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Review Article

Imaging bridges pathology and radiology

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A R T I C L E I N F O

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A B S T R A C T

In recent years, medical disciplines have moved closer together and rigid borders have been increasingly dissolved. The synergetic advantage of combining multiple disciplines is particularly important for radiology, nuclear medicine, and pathology to perform integrative diagnostics. In this review, we discuss how medical subdisciplines can be reintegrated in the future using state-of-the-art methods of digitization, data science, and machine learning. Integration of methods is made possible by the digitalization of radiological and nuclear medical images, as well as pathological images. 3D histology can become a valuable tool, not only for integration into radiological images but also for the visualization of cellular interactions, the so-called connectomes. In human pathology, it has recently become possible to image and calculate the movements and contacts of immunostained cells in fresh tissue explants. Recording the movement of a living cell is proving to be informative and makes it possible to study dynamic connectomes in the diagnosis of lymphoid tissue. By applying computational methods including data science and machine learning, new perspectives for analyzing and understanding diseases become possible.

The multidisciplinary nature of medicine

Medicine has become increasingly multidisciplinary. Multidisciplinary has proven to be highly effective over the past decades. It has been applied in both diagnostics and therapy, where radiologists visualize tumors with X-rays, pathologists examine histological sections, and surgeons excise tumors. However, it is becoming more and more obvious that a comprehensive definition of a clinical picture is not possible through the independent consideration of different tumor characteristics. Experts from various medical disciplines have set up interdisciplinary tumor boards for several years to improve the diagnosis and treatment of individual tumor patients.

An example is the interdisciplinary identification of sentinel lymph nodes (SLNs).[1–3] Here, the average number of extirpated lymph nodes per patient as well as related side effects could be reduced through the incorporation of non-invasive macroscopic methods from nuclear medicine and histological investigations used in pathology.

The formation of interdisciplinary medical specialties and the combination of various types of data leads to an increase in data complexity. The increase in complexity hampers individual experts to evaluate the data on their own. Here, computer-assisted detection (CAD), including machine learning and data analytics, will create opportunities for a new understanding of interdisciplinary tumor characteristics.[4,5]

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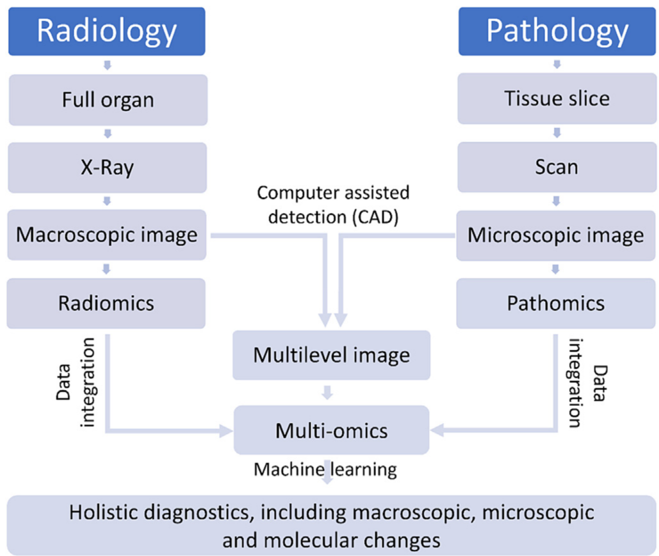

Fig. 1. Workflow to visualize and analyze organs and tissues in radiology and pathology. The flow chart illustrates possibilities to combine disciplines.

It is obvious, that digitalization enables a tremendous power of data acquisition.[6,7] Digitized images change many established procedures in the way to handle clinical diagnostic and therapeutic processes,[8] shown in Fig. 1. Radiology and nuclear medicine pioneered the digitalization of data. Pathology is only starting the digital transformation.[8] Digitalization will bring more and more established disciplines closely together.[6]

A comparison of radiology, nuclear medicine, and pathology

Until now, there are still differences in diagnostic opportunities between radiology and nuclear medicine on the one side and pathology on the other. In radiology and nuclear medicine, non-invasive techniques such as X-ray and ultrasound are used to define tumor infiltrates. The applied techniques lead to macroscopic images that enable the measurement of structures in the resolution of cm and mm. Additionally, biological processes can be visualized with the help of tracers to measure hypoxia or to figure out special pathways. In contrast, pathological examinations are based on invasively obtained biopsy material. Tumor characteristics are defined at a microscopic scale, ranging from mm to µm. In pathology, immunohistochemistry and immunofluorescence provide high specificity and sensitivity to detect and characterize a positive cell within a population of thousands of negative cells. Commonly applied methods are light microscopy, confocal laser, spinning disc laser microscopy, and light sheet microscopy.[9–11] Even higher resolutions are possible by electron microscopy and cryo-electron tomography. The information of the cell can be additionally enriched by molecular features through the detection of proteins (immunohistochemistry), RNAs (*in situ* hybridization), and DNA mutation analysis (deep sequencing, methylation, and others).[12,13]

Apart from the different opportunities that arise from these medical sub-disciplines, they also differ in the challenges that need to be overcome. Imaging techniques in radiology and nuclear medicine face up with lower resolution than microscopic images in pathology. On the other hand, the high resolutions biopsy material has the downside of a restricted and limited area that can be examined. There is also a risk of clinical complications in pathology due to the invasiveness of tissue extirpation.

Digitization and computer-assisted detection in the clinical context

In radiology, the resolution of techniques is steadily increasing. The risk of clinical complications in pathology is steadily decreasing due to smaller biopsies. Even though, both disciplines can benefit from each other. Prerequisites for interdisciplinary workflows are the identification and definition of interfaces. The data must be comparable, standardized, and of high quality.[14] CAD and machine learning methods offer possibilities for data normalization, localization, analysis, and integration.[15,16] The latest developed computational methods propose the simple and practicable integration of standardized pipelines to benefit from CAD methods in everyday clinical practice.[9,10,17–23] Clinical routine shows that many issues and challenges need to be resolved before the advantages of digitalization and CAD methods can be fully exploited.

a) Which data are useful?
b) What is necessary to generalize the quality of medical data?
c) What degree of quality, standardization, and comparability of medical data is sufficient to integrate CAD methods?
d) What kind of CAD methods are applicable in the daily routine?
e) How can machine learning methods be effectively used in the context of medical data which are characterized by their rarity and uniqueness?
f) How can the turnover rate of translational approaches be increased?

A good example of how to push digitalization can be seen in the development of radiology over the last few years. Radiology started digital image processing several years before other clinical disciplines. In radiology, one of the driving forces was the reduction of costs of archives of conventional X-ray images, as well as enhancing the speed to produce these images compared to conventional photographic techniques. In addition, sending conventional images to other clinics is time-consuming.

Concerning digitalization, pathology is several years behind radiology. The reasons are multifaceted. One of the most important reasons is the cost. The implementation of digital pathology is expensive. Associated initial investment volume of a million and more euros is a serious obstacle for many clinics. Note that, the hematopathological examination is balanced with comparable low running costs. Established workflows must be changed dramatically. New generalized guidelines for medical data standardization and quality must be developed and introduced. Standardization and quality control are needed because CAD methods are much more vulnerable to deviations and artifacts of the dataset than visual inspection by humans.

Besides the analysis of raw data, machine learning methods are more and more used for post-processing tasks.[18,24] Modern machine learning algorithms are employed to identify and verify new essentials and correlations of data sets at a scale that may exceed human capabilities. The combination of computational efficiency with the human capability for interpretation and abstraction enables a new level of comprehension of the human organism and neoplastic changes. The usefulness of methods and applications of machine learning systems have to be evaluated to assist physicians in daily standard tasks.[25–27] The specific goals and requirements of digitalization should be discussed, defined, and formulated together by radiology, nuclear medicine, and pathology:

a) Precise the diagnosis
b) Compressing data with archives and files
c) Discovering digital biomarkers
d) Quantifying markers on cell surfaces and intracellular niches etc.

Digitization and computer-assisted detection in the context of science

Computer-aided systems and machine learning methods will be essential aid in diagnostic and therapeutic processes. However, the precise and realistic definition of short-term goals remains open. It has to be distinguished between scientific goals and goals for routine clinical practice. In scientific research, a better understanding of the behavior of tumor cells and their microenvironment could be a priority. Tracking a tumor and its surrounding cells throughout the body with low- and high-resolution imaging techniques will provide valuable insights to the researcher. The additional inclusion of data on cell motility, tissue structures, molecular components of a cell, and signaling pathways will further complement this. In comparison, combining all of these techniques is not practical in clinical practice due to the high cost and time involved.

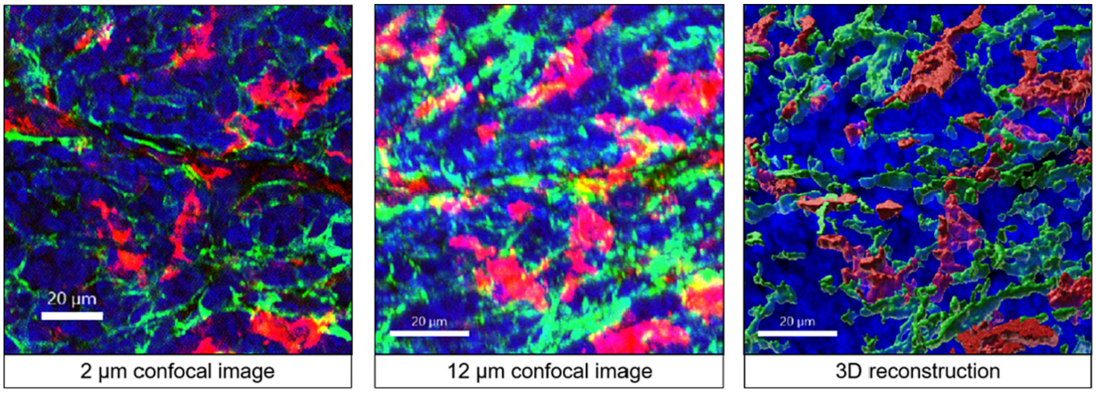

Fig. 2. Sinus network of a human lymph node visualized by confocal microscopy. The tissue sample was immunostained with smooth-muscle actin (green) to visualize fibroblastic reticular cells and CD68 (red) to highlight macrophages. The impact of different tissue preparation and image processing methods is shown.

In the following, we exemplify 2 new technologies that can bridge pathology and radiology. Modern confocal laser microscopes enable efficient 3-dimensional visualization of histological tissue samples. Sensitive photon detectors, fast automated scanners, and stable immunofluorescence produce high-quality images in the µm range in minutes. This detailed visualization of the entire cell surfaces reveals cellular networks, so-called connectomes,[22] e.g., see Fig. 2. Capturing connectomes in different organs such as the immune system can provide new insights into the functional understanding of immune cells and lymph node disorders.[9] In addition, 3D histological sections can enable the localization of microscopic images in 3D radiological images. Thus, 3D connectomes can be linked to radiological 3D visualizations to provide an augmented multi-layered perspective of tumors and organs. This augmented representation could be used to identify and interpret possible correlations of microscopic and macroscopic changes in the future.

To understand the interrelation between cellular networks and phenotypic changes of organs, e.g., lymph nodes, it is indispensable to understand underlying cell dynamics.[28] Investigating large amounts of cells in time and space, machine learning turned out to be helpfull.[28] Cellular interactions in some organs, such as the brain, may be relatively stable and static. In the immune system, the movements of most cells are fast, and interactions are highly dynamic. Several studies in mouse models have characterized the fast speed of T-lymphocytes that migrate along reticulum cell networks in lymph nodes.[29] Immune cells have been tracked in various reactive and neoplastic murine organs.[29] Recently, a technology based on thick slices (400 µm) of human tissues combined with confocal imaging has been established.[11] The approach allows the analysis of dynamic cellular networks in a preserved environment using CAD technologies,[11,19,30] see Fig. 3.

The combination and integration of microscopic cell tracking, macroscopic visualization, and nuclear tracing provide a comprehensive visualization and a completely new understanding of the flow and behavior of reactive and neoplastic cells within and across organs.

The future concept of medicine: Integrative, holistic, and individual diagnostics and therapy

Incorporating multiscale approaches based on radiology, nuclear medicine, and pathology will be a future concept in integrative diagnostic and cell therapy to cover a holistic scope of possible neoplastic changes, as shown in Fig. 4. CAD methods and machine learning will play a major role in aggregating, structuring, and understanding acquired and designed data and abstraction levels. The ongoing integration of CAD methods in clinical practice and the establishment of interdisciplinary workflows will enable inevitable and holistic medical approaches to improve the diagnosis and treatment of individual patients.

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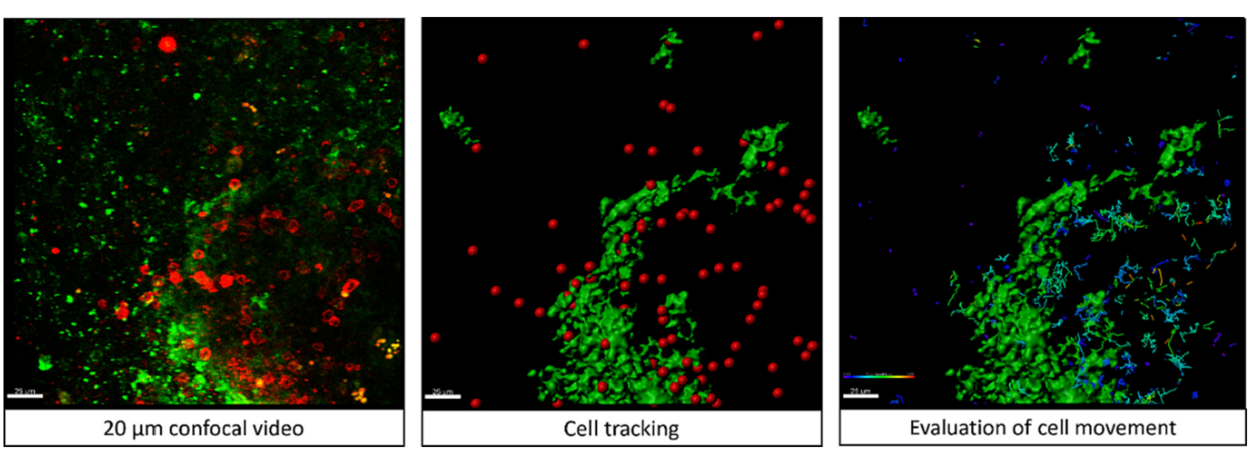

Fig. 3. Movement study of lymphadenitis with confocal laser. Left picture: A confocal image showing the network of follicular dendritic cells (FDC) stained with an anti-CD35 antibody (green), and follicular T helper cells visualized with an anti-PD1 (red) antibody. Middle picture: An image showing the automated detected cells using the spot function of the Imaris software. Right picture: The colors of vectors indicate low speed (blue), medium speed (green), and high speed (red) of follicular T helper cells during a 20-min recording.

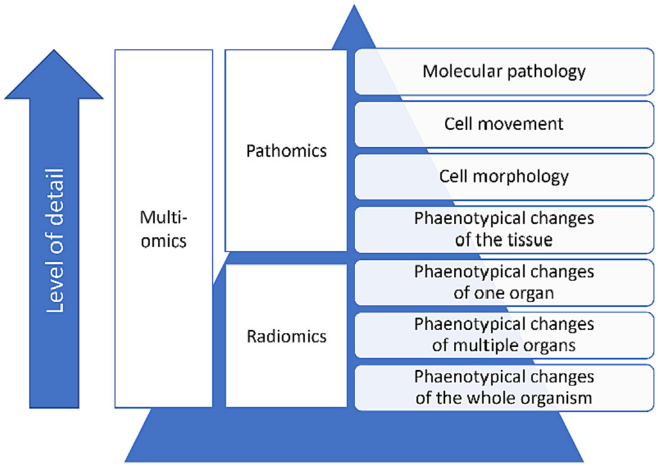

Fig. 4. Features of holistic diagnostics for the incorporation of methods from pathology, radiology, and nuclear medicine.

Author contribution statement

M.L. Hansmann designed the Idea for this review and P. Wurzel directed the review. M.L. Hansmann conceptualized and prepared the Manuscript in cooperation with S. Scharf and P. Wurzel. All authors made contributions on literature search and carefully reviewed the review.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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