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The 2019 WHO classification of tumours of the breast

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Abstract

The newly published World Health Organization (WHO) Classification of Tumours of the breast features significant changes compared to earlier editions. In this review, we outline the major changes in this important reference source for those diagnosing tumours, or engaged in cancer research, and describe the significant changes. For breast cancer, the overview acknowledges the treatment-relevant subtypes of invasive carcinoma (based on ER and HER2 status) and new data is added to support the differences in pathogenesis, treatment response and prognosis of these clinically relevant groupings. The WHO Classification of Tumours is increasingly evidence-based, with a clear update cycle, improved quality of illustrations, as well as content, led by an editorial board comprising pathologists, but increasingly incorporating input from other disciplines. The advent of the new website allows the use of whole slide images, and hyperlinks to evidence or external bodies that produce guidance on staging or reporting.

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 listed in table 1. In this volume of the WHO Classification of Tumours series' fifth edition, which is an update of the fourth-edition breast tumours volume published in 2012,[1] the descriptions of breast tumours follow the familiar systematic approach of previous volumes, with the content now organized 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 FNA considerations, molecular pathology, and genomics, is now presented in the general overview that introduces the sections on invasive breast carcinoma, rather than in the first chapter as in the prior edition. Core biopsy diagnosis, an important preoperative tool, is addressed across multiple sections. The importance of molecular pathology in aiding diagnosis is recognized, 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 organized into chapters by their morphologic subtypes, which remain clinically relevant. However, since 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 ER and HER2 status) and new data is 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 as well as updated sections on additional assays and parameters used in prediction and prognosis (including proliferation markers, AR, response to neoadjuvant therapy, gene expression assays, tumour infiltrating lymphocytes, prognostic scoring systems and PDL1 testing). The overview section of the molecular classification of breast cancers is also updated to include more recent

data supporting classifications schemes that have prognostic associations (including the intrinsic subtypes, integrative cluster subgroups, triple negative sub-classifications, 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^2. This serves to standardize 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 presented 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 recommendation to include parameters about both components). Classification of several patterns previously recognized as separate special rare subtypes have moved under the NST umbrella as "Special morphologic patterns". Carcinomas previously classified as the special subtype "carcinoma with medullary features" (including medullary carcinoma, atypical medullary carcinoma, and invasive carcinoma of no special type (NST) with medullary features) have suffered from poor interobserver reproducibility and overlap in 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, reduce the requirement for discrete separation of these tumours that exist along a morphological continuum. Therefore, for clinical purposes, it is now proposed to consider carcinomas with 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, sebaceous carcinomas, which are rarely encountered, are also now recognized as special patterns of NST along with carcinoma with osteoclast-like stromal giant cells, pleomorphic carcinoma, choriocarcinomatous and

melanotic patterns. Inflammatory and bilateral and non-synchronous breast carcinomas are also now recognized as distinct clinical presentations rather than special subtypes of breast cancer.

Next to classic lobular carcinoma *in situ* (LCIS), the pleomorphic and florid subtypes are now recognized. Pleomorphic LCIS shows marked nuclear atypia, and may include apocrine features, while in florid LCIS, there is marked distention of TDLUs or ducts often forming a mass-like appearance. It is now recognized that some invasive lobular carcinomas may be associated with extracellular mucin production.

Neuroendocrine tumours

Although neuroendocrine neoplasms (NENs) are allocated their own section, harmonized with those of other organ systems on the basis of a recent WHO workshop report,[2] it must be emphasized 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 2 (atypical carcinoid-like) tumours (regarded as carcinomas in the breast), while poorly differentiated NECs are typified by small and large cell carcinoma. Many breast tumours that display varying degrees of neuroendocrine differentiation belong to recognized entities such as hypercellular mucinous carcinoma and solid papillary carcinoma of both in situ and invasive forms. Small cell neuroendocrine carcinoma (SCNEC) does arise in the breast, often admixed with invasive carcinoma NST. Large Cell Neuroendocrine Carcinoma (LCNEC) has been added as an entity arising in the breast, albeit very rare. 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 displaying neuroendocrine expression be based on the recognizable morphological tumour type, such as invasive carcinoma NST, mucinous carcinoma, or solid papillary carcinoma.[3] Because some degree of neuroendocrine expression is relatively common in invasive breast cancer of no special type, 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 based on standard breast cancer parameters (such as ER and HER2 status). Th new WHO Classification is not advocating routine evaluation for neuroendocrine markers in breast cancers.

Other tumour types and newly recognized 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 characterize 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 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.[4] 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 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 ultimately facilitate appropriate therapy and accurate prognostication.

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 it and reviewing the final version.

Conflicts of interest

No authors reported any conflicts of interest to IARC that would affect their participation in forming the classification.

Disclaimer

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

Topic	Status WHO 2012	Change in WHO 2019
Mitotic counts	Expressed per 10 HPF	Given per mm^2
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 recognized as distinct clinical presentations rather than special subtypes
Lobular carcinoma in situ	Classic, pleomorphic, macroacinar, apocrine 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 differentiation in phyllodes tumours	Histological criterion of malignancy by itself	No longer a histological criterion of malignancy by itself
Mucinous cystadenocarcinoma	Not recognized	Recognized as new entity
Breast tumour resembling the tall cell variant of papillary thyroid carcinoma; solid papillary carcinoma with reverse polarity	Similar separately mentioned entities	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

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^2)	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