Permission from Ian Cree (Head, WHO classification of tumours group is obtained)
Foreword

• The most conspicuous change to the format of the books in the fifth edition is that tumour types common to multiple systems are dealt with together – so there are separate chapters on haematolymphoid tumours and mesenchymal tumours. There is also a chapter on genetic tumour syndromes.....

• We have attempted to take a more systematic approach to the multifaceted nature of tumour classification; each tumour type is described on the basis of its localization, clinical features, epidemiology, etiology, pathogenesis, histopathology, diagnostic molecular pathology, staging, and prognosis and prediction.

• We have also included information on macroscopic appearance and cytology, as well as essential and desirable diagnostic criteria. This standardized, modular approach makes it easier for the books to be accessible online, but it also enables us to call attention to areas in which there is little information, and where serious gaps in our knowledge remain to be addressed.

• The organization of the WHO Blue Books content now follows the normal progression from benign to malignant – a break with the fourth edition, but one we hope will be welcome.

Dr Ian A. Cree, Head, WHO Classification of Tumours Group, International Agency for Research on Cancer, August 2019
WHO Classification of Tumours of the Breast

Edited by Sunil R. Lakhani, Ian O. Ellis, Stuart J. Schnitt, Puay Hoon Tan, Marc J. van de Vijver
5th edition of the WHO book 2019
2.7.4: Tubular carcinoma

Definition
Related terminology
Subtype(s)
Localization
Clinical features
Epidemiology
Etiology
Pathogenesis
Macroscopic appearance
Histopathology
Cytology
Diagnostic molecular pathology
Essential and desirable diagnostic criteria
Staging
Prognosis and prediction
References:
1: Introduction to tumours of the breast

2: Epithelial tumours of the breast

2.1: Benign epithelial proliferations and precursors: Introduction
   2.1.1: Usual ductal hyperplasia
   2.1.2: Columnar cell lesions, including flat epithelial atypia
   2.1.3: Atypical ductal hyperplasia

2.2: Adenosis and benign sclerosing lesions: Introduction
   2.2.1: Sclerosing adenosis
   2.2.2: Apocrine adenosis and adenoma
   2.2.3: Microglandular adenosis
   2.2.4: Radial scar / complex sclerosing lesion

2.3: Adenomas: Introduction
   2.3.1: Tubular adenoma
   2.3.2: Lactating adenoma
   2.3.4: Ductal adenoma

2.10: Epithelial-myoepithelial tumours: Introduction
   2.8.1: Pleomorphic adenoma
   2.8.2: Adenomyoepithelioma
   2.8.3: Malignant adenomyoepithelioma

2.4: Papillary neoplasms: Introduction
   2.4.1: Intraductal papilloma
   2.4.5: Papillary ductal carcinoma in situ
   2.4.2: Encapsulated papillary carcinoma
   2.4.3: Solid papillary carcinoma (in situ and invasive)
   2.4.4: Invasive papillary carcinoma

2.5: Non-invasive lobular neoplasia: Introduction
   2.5.1: Atypical lobular hyperplasia
   2.5.2: Lobular carcinoma in situ

2.6: Ductal carcinoma in situ: Introduction
   2.6.1: Ductal carcinoma in situ

2.7: Invasive breast carcinoma: General overview
   2.7.1: Invasive breast carcinoma of no special type
   2.7.1: Microinvasive carcinoma
   2.7.3: Invasive lobular carcinoma
   2.7.4: Tubular carcinoma
   2.7.9: Cribriform carcinoma
   2.7.5: Mucinous carcinoma
   2.7.5.1: Mucinous cystadenocarcinoma
   2.7.6: Invasive micropapillary carcinoma
   2.7.7: Carcino ma with apocrine differentiation
   2.7.8: Metaplastic carcinoma

2.8: Rare and salivary gland-type tumours: Introduction
   2.8.4: Acinic cell carcinoma
   2.8.5: Adenoid cystic carcinoma

5: Intraductal proliferative lesions
   Introduction and overview
   Usual ductal hyperplasia
   Columnar cell lesions
   Atypical ductal hyperplasia
   Ductal carcinoma in situ

5.1: Tumours of the nipple
5.2: Epithelial tumours
   5.2.1: Syringomatous tumour
   5.2.2: Nipple adenoma
   5.2.3: Paget disease of the breast

Mesenchymal tumours of the breast
6.1: Mesenchymal tumours of the breast: Introduction
6.2: Vascular tumours
   6.2.1: Haemangioma
   6.2.2: Angiomatosis
   6.2.3: Atypical vascular lesions
   6.2.4: Postradiation angiosarcoma of the breast
   6.2.5: Primary angiosarcoma of the breast
6.3: Fibroblastic and myofibroblastic tumours
Microinvasive carcinoma

- Some earlier definitions mandated that invasion should be present into the non-specialized stroma, but this is no longer a requirement.
- The distinction between specialized stroma and the non-specialized (interlobular) stroma can generally be made in normal breast histology but becomes less obvious when an inflammatory infiltrate and oedema obscure the boundary.
- Defined as: Invasion beyond the myoepithelium and the basement membrane of the in situ component (≤1mm).
- Sometimes also lower grade DCIS, lobular carcinoma in situ (LCIS) or Paget’s disease of the nipple.

5th edition of the WHO book
Introduction to tumours of the breast

Epithelial tumours of the breast

2.1: Benign epithelial proliferations and precursors: Introduction
   2.1.1: Usual ductal hyperplasia
   2.1.2: Columnar cell lesions, including flat epithelial atypia
   2.1.3: Atypical ductal hyperplasia

2.2: Adenosis and benign sclerosing lesions: Introduction
   2.2.1: Sclerosing adenosis
   2.2.2: Apocrine adenosis and adenoma
   2.2.3: Microglandular adenosis
   2.2.4: Radial scar / complex sclerosing lesion

2.3: Adenomas: Introduction
   2.3.1: Tubular adenoma
   2.3.2: Lactating adenoma
   2.3.4: Ductal adenoma

2.10: Epithelial-myoepithelial tumours: Introduction
   2.8.1: Pleomorphic adenoma
   2.8.2: Adenomyoepithelioma
   2.8.3: Malignant adenomyoepithelioma

2.4: Papillary neoplasms: Introduction
   2.4.1: Intraductal papilloma
   2.4.2: Papillary ductal carcinoma in situ
   2.4.3: Encapsulated papillary carcinoma
   2.4.4: Invasive papillary carcinoma

2.5: Non-invasive lobular neoplasia: Introduction
   2.5.1: Atypical lobular hyperplasia
   2.5.2: Lobular carcinoma in situ

2.6: Ductal carcinoma in situ: Introduction
   2.6.1: Ductal carcinoma in situ

2.7: Invasive breast carcinoma: General overview
   2.7.0: Invasive breast carcinoma of no special type
   2.7.1: Microinvasive carcinoma
   2.7.3: Invasive lobular carcinoma
   2.7.4: Tubular carcinoma
   2.7.9: Cribriform carcinoma
   2.7.5: Mucinous carcinoma
   2.7.5.1: Mucinous cystadenocarcinoma
   2.7.6: Invasive micropapillary carcinoma

8: Benign epithelial proliferations
   Introduction
   Adenosis, sclerosing adenosis and apocrine adenosis
   Microglandular adenosis, atypical microglandular adenosis and microglandular adenosis with carcinoma
   Radial scar and complex sclerosing lesion
   Tubular adenoma
   Lactating adenoma
   Apocrine adenoma
   Ductal adenoma
   Pleomorphic adenoma

4.1: Hamartoma

4.2: Fibro-epithelial tumours (Move authors to other sections and delete)
   4.2.1: Fibroadenoma
   4.2.3: Phyllodes tumour

Tumours of the nipple

5.1: Tumours of the nipple: Introduction

5.2: Epithelial tumours
   5.2.1: Syringomatous tumour
   5.2.2: Nipple adenoma
   5.2.3: Paget disease of the breast

Mesenchymal tumours of the breast

6.1: Mesenchymal tumours of the breast: Introduction

6.2: Vascular tumours
   6.2.1: Haemangioma
   6.2.2: Angiomyosarcoma
   6.2.3: Atypical vascular lesions
   6.2.4: Postradiation angiosarcoma of the breast
   6.2.5: Primary angiosarcoma of the breast

6.3: Fibroblastic and myofibroblastic tumours
3 Special subtypes

Invasive lobular carcinoma
Tubular carcinoma and cribriform carcinoma
Carcinoma with medullary features
Metaplastic carcinoma
Carcinoma with apocrine differentiation
Salivary gland/skin adnexal type tumours
Adenoid cystic carcinoma
Mucopeidermoid carcinoma
Polymorphous carcinoma
Mucinous carcinoma and carcinoma with signet-ring-cell differentiation
Carcinoma with neuroendocrine features
Invasive papillary carcinoma
Invasive micropapillary carcinoma
Inflammatory carcinoma
Bilateral breast carcinoma and non-synchronous breast carcinoma
Exceptionally rare types and variants
  Secretory carcinoma
  Oncocytic carcinoma
  Sebaceous carcinoma
  Lipid-rich carcinoma
  Glycogen-rich clear cell carcinoma
  Acinic cell carcinoma

2.7: Invasive breast carcinoma of no special type
2.7.1: Microinvasive carcinoma
2.7.3: Invasive lobular carcinoma
2.7.4: Tubular carcinoma
2.7.9: Cribriform carcinoma
2.7.5: Mucinous carcinoma
2.7.5.1: Mucinous cystadenocarcinoma
2.7.6: Invasive micropapillary carcinoma
2.7.7: Carcinoma with apocrine differentiation
2.7.8: Metaplastic carcinoma

Rare and salivary gland-type tumours: Introduction
2.8.4: Acinic cell carcinoma
2.8.5: Adenoid cystic carcinoma
2.7.9: Secretory carcinoma
2.8.6: Mucopeidermoid carcinoma
2.8.7: Polymorphous adenocarcinoma
2.9.1: Tall cell carcinoma with reversed polarity

Other epithelial tumours (Introduction) - to be deleted
2.9.2: Oncocytic carcinoma (move text and authors to 2.7.0 NST and delete)
2.9.3: Lipid-rich carcinoma (move text and authors to 2.7.0 NST and delete)
2.9.4: Glycogen-rich clear cell carcinoma (move text and authors to 2.7.0 NST and delete)
2.9.5: Sebaceous carcinoma (move text and authors to 2.7.0 NST and delete)

Neuroendocrine neoplasms: Introduction
3.2.1: Neuroendocrine tumour
3.3.1: Neuroendocrine carcinoma

Epithelial tumours and hamartomas of the breast
Fibroepithelial tumours and hamartomas of the breast: Introduction
4.2.1: Hamartoma
Fibroepithelial tumours (Move authors to other sections and delete)
4.2.2: Fibroadenoma
4.2.3: Phyllodes tumour

Tumours of the nipple
Epithelial tumours
5.2.1: Syringomatous tumour
5.2.2: Nipple adenoma
5.2.3: Paget disease of the breast

Mesenchymal tumours of the breast
6.1: Mesenchymal tumours of the breast: Introduction
6.2: Vascular tumours
   6.2.1: Haemangioma
   6.2.2: Angiomatosis
   6.2.3: Atypical vascular lesions
   6.2.4: Postradiation angiosarcoma of the breast
   6.2.5: Primary angiosarcoma of the breast
6.3: Fibroblastic and myofibroblastic tumours
3 Special subtypes
Invasive lobular carcinoma
Tubular carcinoma and cribriform carcinoma
Carcinoma with medullary features
Metaplastic carcinoma
Carcinoma with apocrine differentiation
Salivary gland/skin adenexal type tumours
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Polymorphous carcinoma
Mucinous carcinoma and carcinoma with signet-ring-cell differentiation
Carcinoma with neuroendocrine features
Invasive papillary carcinoma
Invasive micropapillary carcinoma
Inflammatory carcinoma
Bilateral breast carcinoma and non-synchronous breast carcinoma
Exceptionally rare types and variants
Secretory carcinoma
Oncocytic carcinoma
Sebaceous carcinoma
Lipid-rich carcinoma
Glycogen-rich clear cell carcinoma
Acinic cell carcinoma
2.7: Invasive breast carcinoma: General overview
2.7.0: Invasive breast carcinoma of no special type
2.7.1: Microinvasive carcinoma
2.7.2: Invasive lobular carcinoma
2.7.3: Tubular carcinoma
2.7.4: Cribriform carcinoma
2.7.5: Mucinous carcinoma
2.7.5.1: Mucinous cystadenocarcinoma
2.7.6: Invasive micropapillary carcinoma
2.7.7: Carcinoma with apocrine differentiation
2.7.8: Metaplastic carcinoma

2.8: Rare and salivary gland-type tumours: Introduction
2.8.4: Acinic cell carcinoma
2.8.5: Adenoid cystic carcinoma
2.8.6: Secretory carcinoma
2.8.7: Mucoepidermoid carcinoma
2.8.8: Polymorphous adenocarcinoma
2.8.9: Tall cell carcinoma with reversed polarity

3 Other epithelial tumours (Introduction) - to be deleted

2.10: Neuroendocrine neoplasms: Introduction
3.2.1: Neuroendocrine tumour
3.3.1: Neuroendocrine carcinoma

4 Fibroepithelial tumours and hamartomas of the breast
4.1: Fibroepithelial tumours and hamartomas of the breast: Introduction
4.1.1: Hamartoma
4.2: Fibro-epithelial tumours (Move authors to other sections and delete)
4.2.1: Fibroadenoma
4.2.3: Phyllodes tumour

5 Tumours of the nipple
5.1: Tumours of the nipple: Introduction
5.2: Epithelial tumours
5.2.1: Syringomatous tumour
5.2.2: Nipple adenoma
5.2.3: Paget disease of the breast

6 Mesenchymal tumours of the breast
6.1: Mesenchymal tumours of the breast: Introduction
6.2: Vascular tumours
6.2.1: Haemangiomia
6.2.2: Angiomyosarcoma
6.2.3: Atypical vascular lesions
6.2.4: Postradiation angiosarcoma of the breast
6.2.5: Primary angiosarcoma of the breast
6.3: Fibroblastic and myofibroblastic tumours
Some rare special types

Special morphologic patterns of NST:

- Oncocytic
- Lipid rich,
- Glycogen rich
- Clear cell
- Sebaceous carcinomas
- Similarly, invasive carcinoma with neuroendocrine differentiation, pleomorphic and choriocarcinomatous pattern and tumours with melanocytic features
- Rare tumours with no sufficient clinical evidence available for their designation as special tumour subtypes and their specific pattern is considered as part of the spectrum of differentiation seen in the IBC, NST.
- Considered as morphological patterns of IBC, NST regardless of the extent of differentiation/ pattern and the 90% role for special subtype is not applied to tumours showing any of these patterns

5th edition of the WHO book
Introduction to tumours of the breast

2: Epithelial tumours of the breast

2.1: Benign epithelial proliferations and precursors
   2.1.1: Usual ductal hyperplasia
   2.1.2: Columnar cell lesions, including flat epithelial atypia
   2.1.3: Atypical ductal hyperplasia

2.2: Adenosis and benign sclerosing lesions: Introduction
   2.2.1: Sclerosing adenosis
   2.2.2: Apocrine adenosis and adenoma
   2.2.3: Microglandular adenosis
   2.2.4: Radial scar / complex sclerosing lesion

2.3: Adenomas: Introduction
   2.3.1: Tubular adenoma
   2.3.2: Lactating adenoma
   2.3.4: Ductal adenoma

2.10: Epithelial-myoepithelial tumours: Introduction
   2.8.1: Pleomorphic adenoma
   2.8.2: Adenomyoepithelioma
   2.8.3: Malignant adenomyoepithelioma

2.4: Papillary neoplasms: Introduction
   2.4.1: Intraductal papilloma
   2.4.5: Papillary ductal carcinoma in situ
   2.4.2: Encapsulated papillary carcinoma
   2.4.3: Solid papillary carcinoma (in situ)
   2.4.4: Invasive papillary carcinoma

2.5: Non-invasive lobular neoplasia:
   2.5.1: Atypical lobular hyperplasia
   2.5.2: Lobular carcinoma in situ

2.6: Ductal carcinoma in situ: Introduction
   2.6.1: Ductal carcinoma in situ

2.7: Invasive breast carcinoma: General
   2.7.0: Invasive breast carcinoma of no special type
   2.7.1: Micropapillary carcinoma
   2.7.2: Invasive lobular carcinoma
   2.7.4: Tubular carcinoma
   2.7.9: Cribriform carcinoma
   2.7.5: Mucinous carcinoma
   2.7.5.1: Mucinous cystadenocarcinoma
   2.7.6: Invasive micropapillary carcinoma

   2.7.8: Metaplastic carcinoma
   2.7.9: Carcinoma with medullary features
   2.7.10: Metaplastic carcinoma
   2.7.11: Carcinoma with apocrine differentiation
   2.7.12: Salivary gland/skin adnexal type tumours
   2.7.13: Adenoid cystic carcinoma
   2.7.14: Mucoepidermoid carcinoma

   2.7.15: Mucinous cystadenocarcinoma
   2.7.16: Invasive micropapillary carcinoma

2.8: Rare and salivary gland-type tumours: Introduction
   2.8.4: Acinic cell carcinoma
   2.8.5: Adenoid cystic carcinoma
   2.8.6: Mucoepidermoid carcinoma
   2.8.7: Polymorphous adenocarcinoma
   2.8.9: Tall cell carcinoma with reversed polarity

2.9: Other epithelial tumours (Introduction) - to be deleted
   2.9.2: Oncocytic carcinoma (move text and authors to 2.7.0 NST and delete)
   2.9.3: Lipid-rich carcinoma (move text and authors to 2.7.0 NST and delete)
   2.9.4: Glycogen-rich clear cell carcinoma (move text and authors to 2.7.0 NST and delete)
   2.9.5: Sebaceous carcinoma (move text and authors to 2.7.0 NST and delete)

3.1: Neuroendocrine neoplasms: Introduction
   3.2.1: Neuroendocrine tumour
   3.3.1: Neuroendocrine carcinoma

Fibroepithelial tumours and hamartomas of the breast

4.1: Fibroepithelial tumours and hamartomas of the breast: Introduction
   4.2.1: Hamartoma

3: Special subtypes

Invasive lobular carcinoma
Tubular carcinoma and cribriform carcinoma
Carcinoma with medullary features
Metaplastic carcinoma
Carcinoma with apocrine differentiation
Salivary gland/skin adnexal type tumours
Adenoid cystic carcinoma
Mucoepidermoid carcinoma

6.2.4: Postradiation angiosarcoma of the breast
6.2.5: Primary angiosarcoma of the breast

6.3: Fibroblastic and myofibroblastic tumours
Medullary Carcinoma

• Described as a special type of BC with high grade features but with good prognosis
• Sharply circumscribed soft, rounded tumour mass with pushing rather than infiltrating margin
• Interconnecting sheets of large, bizarre and pleomorphic carcinoma cells forming a syncytial network
• Rich in lympho-plasmacytoid cell infiltrates
• In situ component insignificant
• Typically triple negative
• Better outcome than grade and stage matched NST
**Medullary Carcinoma**

WHO 2012: Carcinomas with medullary features

Definition

Carcinomas with medullary features include

Medullary carcinomas

Atypical medullary carcinomas

* A subset of invasive ductal carcinomas of no special type

These tumours demonstrate all or some of the following features:

- a circumscribed or pushing border
- a syncytial growth pattern
- cells with high-grade nuclei
- prominent lymphoid infiltration
Medullary Carcinoma

Special morphologic patterns of NST:

"Medullary-like" patterns:

• For clinical purposes, it is now proposed that carcinomas with medullary features are considered one end of the spectrum of the TILs-rich IBC, NST, rather than distinct morphologic subtype.

• These can be described as having histologic features that correlate with the "basal-like" molecular profiles, with some quantification of the degree of TILs present, if clinically relevant.

• However, they are categorized diagnostically as IBC, NST with inclusion of descriptive modifiers referring to medullary-like or basal-like features.

5th edition of the WHO book
Special subtypes
Invasive lobular carcinoma
Tubular carcinoma and cribriform carcinoma
Carcinoma with medullary features
Metaplastic carcinoma
Carcinoma with apocrine differentiation
Salivary gland/skin adenexal type tumours
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Polymorphous carcinoma
Mucinous carcinoma and carcinoma with
signet-ring-cell differentiation
Carcinoma with neuroendocrine features
Invasive papillary carcinoma
Invasive micropapillary carcinoma
Inflammatory carcinoma
Bilateral breast carcinoma and non-synchronous breast carcinoma
Exceptionally rare types and variants
  Secretary carcinoma
  Oncocytic carcinoma
  Sebaceous carcinoma
  Lipid-rich carcinoma
  Glycogen-rich clear cell carcinoma
  Acinic cell carcinoma

3.1.3: Invasive tubular carcinoma
2.7.4: Tubular carcinoma
2.7.9: Cribriform carcinoma
2.7.5: Mucinous carcinoma
2.7.5.1: Mucinous cystadenocarcinoma
2.7.8: Invasive micropapillary carcinoma
Mucinous cystadenocarcinoma

- Mucinous cystadenocarcinoma is an invasive breast carcinoma characterized by cystic structures lined by tall columnar cells with abundant intracytoplasmic mucin, resembling pancreato-biliary or ovarian mucinous cystadenocarcinoma.
- Columnar cells show stratification, tufting, and papillary formations. The neoplastic cells have basally located nuclei and contain abundant intracytoplasmic mucin.
Tall cell carcinoma with reversed polarity

- A very rare variant of breast carcinoma showing overlapping features between SPC, papillary DCIS, infiltrating epitheliosis and invasive papillary carcinomas
- Circumscribed nests of epithelial cells distributed most often in dense fibrous stroma with a solid papillary pattern. True papillae and cystic structures containing colloid-like material can be observed in some cases
- Nuclear features resembling tall cell variant of PTC in addition to reverse of polarity
- Most triple-negative phenotype, the remaining cases show weak or focal hormone receptor expression
- Express both low and high molecular weight cytokeratins; NE markers are negative; TTF1-ve
- Myoepithelial cells absent or very focal
- Most commonly associated with $IDH2$ R172 hotspot mutations.
A very rare variant of breast carcinoma, originally designated "breast tumor resembling the tall cell variant of papillary thyroid carcinoma” in 2003 by Eusebi

Different terminology:
Solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasm
Tall cell variant of papillary breast carcinoma (attempt to avoid confusion with papillary thyroid carcinoma)
Solid papillary carcinoma with reverse polarity (SPCRP) (Chiang et al)

5th edition WHO book =
   Tall cell carcinoma with reversed polarity

 Removed words “papillary” or “solid papillary” from name and considered as a variant of invasive carcinoma
Essential and desirable diagnostic criteria

**Essential:**
An invasive breast carcinoma with the neoplastic cell nests arranged in a predominantly solid papillary pattern, composed of columnar epithelial cells showing reverse polarity of the nuclei. Absence of myoepithelial cells around the tumour nests

**Desirable:**
Expression of both low and high molecular weight cytokeratins, and a triple negative or weakly hormone receptor positive phenotype

**Staging:**
Should be staged as *invasive breast carcinoma*
Introduction to tumours of the breast

Epithelial tumours of the breast

2.1: Benign epithelial proliferations and precursors: Introduction
  2.1.1: Usual ductal hyperplasia
  2.1.2: Columnar cell lesions, including flat epithelial atypia
  2.1.3: Atypical ductal hyperplasia

2.2: Adenosis and benign sclerosing lesions: Introduction
  2.2.1: Sclerosing adenosis
  2.2.2: Apocrine adenosis and adenoma
  2.2.3: Microglandular adenosis
  2.2.4: Radial scar / complex sclerosing lesion

2.3: Adenomas: Introduction
  2.3.1: Tubular adenoma
  2.3.2: Lactating adenoma
  2.3.4: Ductal adenoma

2.10: Epithelial-myoeipithelial tumours: Introduction
  2.8.1: Pleomorphic adenoma
  2.8.2: Adenomyoepithelioma
  2.8.3: Malignant adenomyoepitheliosis

2.4: Papillary neoplasms: Introduction
  2.4.1: Intraductal papilloma
  2.4.2: Papillary ductal carcinoma in situ
  2.4.3: Encapsulated papillary carcinoma
  2.4.3: Solid papillary carcinoma (in situ and invasive)

2.5: Non-invasive lobular neoplasia: Introduction
  2.5.1: Atypical lobular hyperplasia
  2.5.2: Lobular carcinoma in situ

2.6: Ductal carcinoma in situ: Introduction
  2.6.1: Ductal carcinoma in situ

2.7: Invasive breast carcinoma: General overview
  2.7.0: Invasive breast carcinoma of no special type
  2.7.1: Microinvasive carcinoma
  2.7.3: Invasive lobular carcinoma
  2.7.4: Tubular carcinoma
  2.7.9: Cribriform carcinoma
  2.7.5: Mucinous carcinoma
  2.7.5.1: Mucinous cystadenocarcinoma
  2.7.6: Invasive micropapillary carcinoma

2.8: Rare and salivary gland-type tumours: Introduction
  2.8.4: Acinic cell carcinoma
  2.8.5: Adenoid cystic carcinoma
  2.8.7: Salivary duct carcinoma

2.9: Other epithelial tumours (Introduction) - to be deleted
  2.9.2: Oncocytic carcinoma (move text and authors to 2.7.0 NST and delete)
  2.9.3: Lipid-rich carcinoma (move text and authors to 2.7.0 NST and delete)
  2.9.4: Glycogen-rich clear cell carcinoma (move text and authors to 2.7.0 NST and delete)
  2.9.5: Sebaceous carcinoma (move text and authors to 2.7.0 NST and delete)

3.1: Neuroendocrine neoplasms: Introduction
  3.2.1: Neuroendocrine tumour

Fibroepithelial tumours and hamartomas of the breast

4.1: Fibroepithelial tumours and hamartomas of the breast: Introduction
  4.1.1: Hamartoma

4.2: Fibro-epithelial tumours (Move authors to other sections and delete)
  4.2.2: Fibroadenoma
  4.2.3: Phylloides tumour

Tumours of the nipple

5.1: Tumours of the nipple: Introduction

5.2: Epithelial tumours
  5.2.1: Syringomatous tumour
  5.2.2: Nipple adenoma
  5.2.3: Paget disease of the breast

Mesenchymal tumours of the breast

6.1: Mesenchymal tumours of the breast: Introduction

6.2: Vascular tumours
  6.2.1: Haemangioma
  6.2.2: Angiomyomatosis
  6.2.3: Atypical vascular lesions
  6.2.4: Postradiation angiosarcoma of the breast
  6.2.5: Primary angiosarcoma of the breast

6.3: Fibroblastic and myofibroblastic tumours
Papillary carcinomas
Neuroendocrine Neoplasms

- In the 2012 fourth-edition volume *WHO classification of tumours of the breast*, NECs were included under the category “carcinomas with neuroendocrine features”

- Defined as tumours exhibiting morphological features similar to those of NETs of the gastrointestinal tract and lung and expressing neuroendocrine markers to any extent

- NETs in the breast were classified into two main categories:
  1. “NETs, well-differentiated”, which included low- and intermediate-grade tumours
  2. “NECs, poorly differentiated / small cell carcinomas” – these neoplasms, based on the description, included small cell NEC (SCNEC) but not large cell NEC (LCNEC)

This classification also acknowledged the existence of a third category, which comprised a subset of breast carcinomas with neuroendocrine differentiation as determined by histochemical and immunohistochemical analysis; this category included breast carcinoma of no special type (NST), as well as special types such as solid papillary carcinoma and the hypercellular subtype of mucinous carcinoma
Neuroendocrine tumour

Definition

• Neuroendocrine tumour (NET) is an invasive tumour characterized by low/intermediate-grade neuroendocrine morphology, supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity for neuroendocrine markers.

Essential and desirable diagnostic criteria

• *Essential*: histological features and immunoprofile characteristic of neuroendocrine differentiation; NETs are not high-grade neoplasms.

• *Desirable*: coexisting ductal carcinoma in situ.
Neuroendocrine carcinoma

Definition

• Neuroendocrine carcinoma (NEC) is an invasive carcinoma characterized by high-grade neuroendocrine morphology (small cell or large cell), supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity for neuroendocrine markers.

Essential and desirable diagnostic criteria

• **Essential**: histological features similar to those of SCNEC and LCNEC of the lung; high-grade tumour.

• **Desirable**: coexisting ductal carcinoma in situ.
Neuroendocrine tumours of the breast
Mixed IBC, NST and special subtypes

• If the special subtype makes up between 10-90% of the cancer the terminology mixed IBC, NST and special subtype carcinoma may be used

• For this type of mixed IBC, NST and special subtype, recommended that both elements present be reported and overall percentage of special subtype (example: "Mixed invasive breast carcinoma NST and invasive lobular carcinoma (30% lobular")

• Grade and biomarker status of both components should be reported, since they can be distinct
Subtype(s) of breast carcinomas:

• Invasive breast carcinomas are grouped into the following biomarker-defined subtypes/groups for treatment purposes based on ER and HER2 status as follows:
  • ER positive, HER2 negative
  • ER positive, HER2 positive
  • ER negative, HER2 positive
  • ER negative, HER2 negative

• Despite the overlapping morphological features of these biomarker-defined subtypes, they show distinct outcomes and responses to therapy in addition to differences in their global genomic and transcriptomic profiles
Diagnostic molecular pathology:

5th edition of the WHO book

Molecular classification

Intrinsic subtypes classification
Integrative clusters (IntClust) classification
Triple-negative breast cancer molecular subclassification
Mutation profiles of IBC
Tumour-infiltrating lymphocytes (TILs):

The presence and extent of TILs in invasive breast carcinomas are gaining importance as a prognostic marker with high TILs associated with a better outcome and a better response to neoadjuvant therapy in Triple-negative and HER2 positive breast carcinomas.

If quantifying TILs, it is recommended to follow the internal consensus scoring recommendations.

Main updates
1. Updates of some subheadings such as pathogenesis, cytology, and essential and desirable diagnostic criteria for each tumour type
2. Some updates of the classification system and arrangements of entities
3. Merging some entities: Medullary carcinomas and some very rare tumour types with NST carcinomas
4. Description of few entities not in the previous edition: Mucinous cystadenocarcinoma, LCNEC, and introduction of new entity “tall cell carcinoma with reversed polarity”
5. Update of NE and papillary tumours sections
6. Some updates on the prognostic variables in breast such as TILs, and molecular features such as mutational profiles, HER2 guidelines, and biomarker-based subtypes defined based of ER and HER2