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EDITORIAL

Contemporary issues in breast pathology

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Editorial

This Annual Review Issue highlights contemporary issues in breast pathology. Updated diagnostic criteria for known entities and new tumor entities, as described in the 2019 (5th Edition) WHO Classification of Breast Tumors, are discussed as are their key clinical features and implications for treatment. Newer therapeutic approaches to breast lesions and new and emerging techniques for evaluation of breast specimens are also addressed.

In their article on *Breast carcinomas of low malignant potential*, Stuart Schnitt and colleagues discuss the clinical, pathologic, immunophenotypic, and molecular features of selected breast carcinomas with a low risk of metastatic spread to lymph nodes and distant sites. This group includes low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, encapsulated papillary carcinoma, solid papillary carcinoma, and tall cell carcinoma with reversed polarity. They emphasize the importance of recognizing and appropriately classifying these tumors to avoid overtreatment of patients.

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Luca Cima and colleagues provide new insights into recently established *triple negative breast cancer (TNBC) sub-categories with a favorable prognosis.* Many of these subtypes share features with salivary gland type carcinomas, including adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, secretory carcinoma, and tumors originating from adenomyoepithelial proliferations. The authors provide comprehensive diagnostic criteria with details of specific molecular alterations. They discuss the therapeutic implications of a diagnosis of low-grade TNBC which differ from those applied in the setting of high grade, No Special Type, TNBC.

Carmen van Dooijweert and colleagues review the topic of *histological grading in breast cancer* with fascinating historical aspects dating back to the 1900s. The authors provide a pragmatic approach to histologic grading by conventional light microscopic evaluation and describe the basics of grading providing didactic H&E sections for different scenarios. The paper addresses prognostic and reproducibility issues, especially in comparison to gene expression profiles, mitotic counts, and Ki67 proliferation index. The value of special stains to better recognize mitotic figures, regular training, and the use of artificial intelligence algorithms in improving grading consistency is emphasized. Gabor Cserni and colleagues provide a historical overview of the introduction of *sentinel lymph node biopsy (SLNB)* into the clinical management of patients with breast cancer. Their article includes a comprehensive review of the SLNB clinical trials that have informed and changed surgical and pathology practice. The review gives an insight into European National recommendations related to SLNB and differing practices in European pathology departments based on replies to questionnaires from pathologists in 38 countries. It highlights difficulties with SLN assessment and classification of residual nodal disease in the post-neoadjuvant setting and the review examines discordance between TNM and Residual Cancer Burden systems guidance in this context.

The introduction of mammographic screening during the past three decades has led to a major increase in the detection of *low-grade ductal carcinoma* in situ *(DCIS)*,

potentially resulting in overtreatment of a condition that may not have presented symptomatically or caused harm during the patient's lifetime. Sarah Pinder and colleagues present the morphological features and current knowledge of the natural history and prognosis of this entity. Their article includes a comprehensive review of the low-risk DCIS clinical trials to evaluate active surveillance as an alternative to surgical excision. The authors address the advantages and disadvantages of active surveillance and conclude that to "observe or excise" is neither "a simple question nor an easy one to answer." Edi Brogi provides a comprehensive review of *classic and variant forms of lobular carcinoma* in situ *(LCIS*) in her article. Helpful hints for distinguishing florid and pleomorphic LCIS from each other and from the classical form of LCIS are provided, and the uses and limitations of E-cadherin, p120 catenin, and beta catenin immunohistochemistry in distinguishing in situ lobular and ductal lesions are clearly discussed and illustrated. The clinical significance of these lesions in core needle biopsy (CNB) and surgical specimens is also discussed.

Melinda Lerwill and colleagues present a detailed overview of *fibroepithelial tumors* with clear diagnostic criteria to facilitate accurate classification. The review includes morphological descriptions of fibroadenoma variants including cellular, juvenile, myxoid, and complex forms. The difficulties in separating cellular fibroadenoma from benign phyllodes tumor, particularly on CNB specimens, are addressed. The authors review the approach to grading phyllodes tumors, updated according to the recent 2019 WHO classification and contemporary management approaches. The discovery of MED12 mutations in the pathogenesis of fibroepithelial tumors and their potential role in refining diagnosis and prognosis is also discussed. In their article, *papillary lesions of the breast*, Janina Kulka and colleagues discuss the clinical, radiologic, pathologic, and relevant molecular features of the spectrum of papillary lesions recognized in the 2019 WHO classification. Also discussed are breast lesions characterized by a micropapillary pattern, other differential diagnostic considerations, and challenges encountered in the evaluation of papillary lesions on CNB with emphasis on the role of immunohistochemistry, including myoepithelial cell markers, in diagnosis. In their review, Emad Rakha and colleagues present *a practical approach to the assessment of breast spindle cell lesions* (SCLs) with emphasis on potential pitfalls and evaluation of CNB specimens. The separation of SCLs into "bland-appearing" and "malignant appearing" rather than benign versus malignant encourages the pathologist to maintain a broad differential diagnosis and to interpret histological findings in clinical context. The review profiles the key features of each entity, including immunohistochemical and molecular characteristics, and includes a series of useful tables.

Cecily Quinn and colleagues review the spectrum *of apocrine change in benign, atypical and malignant breast lesions*. They address the difficulties in classifying intra-duct apocrine epithelial cell proliferations due to lack of validated criteria and maintaining a balance between not over-interpreting the cytonuclear variation and architectural complexity that may be observed in apocrine metaplasia while recognizing the subtle features of non-high-grade apocrine DCIS. The recently recognized entity of apocrine encapsulated papillary carcinoma is discussed. The review includes a section on invasive apocrine carcinoma with an update on recent advances in our understanding of the genetic landscape of these tumors. Stephen Fox and colleagues provide a comprehensive update on *male breast cancer*, which is a rare disease, accounting for less than 1% of all breast cancers, although the incidence is rising. The article summarizes important differences and many similarities between female and male breast cancer including androgen receptor positive luminal tumors and hormone receptor clustering with distinct gender-specific prognosis. The article addresses the limited available data derived from multigene-expression tests and future perspectives on mammographic screening in the male population.

The emerging role of *tumor infiltrating lymphocytes (TILs) and PD-L1 immunoreactivity in TNBC* is summarized by Anne-Vibeke Laenkholm and colleagues with detailed insights into the current prognostic and predictive evidence relating to TILs and PD-L1 scores. It addresses reproducibility in TILs assessment and whether and to what extent different commercially available PD-L1 antibodies are inter-changeable for testing. The authors carefully explain the prognostic information that clinicians can derive from TILs scores and why TILs scores not be used in deciding to de-escalate therapy at this point. The paper analyzes relevant clinical trials, including GeparNuevo, IMPassion 130, and Keynote-173, and explores the interaction between biomarker expression and immunotherapy/chemotherapy benefit in TNBC. Saleh Najjar and Kimberly Allison provide a contemporary review of the recently updated *ASCO/CAP guideline for hormone receptor (ER and PR)* testing which recognizes ER low positive tumors and the *ASCO/CAP HER2* testing guideline update which focuses primarily on less common fluorescence in situ hybridization patterns determined by dual-probe assays (published in 2018). Other biomarkers currently in use, including gene expression profiling assays to assess prognosis and chemotherapy benefit in patients with ER positive cancers and PD-L1 testing to identify patients with TNBC likely to benefit from immune checkpoint inhibitors, are discussed. The role of Ki67 testing in determining the suitability of patients with ER positive breast cancers for treatment with CDK4/6 inhibitors in addition to endocrine therapy and the potential importance of recognizing HER2 low positive cancers to identify patients

who may potentially benefit from HER2 antibody–drug conjugates are also discussed.

Important issues related to the emerging role of *artificial intelligence* are addressed by Mustafa Yousif and colleagues. Rapid advances, due to a combination of the increased use of digital pathology and deep learning neural networks, will potentially have a major impact on the practice of pathology by helping to standardize the diagnosis and classification of breast lesions, evaluate lymph nodes for the presence of metastases, and predict prognosis and response to various forms of therapy. In their article *on real time microscopy*, Dan Lopez and colleagues take us on a journey into the possible future of breast tissue evaluation. The authors discuss various optical imaging modalities that can be used for evaluating breast tissue in the patient without its removal ("in-vivo microscopy") and following removal ("ex-vivo microscopy"). Techniques that have already been used to produce images approximating what is seen on stained, formalin-fixed paraffin-embedded histologic sections (albeit of varying quality and resolution) include confocal microscopy, optical coherence tomography, and stereomicroscopy. Other techniques, currently in the research arena, that may have future clinical applications include light sheet microscopy, microscopy with ultraviolet surface excitation, non-linear microscopy, stimulated Raman scattering microscopy, photoacoustic microscopy, and needle micro-endoscopy. The authors speculate on how these optical imaging techniques might be incorporated into future clinical practice.

In our opinion, the selected 15 topics provide a comprehensive and contemporary update on the importance of conventional morphological parameters, current tumor classification, biomarkers and clinical relevance of distinct histological breast cancer subtypes and their precursor lesions, and emerging technologies to evaluate breast specimens. It has been our great privilege to co-edit this 2022 *Virchow's Archiv* special issue *on Contemporary Issues in Breast Pathology.*