The revolution of 3D pathology for clinical practice in China

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THE FIRST CLINICALLY TRANSLATED 3D PATHOLOGY IMAGING PLATFORM IN CHINA

Histopathology serves as the clinical diagnostic "gold standard." Through the examination of biopsy specimens obtained before or during surgery, pathologists assess microscopic tissue structures to identify disease clues. In standard practice, tissues are physically sectioned into thin slides (typically 3-5 μm thick) for microscopic evaluation, which represents less than 0.1% of the original sample volume. Consequently, there is a pressing need to leverage pathological samples in their entirety via 3D imaging to enable more efficient and information-rich diagnosis.[1]

The convergence of advancements in optical imaging, tissue processing, and data analytics has established a technical foundation for non-destructive 3D pathology, paving the way for its clinical translation. A milestone in this transition was reached in December 2025 with the installation of the Patho One system (Intoto Biotech) at Dongguan People's Hospital, affiliated with Southern Medical University. This event marked the first deployment of a slide-free 3D pathology imaging platform into a clinical trial setting. Concurrently, the research-oriented Pano One system has been adopted by multiple academic institutions across China, marking a significant step towards the new era of 3D pathology for both academic and clinical applications.

TECH UNDER THE SPOTLIGHT: TISSUE CLEARING AND LIGHT SHEET MICROSCOPY

For conventional pathology diagnosis, it relies on physically sectioning

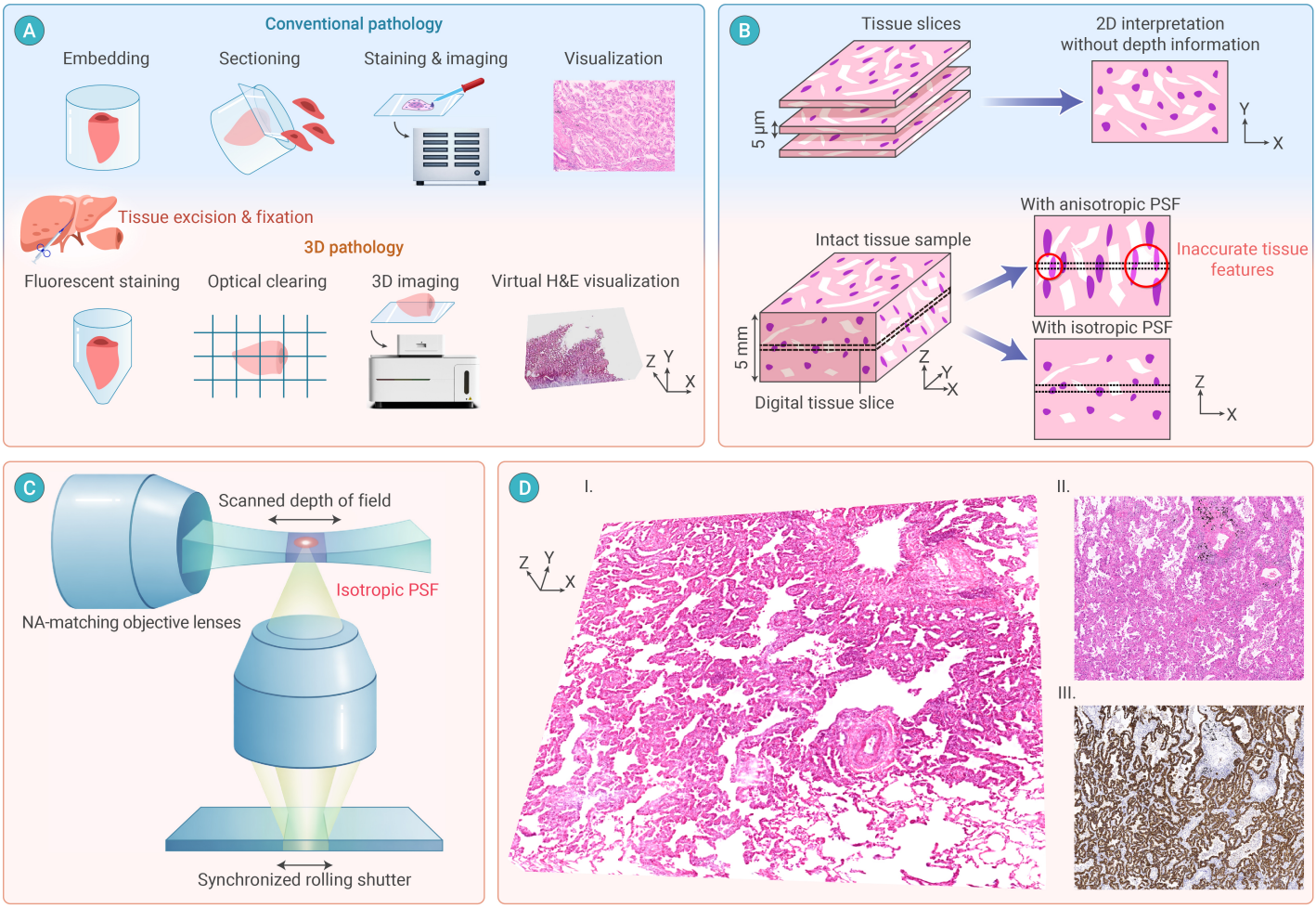

Figure 1. Concepts and applications of Patho One for 3D pathology (A) Procedures for preparing pathological tissue samples for conventional and 3D pathology. (B) Distinctions between interpreting the depth dimension of pathological tissue slices in conventional and 3D pathology. For 3D pathology, spatial resolution isotropy further plays a role in achieving accurate and realistic visualization of tissue features. (C) Patho One adopts focused light sheet with scanning depth of field and NA-matching objective lenses for isotropic, fast optical imaging for 3D pathology. (D) A lung cancer specimen underwent optical clearing and was subsequently imaged using the Patho One platform (I). The specimen was then subjected to reverse transparency processing. Following this, traditional pathology techniques were applied to produce a 4 μm H&E-stained section (II). Immunohistochemical staining for cytokeratin 7 (CK7) was performed, revealing the anticipated positive cytoplasmic staining in tumor cells (III).

FFPE tissues into thin slices for bright-field microscopy—a destructive process that samples only a tiny fraction of the specimen (Figure 1A)—3D pathology addresses this limitation through optical sectioning. At its core is an imaging technique capable of resolving centimeter-scale samples at subcellular resolution. To this end, light sheet fluorescence microscopy (LSFM), combined with tissue clearing and fluorescent labeling (Figure 1A), has emerged as an efficient and viable pipeline for non-destructive, volumetric tissue analysis among various parties worldwide.[2]

3D pathology enables volumetric imaging of intact tissues via optical sectioning. It can provide more comprehensive depth information compared to conventional 2D pathology. The 2D pathology is empirically valid because thin slices are examined independently, and the image contrast (e.g., from H&E staining) is formed without interference from adjacent layers. In 3D pathology, by contrast, imaging is performed on intact tissue volumes. It is therefore critical that the digitally rendered slices be free from distortion to provide pathologists with an accurate representation for diagnosis. Although optical sectioning eliminates background fluorescence from out-of-focus planes, severe distortion can still arise from an anisotropic point spread function (PSF) of the imaging system. Such anisotropy can cause features from neighboring depths to bleed into a selected digital slice, potentially leading to misinterpretation. An isotropic PSF, however, preserves the true spatial proportions of tissue features in the digital copy, allowing the relative sizes and positions of all structures to be accurately visualized in 3D—thereby reducing diagnostic error (Figure 1B).

To achieve an isotropic PSF, the Patho One platform (Intoto Biotech) employs a scanned light-sheet design with a scanning depth of field to image the pathological tissue, maintaining a tightly confined PSF throughout the sample volume (Figure 1C). Specifically, the system scans the light sheet across millimeter-scale tissue areas with minimal optical aberration, capturing hundreds of consecutive optical slices per second.[3] Furthermore, it uses matched numerical apertures (NA) for the illumination and detection objectives, resulting in a highly isotropic PSF (~1:1 spatial ratio) that maximizes the spatial fidelity of the 3D tissue reconstruction.

Biological tissues are optically heterogeneous due to variations in the refractive index (RI) arising from their complex composition of water, lipids, and proteins. This RI mismatch causes light to scatter during imaging, resulting in the loss of ballistic photons, which degrades both signal intensity and spatial resolution. To overcome this barrier, the 3D pathology pipeline from Intoto Biotech incorporates tissue optical clearing (TOC) techniques. TOC homogenizes the RI throughout the sample, enabling clear imaging of intact tissues at millimeter to centimeter scales. Furthermore, the Patho One system is engineered to minimize system-induced artifacts. It utilizes index-matched sample holders and incorporates aberration-correcting optics within the sample chamber. This design accommodates a range of sample and medium RIs, ensuring high-fidelity 3D imaging of pathological tissues.

BROAD PATHOLOGICAL APPLICATIONS AND DIAGNOSTIC ADVANTAGES

3D imaging techniques have been successfully applied to visualize a broad spectrum of human pathological lesions, including prostate cancer, breast cancer, bladder cancer, melanoma, esophageal neoplasia, basal cell carcinoma, and metastatic lymph node tumors. Notably, the 3D images, which are rendered to emulate virtual hematoxylin and eosin (H&E) staining, are readily interpretable by pathologists, enabling seamless integration into standard diagnostic workflows. These images offer distinct advantages for precise pathological grading. For instance, in prostate cancer studies by Glaser et al.[2] the continuous visualization of glandular architecture across tissue volumes enabled a more accurate Gleason score assessment compared to traditional 2D sections. This benefit is anticipated to extend to other critical diagnostic assessments, such as the detection of lymphovascular invasion, extracapsular extension, and lymph node micrometastases.

Furthermore, 3D pathology significantly reduces the turnaround time compared to conventional histology, which requires dehydration, wax infiltration, embedding, and sectioning over a minimum of 24 hours. In contrast, the 3D processing protocol—comprising tissue clearing and fluorescence staining—can be completed within 4–5 hours for core needle biopsy specimens.

In pre-clinical studies, the Patho One system has generated diagnostic-quality images from a diverse array of human tissues (both normal and neoplastic), including gastrointestinal, breast, brain, thyroid, parotid, lung, kidney, and ovarian specimens (Figure 1D). The platform is integrated with stereological measurement software for quantifying key pathological parameters such as tumor size and infiltration depth. Moreover, a reverse transparency technique allows the same imaged specimens to be subsequently used for immunohistochemical analysis, DNA extraction, and Sanger sequencing, yielding satisfactory results. Together, these advancements position 3D pathology as a mature technology ready for clinical adoption with transformative potential.

CHALLENGES AND OPPORTUNITIES IN CLINICAL TRANSLATION OF 3D PATHOLOGY

Platforms of Intoto Biotech's Patho One system demonstrate that 3D pathology is on the cusp of clinical adoption. However, its widespread implementation faces formidable barriers beyond the core imaging technology. First, shifting diagnostic paradigms entails significant economic and training investments. Early adopters must not only master the new technology but also redefine clinical significance within a volumetric context. Second, the workflow introduces technical complexities. Tissue processing requires further optimization for consistency, and the management of large-scale image data (typically hundreds of gigabytes per sample) poses substantial storage and computational challenges. Promisingly, advances in artificial intelligence for pathology data analysis are paving the way for next-generation, AI-driven diagnostic models derived directly from 3D datasets.[4] Such models could streamline analysis and reduce intermediate data burdens, accelerating clinical integration.

Meanwhile, 3D pathology techniques have the potential to be widely utilized in the research and clinical settings to tackle identification and characterization of challenging diseases. The goal for Intoto Biotech's Pano One platform, as well as for many others is to transform pathologists' perspectives, benefitting patients eventually. We envisioned that given its non-destructive nature, 3D pathology can be combined with additional tissue profiling technologies, such as spatial multi-omics, to provide an even more complete functional landscape of tissues.[5]

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.