

Will AI Hasten a Fusion of Pathology and Radiology for Cancer Research, Diagnosis, and Drug Development?

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What do pathologists do?

Pathology is the medical specialty of diagnosing disease from tissues and liquids; in oncology, this is done by analyzing a portion of the tumor tissue via biopsies, resections, or cells in fluids. These tissues/cells are then chemically (e.g., hematoxylin and eosin, or papanicolaou) or immunohistochemically stained and viewed by a pathologist under a microscope. Pathologists provide the gold standard for diagnosis and with the use of molecular tools, help clinicians provide treatment recommendations [1]. Limitations of pathology include the sub-sampling of the tumor and visual analysis by only human cognition.

With the advent of digital slide scanners, glass tissue slides can be converted into gigapixel-sized images [2]. With this transition to digital, pathologists can utilize image analysis algorithms to help interpret these images. More specifically, Artificial Intelligence (AI) algorithms are showing tremendous progress in helping pathologists identify and grade tumors [3-4]. Furthermore, by analyzing large imaging data sets with AI, it has been shown that these algorithms can perform tasks that pathologists cannot do such as predicting gene mutations, RNA transcriptional profiles, and even survival outcomes [5].

What do radiologists do?

Radiology is the medical discipline that uses medical imaging to diagnose and treat diseases. Commonly used imaging modalities include but are not limited to X-ray, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and positron emission tomography (PET). There are mainly two types of radiology applications - diagnostic radiology and interventional radiology. In oncology, diagnostic radiology involves detecting and characterizing tumors, in addition to monitoring a patient's response to treatment. Meanwhile, interventional radiology uses imaging to help guide procedures to make more definitive diagnoses or direct further medical treatment. Example procedures include image-guided biopsy and tumor ablation therapy.

Radiology began its transformation into a digital specialty in 1978, based upon continuously evolving technologies (DICOM, radiography detector array, high-speed networks, etc.) [6]. As a result, AI methods have been applied to radiology image analysis for several decades. Most early AI methods, however, have often performed inferior to radiologists at the same task. Thus, they usually served as a second read in diagnostic tasks and relied on the clinician's correction. Earlier developed computer-aided detection/diagnosis (CAD) systems also struggled to show improvement when comparing the performance between aided and unaided readers. Recent deep learning algorithms, however, can match and even surpass radiologists in narrow task-specific applications thanks to big data and advanced AI techniques [7]. While medical imaging is primarily used to determine the present condition of a patient's disease, efforts are also underway to extract quantitative information to enable earlier identification of disease, detect changes in disease status, and assess treatment efficacy. AI tools have been developed to automate such quantitative tasks to a certain extent, such as segmenting and quantifying the volume of a lesion, which are typically tedious and time-consuming for human experts to perform. However, making radiology a more quantitative science is hindered by its resolution and reproducibility due to a wide range of variations in image acquisition conditions.

How similar/different are pathology and radiology images?

While AI has demonstrated remarkable capabilities as applied to pathology and radiology images, it is important to discuss how interpretations

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Citation: Li Q, Dillon LAL, Hipp J (2021) Will AI Hasten a Fusion of Pathology and Radiology for Cancer Research, Diagnosis, and Drug Development? *J Clin Anat Pathol*, 6(1): 110. DOI: <https://doi.org/10.47275/2332-4864-110>

Received: January 22, 2021; **Accepted:** January 22 29, 2021; **Published:** February 08, 2021

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of these images are currently utilized in clinical practice. For example, radiology images, while able to assess the entire tumor, often provide 'impressions' of the lesion's disease state. It is then up to the oncologist to interpret the images in the context of other patient variables to make a treatment recommendation. Radiology can identify tumors and make recommendations about the potential malignancy and stage; however, the pathology analysis is often needed for a definitive assessment. In contrast, while the pathology image often represents a sub-set of the entire lesion, its interpretation often points to direct, actionable next steps for the oncologist. Also, the radiology image is a direct representation of the lesion density and/or function itself, while pathology differs in that the lesion is first made into a glass tissue slide which then undergoes staining and digitization. Thus, the pathology image provides a 'window' into the tumor itself, which then is often analyzed by molecular techniques such as immunohistochemical staining and molecular sequencing.

Early work has shown that AI algorithms trained on radiology images alone may determine the malignancy and subtype of a lesion, detect certain gene mutations, and provide prognostic and predictive information [7]. These new developments may enable future applications of radiology to assist clinicians in making diagnosis and treatment decisions earlier on in the patient workup. However, before they are clinically validated, their use in practice is limited.

What happens when leveraging both pathology and radiology via AI?

In cancer patient diagnosis and treatment, there are opportunities to leverage both radiology and pathology data for better prediction of disease status and patient outcome. With AI, thousands of features can be extracted from both datasets. There are at least two approaches to fuse them: one is to combine the features and hope to gain improvements in specific clinical tasks assuming there is complementary information embedded in each data type; the other approach is to identify correlations between the two datasets to enhance the understanding and utility of each data type. There are many ways to integrate data from two modalities in machine learning. For instance, autoencoder, a type of AI algorithm, can learn a low dimensional representation (e.g., a series of numbers or a feature vector) from high dimensional data (e.g., images, natural language) while retaining important information. With such algorithms, one can encode data from each modality into its feature vector and then concatenate them into one as input for building a classifier or prediction model [8]. For the second type of fusion, with accurate radiology-pathology co-registration (i.e., spatially aligning the *in vivo* radiographic imaging and *ex vivo* histology), one may discover radiographic imaging features correlated with tissue histomorphometric changes and thereby better characterize disease [9-10]. If one can correlate radiological changes to pathological changes such as immune cell infiltration or necrosis seen in the tumor microenvironment, it might lead to more biologically meaningful biomarkers to patient response in comparison to the commonly used RECIST criteria [11]. Even without highly accurate alignment, in radiomic model development, one can still select well-known prognostic and/or predictive pathological measurements as tumor-level labels [12-13]. The validated pathology-informed radiomic score can further be estimated for tumors without a tissue sample. This potentially provides a way to investigate the pathological or molecular heterogeneity of tumors via a non-invasive approach.

Do technologies exist which can bridge between both pathology and radiology?

Aside from image analysis and machine learning techniques, there are also new technologies that directly bridge pathology and radiology. For example, immunoPET - a molecular imaging technique that uses PET to visualize the distribution of radiotracers against targeted immune markers - enables the imaging of specific markers on immune or tumor cells which are conventionally assessed in pathology with the use of immunohistochemical stains [14]. ImmunoPET can provide a whole-body assessment of the distribution of the target biomarker, including information on heterogeneity within and between lesions for a given patient. ImmunoPET is beginning to be used in the clinic, including to assess PD1, CD8, Granzyme B, AraG, PDL1, and HER2 [15-20]. As clinical implementation continues, it will be important to better understand the technical limitations of the technology - including its reproducibility, spatial resolution, the limit of detection - and how the distribution of immunoPET markers, and changes in these over times, relate to patient response to treatment.

A fusion of pathology and radiology for drug discovery, clinical care/primary diagnosis, and CDx

When it comes to clinical care, a fusion of pathology and radiology has the potential to improve diagnostic accuracy. More importantly, the use of radiology imaging for the prediction of patient response to treatment has not yet been maximized. One advantage of radiology imaging is that it is relatively inexpensive and practical to obtain at multiple time points and is non-invasive. However, in clinical trials for cancer patients, RECIST measurements remain the primary metric to track disease change. By leveraging molecular-level information contained in radiology images via methods described earlier, we foresee earlier treatment adaptation based on more sophisticated radiomic/delta-radiomic features combined with pathologic information. Predictive models built from radiology and pathology data may also lead to image based CDx (Companion Diagnostics), either for new indications for use or for existing indications to replace approved non-imaging CDx which may have inferior performance and/or greater cost. These developments, if successful, will accelerate the introduction of new therapeutics, improving patient selection for clinical studies and advancing precision medicine.

How may the roles of pathologists and radiologists change in the future?

Based on the above, we see a potential dovetailing of the medical disciplines of pathology and radiology to provide a synergistic enhancement of patient care. One could imagine future medical trainees may undergo cross-disciplinary sub-specialty training to interpret the results of AI and image analysis. This would not be new to medicine as one looks at the current paradigm of pathology and dermatology training where dermatologists can undergo partial pathology training to diagnose dermatopathology specimens. Based on the complexity of the pathology diagnostic workflow, we see an initial potential trend where pathologists undergo radiology-specific AI training and use information from, for example, CT and/or immunoPET images to augment their pathology diagnoses.

Conclusion

The futures of pathology and radiology will almost certainly change due to the adoption of AI algorithms and newer imaging modalities such as immunoPET. How and when these changes will occur is unknown but will likely start in the drug development/clinical trial space where decision-making on the continuation of drug trials is based on patient pools where translational science decisions, rather than clinical decisions are made by drug project teams. The demonstration of value in the clinical trial setting will then likely drive adaptation/adoption of patho-radiomic AI methods in the clinical workflow.

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