Contribution of Measurement to morphologic Diagnostics

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Interactive publication of

Limits of Morphological Diagnostics

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Abstract

Background: Morphological findings have a particularly high significance in medical diagnostics. In most diseases they are regarded as “gold standard” and as a benchmark for the results of other methods of examination. The basis of morphological diagnostics is the intuitive pattern recognition leading either to a definite medical diagnosis or to a differential diagnosis. The clarification of the differential diagnosis may be assisted by algorithms and other decision making methods.

General survey: Morphological diagnostics encounters epistemological, individual, methodological, communicative, economical and ethical limits. Objective limits result from cognitive science and methodology. A fundamental methodological limit consists in the static method of approach to a dynamic process. Subjective limits are the result of individual differences in diagnostic capabilities and in deficiencies in the communication between pathologists and clinicians.

Conclusions: The limits of morphological diagnostics cannot be suspended but they may be shifted outwards. Deficiencies in morphological diagnostics may be negotiated by training and experience. Telepathology, digital pathology and virtual microscopy are valuable tools to improve the quality of morphological diagnostics.
Interactive contribution:

Pathologists' diagnostics are based upon morphology, which means to distinguish between structure and function. Morphology is the evaluation of biological structures. These are ordered clusters of material (genes, nuclei, cells, organs, etc.) that remain constant during the period of detection and observation. The observation time is an important factor that defines biological structures and diagnostics too. The implementation of measurement-based diagnostic algorithms improves the accuracy and serves for quality assurance in tissue-based diagnosis.

Keywords: Morphological diagnostics; epistemological, methodological, individual, communicative, economical and ethical limits.

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Introduction contribution

In principle, medical diagnosis forecasts and contributes to the interaction on the development of health aberrations. Starting from a broad set of information it finally ends in a digital (yes or no) decision. For example, whether anti-inflammatory drugs should be given to a child or not, whether on a cancer should be operated or not, whether additional therapeutic actions should be undertaken or not [1]. The general algorithm is shown in (fig. 1). Tissue-based diagnosis should be distinguished between conventional, prognosis-associated, predictive, and risk-associated kinds (fig. 2) [2]. Conventional diagnosis requires at least microscopic images acquired from HE stained glass slides. Immunohistochemistry is mandatory to state prognosis-associated and predictive diagnoses, whereas DNA and gene analysis is mandatory to state risk-associated diagnoses. Digital pathology requires virtual slides or digitized snapshots of appropriately stained glass slides if it should be included into the pathology laboratory work flow (fig. 3). Completely digitized images (virtual slides, VS) form the basis of image analysis and adequate measurements. Most of the measurements analyze objects, such as nuclei, membranes, vessels, etc., some investigate in structures which are per definition higher order objects, and only a few focus on textures, which are pixel-based objects [3]. All these quantitative image analyses contribute to improved morphological diagnosis in terms of specificity and sensitivity.

Definition of terms

Conceptually we have to distinguish between medical diagnosis and medical diagnostics. In general diagnosis means the allocation of phenomena and facts to a definite category. In analogy, the medical diagnosis is the allocation of findings to a disease entity. Diagnostics is the way how to get to the diagnosis. The methods to
render a diagnosis include the clinical history, clinical examination, radiological findings as well as the histo- or cytopathological examination.

Two different types of diagnoses are possible: a positive diagnosis and a diagnosis per exclusion.

A positive diagnosis relies on findings with a high specificity for a certain disease. But such specific findings are still rare and most of diagnoses are diagnoses of exclusion based on a differential diagnosis.

A differential diagnosis considers all conceivable diseases which may be the cause of special findings or symptoms. As the result of differential diagnostic considerations all other debated diseases except one are excluded by means of immunohistochemical, molecular or cytogenetic methods.

![Figure 1: Cryptococcal meningitis, cytological finding of cerebrospinal fluid as an example of a positive diagnosis.](image1)

![Figure 2: Histological picture of a non-neural granular cell tumor, a case from the Histopathology Forum of iPath, as an example of a differential diagnosis.](image2)

[Figure 1] shows an example of a positive diagnosis. This cytological picture of cerebrospinal fluid is specific for cryptococcal meningitis. The once acquired visual engramm allows a definite diagnostic assessment.

The microscopic picture of a skin tumor in [Figure 2] is also characteristic, but it is not specific. The tumor consists of strands and nests of clear cells with small bland nuclei. The strands are separated by small arborized capillary vessels. The growth pattern is reminiscent of endocrine tumors. This tumor was presented and discussed 10 years
ago in the iPath telepathology system. It stems from the lower leg of a 49 years old Lithuanian patient. The differential diagnosis includes 10 tumor entities with significant differences in dignity and prognosis. Metastatic renal clear cell carcinomas and clear cell sarcomas are clear cut malignant; granular cell tumors, xanthomas and clear cell dermatofibromas are benign tumors; and dermatofibrosarcomas, PEComas and neuroendocrine tumors are potentially malignant.

**Differential diagnoses:**
- Dermatofibroma, clear cell type;
- Dermatofibrosarcoma protuberans;
- Renal clear cell carcinoma;
- PECOMA;
- Clear cell sarcoma;
- Clear cell parangangioma and neuroendocrine tumors;
- Xanthoma;
- Neural granular cell tumor;
- Non neural granular cell tumor

**Immunophenotype**
- S100 –
- Chromogranin –
- HMB 45 –
- Panzytokeratin –
- NSE +
- Vimentin +
- CD68 –
- SMA –
- Desmin –
- CD34 –

The results of immunostains allow in this case the exclusion of 9 from 10 differentials. The expression of vimentin and neuron specific enolase leads to the final diagnosis of a non-neural granular cell tumor. These tumors are negative for S100-protein and have to be distinguished from the more common S100-positive neural granular cell tumors [2].

The differential diagnosis is the real intellectual effort of pathologists in morphological diagnostics. As benchmark and claim on this effort hold that, what Karl Popper generally stated for all scientific activities [3]:

We cannot be sure that our theory is not invalid. All what we can do is to search for its falsifiability. That is done by trying to disprove the theory and by a serious investigation in the light of our objective knowledge and with all our inventive talent“.

**Significance of morphological diagnostics**

Morphological findings have a particularly high significance in medical diagnostics. In most of diseases morphological findings are regarded as „gold standard“and as the benchmark for the results of other methods of examination.
For example, the results of PSA-tests as a screening method for prostatic carcinomas are validated on the findings of prostatic needle biopsies. The specificity and sensitivity of morphological findings is usually higher if compared with other methods of examination. This is the rational basis of the relationship between pathologists and clinicians. This relationship is nowadays closer than before and obtained a new dimension by the predictive pathology. Such an evolution could never be anticipated. A hundred years ago many pathologists forecasted a dismal prognosis for their own specialty and declared a decline of morphological requirements. The opposite has happened since then. The morphology asserted its position and the morphological requirement is at present greater than before. The reasons for that development are not only the improved techniques for biopsies but, first of all, the method of morphological examination allows to get a correct diagnosis in an acceptable time and with a comparatively low expenditure.

**Interactive Contribution**

The specificity of conventional tissue-based diagnosis is remarkably improved by immunohistochemistry / ligand histochemistry and molecular genetic examinations. These are mandatory to clearly identify therapeutic issues of certain cancer cell types such as lymphomas, or breast carcinomas, lung cancer, etc. [4]. The application of Image analysis to state prognosis-associated and predictive diagnosis is often performed on visualization of antigen-antibody expressions such as Her2/new or hormone receptors, and graded into clinically useful terms, such as grade 1, 2, or 3. Improved therapeutic advises can be offerted if more detailed measurement results are transmitted to the clinicians. The constraint of such algorithms can be seen in missing communication standards.

**Theoretical basics of morphological diagnostics**

The origin and basis of morphological diagnostics is the intuitive pattern recognition. It leads either directly to the diagnosis or to a differential diagnosis which may be settled with ancillary methods. For the clarification of the differential diagnosis there are algorithms and other decision making aids, usually with a hierarchic structure, which enable the consideration of additional, for instance immunohistochemical, findings.

The Bayes’s theorem [1] relies on the probability theory and indicates the calculation with conditional probabilities. The presented formula considers only two events but it can be expanded and applied to any number of events.
Calculation with conditional probabilities:

- \( P(A) \) a priori probability for \( A \).
- \( P(B|A) \) probability for \( B \) under condition of \( A \).
- \( PPV \): positive predictive value (probability of a certain disease in case of a positive test result).

Based on this theorem the probability of a certain disease can be predicted. The positive predictive value (PPV) is calculated from the prevalence of the disease and the sensitivity and specificity of a diagnostic test or procedure. The calculated value indicates the probability of a certain disease for a positive test result.

Moreover the application of the Bayesian rule offers a decision support in problematic cases with ambivalent morphological findings. In biopsies, for example, it is not always possible to distinguish between a Spitz’nevus and a malignant melanoma, or between a giant cell tumor of bone and an aneurysmic bone cyst. In such cases information about the probability of eligible diseases in the age group of the patient may be helpful. It can be calculated from the prevalence and the age distribution of the diseases.

**Limits of morphological diagnostics**

The limits of morphological diagnostics may be arranged from different points of view:

- Epistemological limits,
- Individual limits,
- Methodological limits,
- Communicative limits,
- Economical limits,
- Ethical limits.
Objective limits result from cognitive science and methodology. Together with economical limits they are felt from physicians and patients as fateful.

Subjective limits are the result of individual differences in diagnostic capabilities and of deficiencies in the communication between pathologists and clinicians.

Ethical limits are also of subjective nature. Like their colleagues in other medical disciplines pathologists are bound to the professional code of ethics.

**Epistemological limits**

Essential limits of morphological diagnostics consist in the perception and the process of cognition. The German philosopher I. Kant came to the conclusion:

„Pure apperception without terms is blind and terms without apperception are empty“.

The second part of this sentence has to be modified in views of the modern physics. But the first part is indisputable valid. The recognition and interpretation of images requires knowledge which has to be acquired by experience and education. That’s not only true for the pathology and other empirical sciences, it is the same for the art. J. W. Goethe as a painter and morphologist summarized that in his statement:

„You see only what you know“.

Figure 3: Demonstration of Helicobacter pylori in a Giemsa-stained slide of a gastric biopsy.
One of the most impressive proofs for this insight in modern medicine is the rediscovery of Helicobacter pylori.

Spirilliform bacteria were seen hundred years ago in human beings and animals on the surface of the gastric mucosa but their significance remained open. Later on this observation has been forgotten. It was a widespread conception that bacteria are not viable in the environment of gastric acid.

Since the emergence of gastric biopsies in the fifties of the last century many pathologists have registered inconspicuous tiny bacteria on the surface of the gastric mucosa and believed these might be artefacts or apathogenic bacteria.

Neither pathologists became aware in Giemsa-stained slides for the diagnosis of malignant lymphomas with a more selective demonstration of the microorganisms [Figure 3]. Marshall and Warren, a microbiologist and a pathologist from Australia did not resign to this fact and detected in 1984 Helicobacter pylori as the cause of most cases of gastritis and peptic ulcers [4]. Twenty years later their detection was honored with the Nobel Prize. The circumstances of the rediscovery remind to the early history of bacteriology. Like M. v. Pettenkofer’s self-experiment with cholera bacilli Marshall drunk a test tube with Helicobacter pylori and became promptly ill from a peptic ulcer which could be cured with bismuth and antibiotics. The wife of his colleague Warren was then the first patient with a successful Helicobacter eradication.

Since that time most cases of peptic ulcers and gastritis have not been furthermore considered as psychosomatic but as infectious diseases. Moreover, the detection of Helicobacter pylori brought the crucial breakthrough in the pathogenesis of MALT-lymphomas.

**Individual limits**

Individual limits of morphological diagnostics depend on experience and education.

In the professional life of a pathologist different stages of diagnostic certainty may be distinguished:

- 1st stage: justified uncertainty
- 2nd stage: unjustified certainty
3rd stage: unjustified uncertainty
4th stage: justified certainty (?)

Medical assistants start their education in a stage of justified uncertainty. It follows the stage of unjustified certainty usually after the certification as specialists. With an increasing body of experience the second stage is replaced by the third stage of unjustified uncertainty. The majority of pathologists persist in this stage up to retirement. The last stage of justified certainty is equivalent to inerrability and should be reserved to higher instances. Experienced chiefs and directors of institutes with enough self-criticism will be well-advised if they don’t identify theirselves with this last stage and elderly colleagues should take care this stage may be confused with old age obstinacy.

Methodological limits

A fundamental methodological limitation of morphological diagnostics consists in the static method of approach to a dynamic process. Diseases proceed in the dimension of time. With biopsies we record only a temporary state or a snapshot of a contiguous film from which we have to draw conclusions about the entire action.

The quality of morphological diagnostics is essentially determined by the application of modern methods which are not available everywhere especially not in developing countries. In routine pathology such ancillary methods are really required in about 5% of cases. But in some areas, for instance in hematopathology and oncopathology modern diagnostics is not imaginable without immunohistochemical or molecular methods.

Another point of view concerns the quality of the applied methods as well as an adequate fixation, staining and preparation of specimens.

Of course we are relied on tissue material which is provided from clinicians and of which we assume it is representative of the whole clinical finding. Problems may result from the heterogeneity of tumors and of discontinuous morphological findings in inflammatory and degenerative diseases.
Figure 4: Two histological pictures from a Sertoli-Leydig cell tumor. Only B is representative.

[Figure 4] demonstrates the significance of a representative picture selection. It’s an ovarian tumor from a 20 years old woman. The left side of the figure is characteristic of an ovarian fibroma. But the right side contains sheets of typical Leydig cells and leads to the diagnosis of a Sertoli-Leydig cell tumor.

Adequate image selection plays an important role in telepathology. Inadequate image selection and poor image quality are frequent causes of diagnostic discordance.

Communicative limits

Another cause of diagnostic discordance in telepathology is a deficient communication.

However, deficiencies in communication are not confined to telepathology but a general problem in morphological diagnostics.

The communication in pathology happens on two levels:

The first level is the communication with clinicians. A lack of information about the clinical history, localization or radiological finding is the most frequent cause of doubtful and inaccurate morphological diagnoses.
The second level is the communication of pathologists among each other about the exchange of previous findings, the realization of supplementary examinations and the usage of reference centers. This level includes the consultation of colleagues in the same or another institution as well as the teleconsultation.

An essential point of communication in telepathology is the request for additional images and information.

**Economical and ethical limits**

The foreseeable benefit for the patient is the crucial precondition for the application of morphological diagnostics. The benefit must not ever be an active therapy it may be also the justification for a wait and watch management or for the termination of a running therapy.

The foreseeable benefit has to be opposed to the risk, the costs and the impairment of the patient. Risk and impairment are usually in charge of clinicians or surgeons. The costs become a limiting factor, if patients or health insurance companies are not willing or able to bear the expenses.

Ethical problems arise, if necessary but expensive ancillary methods cannot be applied for economical restraints. Particularly immunostains are often not possible because patients in developing countries are not able for the assumption of additional costs.

**Interactive Contribution**

Every technique has its limitations. Quantitative morphology can improve the recognition of image content information (ICI), which is the information of an image that is not dependent upon the viewer or pathologist [5]. Obviously, the pathologist has to understand the submitted image content information in order to perform appropriate reactions (see fig. 4) [4]. Interestingly, ICI is transmitted in images too, and only in series of numbers or in mathematical functions, if computerized interpretation is wanted [5]. These images require new training and understanding. They can offer images that are easier to interpret than the original counterparts (see fig. 4).

**Conclusions and outlook**

In summary it can be stated:
1) The limits of morphological diagnostics cannot be suspended but they may be shifted outwards.

2) Deficiencies in morphological diagnostics may be completely or partially negotiated by training and experience.

3) Telepathology and virtual microscopy are valuable tools to improve the quality of morphological diagnostics.

**Interactive Contribution**

Digital pathology is often thought to only alter the diagnostic procedures in tissue-based diagnosis. Certainly, it does fullfill this job; however, it possesses a higher impact on the medical field of pathology, as shown in (fig. 4). It will most likely change important issues of surgical pathology, such as the pathologist’s reputation, understanding natural biological laws, judgment of biological structures in relation to function, or analysis of structures in relation to their position within and influence on the whole body

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1. References


Interactive Contribution

1. Kayser, K., et al., The concept of entropy in histopathological diagnosis and targeted therapy. Diagnostic pathology 2015, 1:97, ISSN 2364-4893


Proposed algorithm of medical diagnostics

- Symptoms – complains → crude diagnosis
  ↓
- Serum analysis → details (malignancy?)
  ↓
- Live imaging → localized lesion?
  ↓
- Tissue analysis → Disease details
  ↓
- Therapy

Fig. 1

Diagnosis types

- Classic diagnosis: HE stain; often “gold-standard”

- Prognosis estimation (quantitative immunohistochemistry)

- Therapy advises (quantitative immunohistochemistry, gene analysis, predictive diagnosis)

- Risk estimation (array technique): disease risk prior to manifestation

Fig. 2
Fig. 3

Fig. 4