

## Commentary

### The 2019 World Health Organization classification of tumours of the breast

DOI: 10.1111/his.14091

© 2020 The Authors. *Histopathology* published by John Wiley & Sons Ltd

#### Introduction

The classification of breast tumours continues to evolve, with the integration of new knowledge from research rapidly being translated into clinical practice. Major changes are shown in Table 1. In this volume of the World Health Organization (WHO) classification of tumours series' fifth edition, which is an update of the fourth-edition breast tumours volume published in 2012,<sup>1</sup> the descriptions of breast tumours follow the familiar systematic approach of previous volumes, with the content now organised in sequence from benign epithelial proliferations and precursors, through benign neoplasms, to *in-situ* and invasive breast cancer, followed by mesenchymal and haematolymphoid neoplasms, tumours of the male breast, and genetic tumour syndromes.

A brief introduction prefaces the content pertaining to each major tumour group, to provide a general perspective and highlight key modifications. In the current volume, information on epidemiology, imaging, clinical features, grading, staging, molecular testing for hormone receptors and *ERBB2* (HER2), post-therapy effects, core needle biopsy and fine-needle aspiration considerations, molecular pathology and genomics is now presented in the general overview that introduces the sections on invasive breast carcinoma (IBC), rather than in the first chapter as in the previous edition. Core biopsy diagnosis, an important preoperative tool, is addressed across multiple sections. The importance of molecular pathology in aiding diagnosis is recognised, with a specific subsection for each tumour type. Essential and desirable diagnostic criteria are also included, to reinforce key histopathological clues.

#### Breast carcinoma

Invasive breast cancers are still organised into chapters by their morphological subtypes, which remain clinically relevant. However, as the majority of cases are of no special type (NST), additional prognostic

and predictive factors that aid significantly in treatment and outcome stratification are also focused on and reviewed in more depth in the invasive carcinoma overview section. The overview acknowledges the treatment-relevant subtypes of invasive carcinoma [based on oestrogen receptor (ER) and HER2 status], and new data are added to support the differences in pathogenesis, treatment response and prognosis of these clinically relevant groupings. Updates in defining and testing hormone receptor and HER2 status are presented, and there are updated sections on additional assays and parameters used in prediction and prognosis (including proliferation markers, androgen receptor, response to neoadjuvant therapy, gene expression assays, tumour-infiltrating lymphocytes (TILs), prognostic scoring systems, and programmed death-ligand 1 testing). The overview section of the molecular classification of breast cancers is also updated to include more recent data supporting classification schemes that have prognostic associations (including the intrinsic subtypes, integrative cluster subgroups, triple-negative subclassifications, and mutation-based profiling).

Standard prognostic indicators, such as tumour size, lymph node status, and Nottingham grade, continue to be highly relevant. An important change in this edition is the conversion of mitotic count from the traditional denominator of 10 high-power fields to a defined area expressed in mm<sup>2</sup>. This serves to standardise the true area over which mitoses are enumerated, because different microscopes have high-power fields of different sizes. This change will also be helpful for anyone reporting using digital systems. The score thresholds for mitotic counts based on the diameter of the high-power field and its corresponding area are shown in Table 2.

Updates to the 'Invasive breast carcinoma, NST' section include a revised definition of the mixed NST–special subtype (now expanded to include cases with 10–90% special subtype admixed with NST, with a recommendation to include parameters regarding both components). Classification of several patterns previously recognised as separate special rare subtypes have moved under the NST umbrella as 'special morphological patterns'. Carcinomas previously classified as the special subtype 'carcinoma with medullary features' (including medullary carcinoma, atypical medullary carcinoma, and invasive carcinoma NST with medullary features) have suffered from poor interobserver reproducibility and overlap in

**Table 1.** Major changes within the new classification of tumours of the breast

| Topic  | Status in WHO 2012                             | Change in WHO 2019   |
|--|--|--|
| Mitotic counts   | Expressed per 10 HPFs                          | Given per mm <sup>2</sup>  |
| Carcinoma with medullary features  | Separate entity                                | Now regarded as TIL-rich IBC-NST   |
| Oncocytic, lipid-rich, glycogen-rich clear cell, sebaceous, pleomorphic, melanotic, oncocytic and choriocarcinomatous carcinomas, carcinoma with osteoclast-like giant stromal giant cells | Separate entities                              | Now regarded as rare variants of carcinoma NST                                 |
| Inflammatory, bilateral and non-synchronous breast carcinomas  | Separate entities                              | Now recognised as distinct clinical presentations rather than special subtypes |
| Lobular carcinoma <i>in situ</i>   | Classic, pleomorphic types                     | Classic, pleomorphic and florid types  |
| Neuroendocrine neoplasms   | –  | True primary neuroendocrine neoplasms are typed as NET, SCNEC, or LCNEC        |
| Neuroendocrine differentiation   | –  | Overridden by morphological tumour type (NST, mucinous, solid papillary)       |
| Well-differentiated liposarcoma in phyllodes tumours   | Histological criterion of malignancy by itself | No longer a histological criterion of malignancy by itself                     |
| Mucinous cystadenocarcinoma  | Not recognised                                 | Recognised as a new entity   |
| Breast tumour resembling the tall cell variant of papillary thyroid carcinoma; solid papillary carcinoma with reverse polarity   | –  | Now grouped as tall cell carcinoma with reversed polarity                      |
| Periductal stromal tumour  | Separate fibroepithelial entity                | Variant of phyllodes tumour  |
| Mesenchymal tumours, haematolymphoid tumours, and genetic tumour syndromes   | –  | Covered in dedicated chapters  |

IBC-NST, invasive breast carcinoma no special type; HPF, high-power field; LCNEC, large-cell neuroendocrine carcinoma; NET, neuroendocrine tumour; NST, no special type; SCNEC, small-cell neuroendocrine carcinoma; TIL, tumour-infiltrating lymphocyte; WHO, World Health Organization.

features with carcinomas that have basal-like molecular profiles and carcinomas associated with BRCA1 mutations. In addition, the increasing affirmation of the prognostic importance of TILs in high-grade breast cancers in explaining their good prognosis, including high-grade cancers not meeting strict medullary criteria, reduces the requirement for discrete separation of these tumours, which exist along a morphological continuum. Therefore, for clinical purposes, it is now proposed to consider carcinomas with a medullary pattern as representing one end of the spectrum of the TIL-rich IBC-NSTs rather than a distinct morphological subtype, and to use the term 'IBC-NST with medullary pattern'. In addition, oncocytic, lipid-rich, glycogen-rich clear cell, and sebaceous carcinomas, which are rarely encountered, are

also now recognised as special patterns of NST along with carcinoma with osteoclast-like stromal giant cells, pleomorphic carcinoma, and choriocarcinomatous and melanotic patterns. Inflammatory, bilateral and non-synchronous breast carcinomas are also now recognised as distinct clinical presentations rather than special subtypes of breast cancer.

As well as classic lobular carcinoma *in situ* (LCIS), the pleomorphic and florid subtypes are now recognised. Pleomorphic LCIS shows marked nuclear atypia, and may include apocrine features, whereas in florid LCIS there is marked distension of terminal duct lobular units or ducts, often forming a mass-like appearance. It is now recognised that some invasive lobular carcinomas may be associated with extracellular mucin production.

**Table 2.** Score thresholds for mitotic counts based on the diameter of the high-power field and its corresponding area

| Field diameter (mm) | Field area (mm <sup>2</sup> ) | Mitotic count (score) |       |     |
|---------------------|-------------------------------|-----------------------|-------|-----|
|                     |                               | 1                     | 2     | 3   |
| 0.40                | 0.126                         | ≤4                    | 5–9   | ≥10 |
| 0.41                | 0.132                         | ≤4                    | 5–9   | ≥10 |
| 0.42                | 0.138                         | ≤5                    | 6–10  | ≥11 |
| 0.43                | 0.145                         | ≤5                    | 6–10  | ≥11 |
| 0.44                | 0.152                         | ≤5                    | 6–11  | ≥12 |
| 0.45                | 0.159                         | ≤5                    | 6–11  | ≥12 |
| 0.46                | 0.166                         | ≤6                    | 7–12  | ≥13 |
| 0.47                | 0.173                         | ≤6                    | 7–12  | ≥13 |
| 0.48                | 0.181                         | ≤6                    | 7–13  | ≥14 |
| 0.49                | 0.188                         | ≤6                    | 7–13  | ≥14 |
| 0.50                | 0.196                         | ≤7                    | 8–14  | ≥15 |
| 0.51                | 0.204                         | ≤7                    | 8–14  | ≥15 |
| 0.52                | 0.212                         | ≤7                    | 8–15  | ≥16 |
| 0.53                | 0.221                         | ≤8                    | 9–16  | ≥17 |
| 0.54                | 0.229                         | ≤8                    | 9–16  | ≥17 |
| 0.55                | 0.237                         | ≤8                    | 9–17  | ≥18 |
| 0.56                | 0.246                         | ≤8                    | 9–17  | ≥18 |
| 0.57                | 0.255                         | ≤9                    | 10–18 | ≥19 |
| 0.58                | 0.264                         | ≤9                    | 10–19 | ≥20 |
| 0.59                | 0.273                         | ≤9                    | 10–19 | ≥20 |
| 0.60                | 0.283                         | ≤10                   | 11–20 | ≥21 |
| 0.61                | 0.292                         | ≤10                   | 11–21 | ≥22 |
| 0.62                | 0.302                         | ≤11                   | 12–22 | ≥23 |
| 0.63                | 0.312                         | ≤11                   | 12–22 | ≥23 |
| 0.64                | 0.322                         | ≤11                   | 12–23 | ≥24 |
| 0.65                | 0.332                         | ≤12                   | 13–24 | ≥25 |
| 0.66                | 0.342                         | ≤12                   | 13–24 | ≥25 |
| 0.67                | 0.352                         | ≤12                   | 13–25 | ≥26 |
| 0.68                | 0.363                         | ≤13                   | 14–26 | ≥27 |
| 0.69                | 0.374                         | ≤13                   | 14–27 | ≥28 |

### Neuroendocrine tumours

Although neuroendocrine neoplasms (NENs) are allocated their own section, harmonised with those of other

organ systems on the basis of a recent WHO workshop report,<sup>2</sup> it must be emphasised that true primary neuroendocrine tumours (NETs) of the breast remain uncommon and poorly defined. According to the proposed consensus terminology, well-differentiated NETs broadly correspond to grade 1 (carcinoid-like) and grade 2 (atypical carcinoid-like) tumours (regarded as carcinomas in the breast), whereas poorly differentiated neuroendocrine carcinomas (NECs) are typified by small-cell and large-cell carcinoma. Many breast tumours that show varying degrees of neuroendocrine differentiation belong to recognised entities, such as hypercellular mucinous carcinoma and solid papillary carcinoma of both *in-situ* and invasive types. Small-cell NEC does arise in the breast, often admixed with invasive carcinoma NST. Large-cell NEC has been added as an entity arising in the breast, albeit encountered very rarely. For well-differentiated NETs resembling carcinoid or atypical carcinoid tumour, it is prudent to exclude metastasis from another site. It is recommended that the classification of breast tumours showing neuroendocrine expression be based on the recognisable morphological tumour type, such as invasive carcinoma NST, mucinous carcinoma, or solid papillary carcinoma.<sup>3</sup> Because some degree of neuroendocrine expression is relatively common in invasive breast cancer NST, most breast cancers with neuroendocrine expression will ultimately be classified as invasive carcinoma NST with neuroendocrine differentiation. Only if neuroendocrine histological features and neuroendocrine marker expression are distinct or uniform enough to classify a cancer as one of the rare NETs or NECs of the breast should NEN terminology be used. NET or NEC of the breast are currently treated on the basis of standard breast cancer parameters (such as ER and HER2 status). The new WHO classification is not advocating routine evaluation for neuroendocrine markers in breast cancers.

### Other tumour types and newly recognised entities

One important change in the classification of fibroepithelial tumours is the removal of well-differentiated liposarcoma as a histological criterion of malignancy in breast phyllodes tumours in the absence of additional supporting microscopic alterations. Evidence has emerged that these abnormal adipocyte populations residing within phyllodes tumours do not harbour the *MDM2* aberrations that characterise well-differentiated liposarcomas elsewhere. In light of the consensus opinion that this heterologous element does not have metastatic potential, it was agreed that

its presence alone should not warrant a malignant grade in phyllodes tumours unless there are other histological changes of malignancy.

A new entity included in this volume is mucinous cystadenocarcinoma, a unique invasive malignancy with a relatively good prognosis, featuring luminal mucin and cytomorphology resembling pancreatobiliary and ovarian mucinous cystadenocarcinoma. The entity ‘tall cell carcinoma with reversed polarity’ is introduced in the section about rare and salivary gland-type tumours, as there have been multiple reports of this entity, previously termed ‘breast tumour resembling the tall cell variant of papillary thyroid carcinoma’ as well as ‘solid papillary carcinoma with reverse polarity’, with these descriptions united by the consistent finding of *IDH2* and *PIK3CA* mutations.<sup>4</sup> The new terminology of ‘tall cell carcinoma with reversed polarity’ incorporates portions of earlier terms used to describe this entity—‘tall cell’ and ‘reversed polarity’. This revised term was a consensus agreement achieved during the WHO Editorial Board Meeting. It was also felt that having ‘papillary thyroid carcinoma’ in the terminology may be confusing and misleading. Periductal stromal tumour is now considered to be a variant of phyllodes tumour.

Mesenchymal tumours, haematolymphoid tumours and genetic tumour syndromes are covered in dedicated chapters in alignment with the approach being taken throughout this fifth edition of the series.

## Conclusion

Tumour classification is a dynamic process, integrating multiple sources of information that have emerged since the previous WHO update. Digital pathology, which is becoming widely available, may enable the application of new artificial intelligence and computer learning tools to refine breast and other tumour classifications that will ultimately facilitate appropriate therapy and accurate prognostication.

## Conflicts of interest

No authors reported any conflicts of interest to the International Agency for Research on Cancer (IARC) that would affect their participation in forming the classification.

## Disclaimer

The content of this article represents the personal views of the authors, and does not represent the

views of the authors’ employers and associated institutions. Where authors are identified as personnel of the IARC/WHO, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy or views of the IARC/WHO.

## Author contributions

The authors are standing and expert members of the WHO Classification of Tumours Editorial Board, or the IARC Secretariat. This commentary is based on the introduction to tumours of the breast. All authors were involved in the conception of the article, writing the article, and reviewing the final version.

Puay Hoon Tan<sup>1</sup>  
 Ian Ellis<sup>2</sup>   
 Kimberly Allison<sup>3</sup>  
 Edi Brogi<sup>4</sup>   
 Stephen B Fox<sup>5</sup>  
 Sunil Lakhani<sup>6</sup>   
 Alexander J Lazar<sup>7</sup>  
 Elizabeth A Morris<sup>4</sup>  
 Aysegul Sahin<sup>7</sup>   
 Roberto Salgado<sup>8</sup>   
 Anna Sapino<sup>9,10</sup>   
 Hironobu Sasano<sup>11</sup>  
 Stuart Schnitt<sup>12</sup>  
 Christos Sotiriou<sup>13</sup>   
 Paul van Diest<sup>14</sup>  
 Valerie A White<sup>15</sup>   
 Dilani Lokuhetty<sup>15</sup>   
 Ian A Cree<sup>15</sup> 

for the WHO Classification of Tumours Editorial Board

<sup>1</sup>Singapore General Hospital, Singapore, <sup>2</sup>University of Nottingham and Nottingham University Hospitals, Nottingham, UK, <sup>3</sup>Stanford University School of Medicine, Stanford, CA, <sup>4</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA, <sup>5</sup>Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, <sup>6</sup>University of Queensland and Pathology Queensland, Royal Brisbane and Women’s Hospital, Herston, Australia, <sup>7</sup>University of Texas MD Anderson Cancer, Houston, TX, USA, <sup>8</sup>GZA-ZNA Hospitals, Antwerp, Belgium, <sup>9</sup>Department of Medical Sciences, University of Torino, Torino, <sup>10</sup>Candiolo Cancer Institute-FPO, IRCCS, Candiolo, Italy, <sup>11</sup>Tohoku University School of Medicine, Sendai, Japan, <sup>12</sup>Brigham and Women’s Hospital/Dana-Farber Cancer Institute, Boston, MA, USA, <sup>13</sup>Institut Jules Bordet (Université Libre de Bruxelles), Brussels,

Belgium, <sup>14</sup>University Medical Centre Utrecht, Utrecht, The Netherlands, and <sup>15</sup>International Agency for Research on Cancer, Lyon, France

## References

1. Lakhani SR, Ellis IO, Schnitt SJ *et al.* eds. *World Health Organization classification of tumours of the breast*. 4th ed. Lyon: IARC Press, 2012.
2. Rindi G, Klimstra DS, Abedi-Ardekani B *et al.* A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod. Pathol.* 2018; **31**: 1770–1786.
3. Tan PH, Schnitt SJ, van de Vijver MJ *et al.* Papillary and neuroendocrine breast lesions: the WHO stance. *Histopathology* 2015; **66**: 761–770.
4. Lozada JR, Basili T, Pareja F *et al.* Solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasms (solid papillary carcinomas with reverse polarity) harbour recurrent mutations affecting IDH2 and PIK3CA: a validation cohort. *Histopathology* 2018; **73**: 339–344.