Virchows Archiv (2019) 474:267–268
https://doi.org/10.1007/s00428-019-02548-2

NEWS

In this issue

Published online: 23 February 2019

This issue opens with a review by Santos-Silva et al. (https://doi.org/10.1007/s00428-018-02519-z) of the published literature on validation studies of diagnostic pathology using digital microscopy. The authors identified papers containing information on diagnostic accuracy using digital microscopy of more than 2000 cases. The good news is excellent intra-observer agreement with κ coefficients upwards of 0.8 to almost perfect. A discordance between the slide based and the digital histology-based diagnosis was noted in around 5% of cases. Half of the discordances occurred in cases in which uncertainty remained as to the final diagnosis. Strikingly, in about one third of the cases with a discrepancy between the slide diagnosis and the diagnosis by digital microscopy the digital histology diagnosis was deemed the best. Even though some studies reported image limitations as reason for (some of the) discordances, progress in digital imaging technology has been such that equipment is no longer a limiting factor. The only resolution issue that might persist is the recognition of micro-organisms. Some of the cited causes of a discrepancy were not related to digital microscopy per se (lack of clinical information, poor biopsy quality, insufficient marker studies). The paper provides additional evidence corroborating the validity of using digital histology for histopathological diagnosis.

Simons et al. (https://doi.org/10.1007/s00428-018-2504-0) tackle a disturbingly persistent diagnostic conundrum: how to distinguish between a primary mucinous ovarian carcinoma and a mucinous carcinoma metastatic to the ovary. In an attempt to develop a diagnostic algorithm, they managed to put together a cohort of almost 2000 cases, using the unique Dutch Pathology Registry which contains the histopathological diagnoses of all cases diagnosed in the country since the late eighties of the past century. Imagine the kind of cohorts that could be used for studies if this type of registry would exist in more and larger countries! The authors created an algorithm based on signet ring cell histology, laterality and a nomogram parameter using age and size, capable of diagnosing ovarian metastases of mucinous carcinomas with a sensitivity of 90% and a specificity of 60%. This small incremental improvement by itself provides no final solutions, and the authors carefully state that a conclusive diagnosis can only be reached when histology, markers and clinical and imaging data are taken into consideration.

The paper by Shinto et al. (https://doi.org/10.1007/s00428-018-02514-4) is an example of a well conducted immunohistochemical biomarker study. The authors addressed the question whether expression of mesothelin has prognostic value in colorectal cancer. Interindividual reproducibility in the visual assessment of the staining pattern was addressed. Cut-off values for making a positive or negative call were determined by ROC curve analysis. Results of immunohistochemistry were corroborated by Western blotting and RT-PCR experiments on subsets of cases. A distinction was made between a luminal and a non-luminal staining pattern. The main result of the study is the prognostic value of mesothelin expression, mainly in a non-luminal pattern, for both stage II and stage III patients. For two reasons the study is not ideal. Firstly, a validation set is missing, and this step in biomarker validation should be regarded as indispensable. Secondly, the mesothelin marker can be added to an almost endless list of similar immunohistochemical markers with prognostic value and the authors did not address its potential added value over other markers. It is most unlikely that new single markers will become essential in clinical decision making in colorectal cancer management.

A particularly interesting paper is that by Pool et al. (https://doi.org/10.1007/s00428-018-02512-6) on the follicular variant papillary thyroid carcinomas without evidence of invasive growth. For these lesions that carry a very low risk of metastasis, the term ‘non-invasive follicular thyroid neoplasm with papillary-like nuclear features’ (NIFTP) was introduced in a paper that was published just prior to the consensus meeting that led to the WHO classification of tumors of endocrine organs. Consensus could not be reached as leading thyroid pathologists considered a more generic terminology of ‘unknown malignant potential’ more appropriate while the group who published the NIFTP paper pushed their terminology through. The Pool paper provides evidence that tumors with a ‘BRAF-like’ gene

expression pattern are mostly invasive while those with a 'THADA-like' gene expression pattern are mostly non-invasive. A 'RAS-family-like' expression pattern did not discriminate between invasive and non-invasive tumors. Strikingly, NIFTPs appear to be molecularly heterogeneous, some being 'BRAF-like' while others 'THADA-like' or 'RAS-family-like'. The authors prudently conclude that molecular analysis cannot be used to define NIFTP. One could go one step further to conclude that this molecular heterogeneity casts doubt on the validity of the NIFTP concept. Only careful molecular dissection of large patient cohorts with a follicular variant papillary thyroid carcinoma without evidence of invasive growth followed over a long period of time will tell if NIFTP as an entity is there to stay.

One might have the impression that after a century and a half of detailed morphological analysis all is known about tumor morphology. Tot (https://doi.org/10.1007/s00428-018-2488-9) proves us wrong in reporting the morphology of breast carcinomas with acrosyringeal and eccrine ductal metaplasia, in relation to clinical and marker characteristics. Invariably, this somewhat novel histotype of breast cancer was triple negative, but the cases were clinically heterogeneous. The cover image is from this study and shows a bizarre gland-like structure composed of cells with a dense eosinophilic cytoplasm.

Finally, Fukuda et al. (https://doi.org/10.1007/s00428-018-2509-8) report on Xp11 translocations in renal cell carcinomas which lead to fusion genes involving the TFE3 gene, encoding a member of the microphthalmia-associated transcription factor family. The authors identified Ewing sarcoma breakpoint region 1 (EWSR1) as a novel fusion partner of TFE3. This finding expands the genomic spectrum of Xp11 translocations in renal cell carcinoma and suggests a role for the microphthalmia-associated transcription factor family in the pathogenesis of (some) renal cell carcinomas.