites for cellular adhesion, which are crucial for cells to interact with adjacent cells and surroundings, preserving the specificity and homeostasis of the original tissue and its regular functioning [77,78].

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. 3D patient-derived organoids maintain various features of the original tumor like intratumoral heterogeneity, secondary architecture, and polyclonality and are seen as a means of overcoming many traditional shortcomings [64].

Automation has the ability to address multiple issues inherent in traditional and manual assays. Variability in culture experiments and even in organoid assays are well recognized as problematic. Disparities in cell procurement, sample storage, media composition and downstream experimental protocols are only a few examples of considerations that have the potential to introduce experimental variability [79].

It is accepted that industrial developments including automation and miniaturization will be at the core of addressing many challenges associated with traditional assays [80–84]. Prior publications have identified assay variability issues due to extracellular culture matrices [81,85–89], manual handling inconsistencies [83], and media variability [81,89]. Automation will also facilitate clinically relevant turnaround times. These are key to any assay that will be adopted widely [90], with the success of patient-derived organoid-based drug screening in personalized cancer care being dependent on rapid turnaround from tumor sampling to drug recommendation to guide treatment decisions in a clinically relevant timeframe [85,91].

1.5. Modern Approaches to Breast MPE

Several studies in recent years have described success in establishing patient-specific organoids from MPE underlying breast cancer [92]. Organoids have been reported to retain the histological features, receptor status and the hotspot mutations of the parent cancer [93]. Immune cell subtypes have also been shown to be similar between breast primary tumor and breast MPEs in pilot studies [94]. Furthermore, dose response testing has been shown to mirror the drug sensitivity profile of the patient [95,96]. 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 [97].

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 [98]. 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 [99]. 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 [100], we have observed promising early results suggesting the feasibility of up-scaling functional precision medicine in the context of solid [101–104] and liquid tumors [105,106] including breast cancer [107]. Our automated instrument automatically encapsulates cells present in a fresh patient sample and is compatible with downstream analysis by flow cytometry or brightfield microscopy combined with fluorophore-conjugated antibody staining and combined with computational imaging analysis (Figure 1). Tumor and key functional components are collectively encapsulated in hydrogel droplets which are solidified through exposure to electronically controlled light or temperature changes [100]. We have demonstrated the ability to retain stromal functional immune microenvironment components and demonstrated effects of immuno-oncology agents [101,108]. Immune-tumor cell interactions can be optionally observed utilizing longitudinal imaging, depending on study requirements. NGS can be utilized as required by a study [101,108], pre or post droplet generation. We have had success generating models from breast MPE samples, achieving success rates that substantially outperform published rates of 20-33% [95,96]. 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. Our prior work has demonstrated turnaround times compatible with clinical treatment selection, as well as correlation between patient-derived organoid drug responses and clinical response in retrospective studies [101,103,106], with further peer-reviewed studies currently in press. Collectively these findings add confidence in our ability to successfully deploy clinically valuable predictive assays in breast MPE, and we plan to actively devote efforts to this nascent area of research, while encouraging others in the field to consider similarly expanding their own efforts, based on the patients’ need and the rich possibilities for improved treatment described in this perspective.

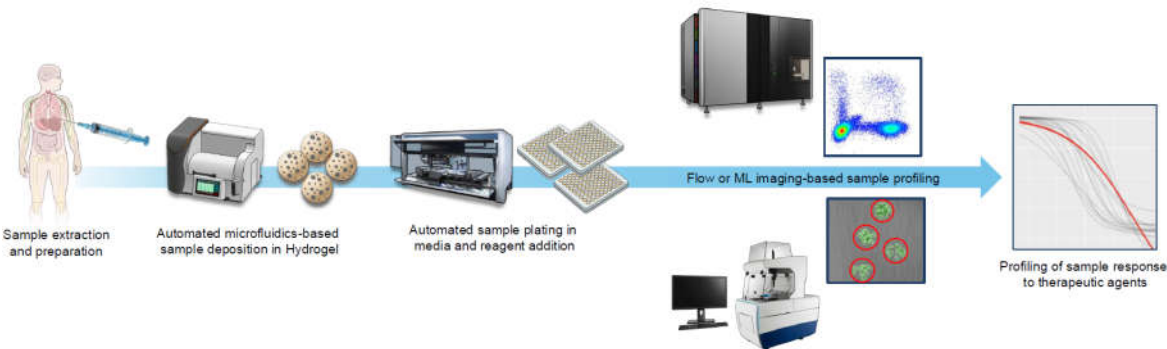


Figure 1. Schematic of our workflow. Samples are acquired from a patient and deposited in uniform, microfluidics-created, spherical hydrogel scaffolds with proprietary technology. Automated processing enables deposition of these in reaction plates with media where they can be maintained, profiled and 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.

1.6. 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 [109]. 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 [110,111]. Despite some success, a central hurdle to successful clinical implementation of traditional organoid technologies has been the lack of a representative tumor microenvironment [112,113]. 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 technology and techniques that enable large-scale testing of breast MPE models with replication of tumor phenotype and microenvironment. Furthermore, the platform’s automated and microfluidic-controlled deposition of a primary cellular tumor sample in uniform 3D hydrogel spheres, reduces processing times from weeks or months [114,115] to days [100,101,107,116]. Ultimately this offers the potential for *ex vivo* testing at 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. We look forward to a period of combined precision and functional precision medicine where ourselves and our colleagues in the field can realize the potential of the latest technological advances to reimagine treatment paradigms in breast cancer-related MPE, along with other underserved disease areas where standard-of-care has stagnated, and the potential for improved care is significant.

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