Lung Cancer and Molecular Testing in Small Biopsies Versus Cytology: *The Logics of Worlds*

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The 8th Annual National Molecular Cytopathology Meeting, held in Naples, Italy, on December 2 to 3, 2019, addressed updates in diagnostic cytopathology and molecular classifications and specifically focused on lung cancer biomarker testing in cytology samples. Lung cancer continues to be the most commonly diagnosed noncutaneous malignancy in the world. In the majority of patients, lung cancers are frequently identified when they cannot be surgically accessed, and this leads to the use of cytology for a diagnosis and theragnostic testing. The meeting was an international forum for discussing new roles and updates for cytopathology in molecular testing as the basis for provoking new trends and novel approaches. The relevant literature is referenced. The significance of these updates for the practice of pathology in general is discussed. ***Cancer Cytopathol* 2020;128:637-641**. © *2020 American Cancer Society*.

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INTRODUCTION

This commentary summarizes relevant updates to the practice of lung cytopathology with respect to molecular diagnostics as discussed during the 8th Annual National Molecular Cytopathology Meeting directed by Professor Giancarlo Troncone on December 2 to 3, 2019, in Naples, Italy. We specifically discuss considerations from the presenters about the role of cytopathology specimens versus small surgical biopsies in obtaining a primary diagnosis and performing ancillary testing for lung cancers. The relevant literature is referenced. We discuss the significance of these updates to the practice of pathology in general.

A FABLE

Not that long ago, though further back than some remember, the pathologist's role in patient care essentially ended with a definitive diagnosis. An ideal specimen was simply one that could secure the identity of a tumor. As theragnostic postdiagnostic testing has evolved, the pathologist's role in patient care has persisted past the point of diagnosis. Whenever a new test comes into being, a hierarchy of specimens evolves. Some specimen types are considered gold standards, whereas others are considered less than ideal.

In lung cancer, surgical biopsies have been treated as the ideal specimens for postdiagnostic and theragnostic molecular testing.[1-8] Because cytopathology offers a unique opportunity for a direct role in the procurement of specimens through rapid onsite evaluation (ROSE), cytopathologists have been directly and dramatically

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affected by this apparent fall from ideality. The specimen procured with the help of a cytopathologist has been overshadowed by surgical specimens.

However, that shadow is lifting. The last decade has demonstrated that cytology offers highly reliable specimens for diagnostic interpretation in comparison with small surgical biopsies. Moreover, cytology specimens and surgical specimens can coexist as alternative and parallel diagnostic worlds.

WHAT IS AN IDEAL?

Plato of Athens, who lived in ancient Greece around 400 BCE, anticipated this dilemma of the contemporary cytopathologist. Plato described an abstract, higher layer of reality composed of ideal forms. These ideal forms are eternal and changeless and represent the paradigms that we use to understand and evaluate our world. For Plato, all things that exist, from biopsies to microscopes to tumors to pathologists themselves, are connected to some ideal form. When we say that something is ideal, we are evaluating how closely a specific entity corresponds to its perfected abstract form. For Plato, the actual entities that we encounter in life are the flawed shadows of their ideal forms.[9] For molecular testing, the surgical pathology specimen has been the ideal form, whereas the cytopathology specimen has been the flawed, imperfect shadow.

IS CYTOPATHOLOGY THE FLAWED SHADOW OF SURGICAL PATHOLOGY?

The 8th Annual National Molecular Cytopathology Meeting, held in Naples, Italy, addressed updates in diagnostic cytopathology and molecular classifications and specifically focused on lung cancer biomarker testing in cytology samples. The meeting was an international forum for discussing new roles and updates for cytopathology in molecular testing as the basis for provoking new trends and novel approaches. Diverse symposium speakers thematically and explicitly emphasized the significant role of cytology in achieving optimal molecular testing results.

In 2015, the World Health Organization issued several major revisions to the diagnostic categories of lung cancer, mostly because of molecular profile discoveries. These new World Health Organization classifications included cytological specimens alongside surgical specimens in tumor classification as diagnostically equivalent.[10] Despite its small size, a cytopathology specimen can routinely afford a correct, full-fidelity diagnosis and provide ample material for necessary ancillary testing in accordance with the standard of care.[11-17] As a diagnostic modality, a cytopathological specimen demonstrates equivalency to a surgical specimen specifically because of the veridical richness of cytomorphology and its relation to molecular pathology.

For lung cancers, the last decade has produced rapid advances in molecular testing reciprocally with novel therapies. Patients presenting at advanced stages and with unresectable lung tumors, which represent more than 70% of cases, have particularly benefitted.[2,10,18-26] This can be partially attributed to basing therapeutic decisions on tumor typing, which is increasingly possible with cytology. The technological reach of molecular diagnosis has also allowed increasing prominence for cytopathology.

Traditionally, molecular testing has required formalin-fixed, paraffin-embedded tissue. As such, formalin-fixed, paraffin-embedded cell blocks are the most widely used cytological specimens for molecular testing because of validation similarity with traditional histological samples.[11,27] However, the updated molecular testing guidelines from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology in 2018 concur that any cytological sample, characterized by adequate and well-preserved material, can be used for molecular testing, including smear slides used to judge adequacy during ROSE. These guidelines explicitly include cytological specimens among surgical specimens for the testing of routinely treatable mutations when patients are diagnosed with lung adenocarcinoma and/or not otherwise specified.[23-25] This would allow for the exploration of the utility of cytopathology specimens in both obtaining a primary diagnosis and performing consequent molecular testing.

Subsequently, an increasing number of publications have articulated the central role of cytopathology specimens in obtaining the necessary lung cancer diagnosis with reliable subsequent molecular testing. In fact, molecular cytopathology is often better than surgical pathology in many settings.[1,11,12,14,15,27] Cytological samples frequently demonstrate higher tumor yields than concurrent surgical biopsy specimens. Furthermore, diagnostic material can be apportioned among different media during

ROSE, such as cell blocks, smears, and liquid-based preparations, and this allows for more diverse types of analysis during all phases of testing.[14-17] In summary, recent history has demonstrated the superior ability of cytopathology specimens for obtaining an accurate diagnosis and performing the necessary theragnostic molecular testing.

The Naples meeting summarily confirmed the essential role of cytology in lung cancer diagnosis and treatment. Speakers documented that molecular testing can be run on small biopsies and cytology specimens with comparable results. For example, Dooms et al[18] described a randomized trial comparing 2 different needle sizes (19 and 22 gauge) with resultant, successful next-generation sequencing. Success was obtained with 96% of the samples, regardless of the needle sizes, with comparable nondiagnostic biopsy rates. Although tissue samples might be smaller, the art of cytomorphological evaluation and the practice of molecular diagnosis have more than compensated.

To summarize this conference, cytopathological methods can produce an ideal specimen for the diagnosis and theragnostic testing of lung cancers independent of surgical biopsies. The power of molecular diagnosis has not eliminated the practice of cytomorphological analysis; it has increased its importance. The diagnostic judgment of the cytopathologist during ROSE and cytomorphological and immunohistochemical analysis represents an ideal diagnostic pathway for patients with lung cancer.

A FABLE REVISITED

These developments in cytomorphological analysis and theragnostic molecular diagnosis have prompted a re-evaluation of the practice of cytopathology and its role in the care of patients with lung tumors. Cytopathology specimens are not a degraded shadow of surgical pathology specimens. They have an independent dignity. New techniques developed in the last decade have allowed for high-quality molecular results to be obtained from a multiplicity of cytopathological specimens in addition to traditional surgical pathology specimens.[11-15,27] Interestingly, ROSE is increasingly important because of the triage possibilities afforded by postdiagnostic molecular testing. Cytomorphological analysis is now more evolved than ever and does not simply serve as an adequacy gesture for molecular analysis. However, this change was possible only with a re-investment in the development of cytomorphological diagnosis, the evolution of molecular diagnosis techniques, and resistance to the dominant conceptual apparatus, the idea that cytopathology is the shadow of surgical pathology. It seems that the implicit conceptual apparatus underwriting pathology might need its own re-evaluation. Plato's idealism does not capture our present situation. Cytopathology is its own rich world.

A pathologist's decision to discard, rescue, rehabilitate, demonstrate, or explore is underwritten by a conceptual apparatus that allows the pathologist to organize, capture, and use what he or she perceives. This happens during all thinking, including clinical work and research. As the meeting in Naples demonstrated, the last decade has proved verdant for the development of cytopathology. Similarly, the 4000 years since the time of Plato have produced developments in the science of conceptual apparatuses, which is also called philosophy. Conceptual apparatuses are not static; like any laboratory process, they can be developed, improved, or discarded. However, instead of totally discarding Plato's idealism, we can reciprocally redeploy the conclusion of the Naples conference. Idealism itself can evolve to help us to understand our present and inspire new pathways forward.

Plato seems to argue for a world bound to static ideal forms. However, cytopathology has been anything but static, and many specimens can produce excellent results despite being less than ideal. Changeless order should not be sought or accepted as an ideal because it does not reflect our practice as physicians and scientists and represents a misunderstanding of the concept of the ideal.[28] Although some specimens are certainly better than others for different tests, these hierarchies are contingent and not fixed in time. New molecular techniques have prompted advances in cytomorphology itself and allowed for new gold standards to come into being. Rather than 1 world of specimens with corresponding ideals, we now have multiple worlds of specimens, each with its own ideals. To navigate this complexity, we need similar developments in our thinking. Instead of a single world, we can now have multiple worlds.

Alain Badiou, a modern student of Plato, argues that every entity itself constitutes a world and that "every

world is capable of producing its own truth within itself."[29] For every tumor, there are multiple ways to obtain a specimen, from radical resection to fine-needle aspiration biopsy. There are multiple ways to handle the specimen at the time of acquisition, from smears, touch preparations, Papanicolaou staining, liquid-based preparations, and Diff-Quik to direct formalin fixation. There are multiple visible features of the cells on a slide that any pathologist might apprehend to obtain the diagnosis. There are multiple tests available after a diagnosis that may be important to treatment, and there are multiple laboratories available to perform them. This proliferation of multiplicities can be overwhelming and deconstructs traditional hierarchies. Which way is up? Is there an up? Perhaps we can relax our commitment to rigid hierarchies amid all this complexity and find a more elegant concept to navigate our present and future.

As physicians, we know that each patient is singularly important. Each patient is his or her own world and, therefore, has his or her own ideal. Similarly, each specimen is singularly important. However, there are many specimens. Appreciating this duality is a logic of worlds. So instead of lamenting that a particular specimen is not ideal, let us instead find the individual ideal context for each specimen or create this context.

The 8th Annual National Molecular Cytopathology Meeting did not occur because pathologists lamented the obsolescence of lung cytopathology. The contributing scientists confronted the multiplicity of advancements with their own proliferation of creativity. They implicitly grasped the insight of Gilles Deleuze, philosopher of multiplicities, and asked "what a body is capable of doing."[30] Their answers to this question created new techniques and invigorated the role of the cytopathologist. Cytopathological specimens have new capabilities. The importance of cytopathological decision making during ROSE has brought the decisional apparatus of the pathologist closer than ever to the patient. As techniques become more numerous, the potentialities of each specimen expand. Concurrently, the judgment of the pathologist becomes more frequent and necessary. Molecular diagnostics has not effaced the need for cytomorphology but rather has increased its importance. Molecular cytopathology has its own ideal, and the mapping of it has just begun.

The future of pathology lies not in reaffirming gold standards but in asking what a body can do. What is the gold standard for this specimen for this patient in this context? How can your judgment and creativity achieve that?

Until another Plato's theory is coming up to be evaluated and revised.

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