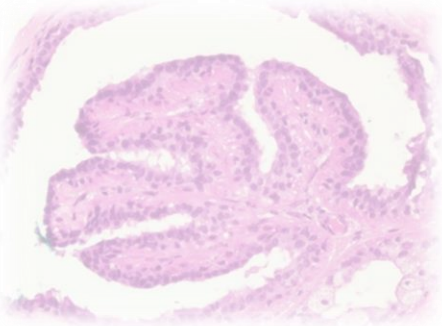
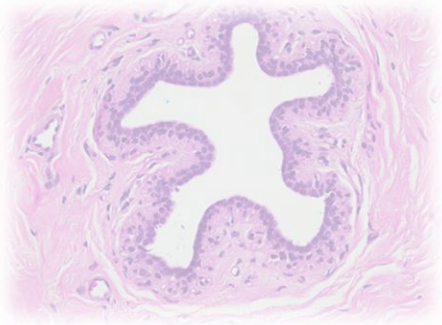
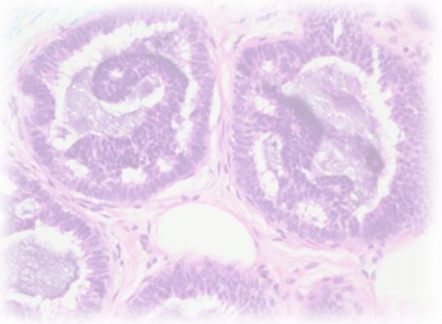
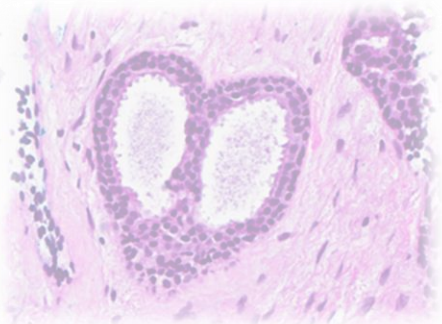
Breast Pathology Course 2019









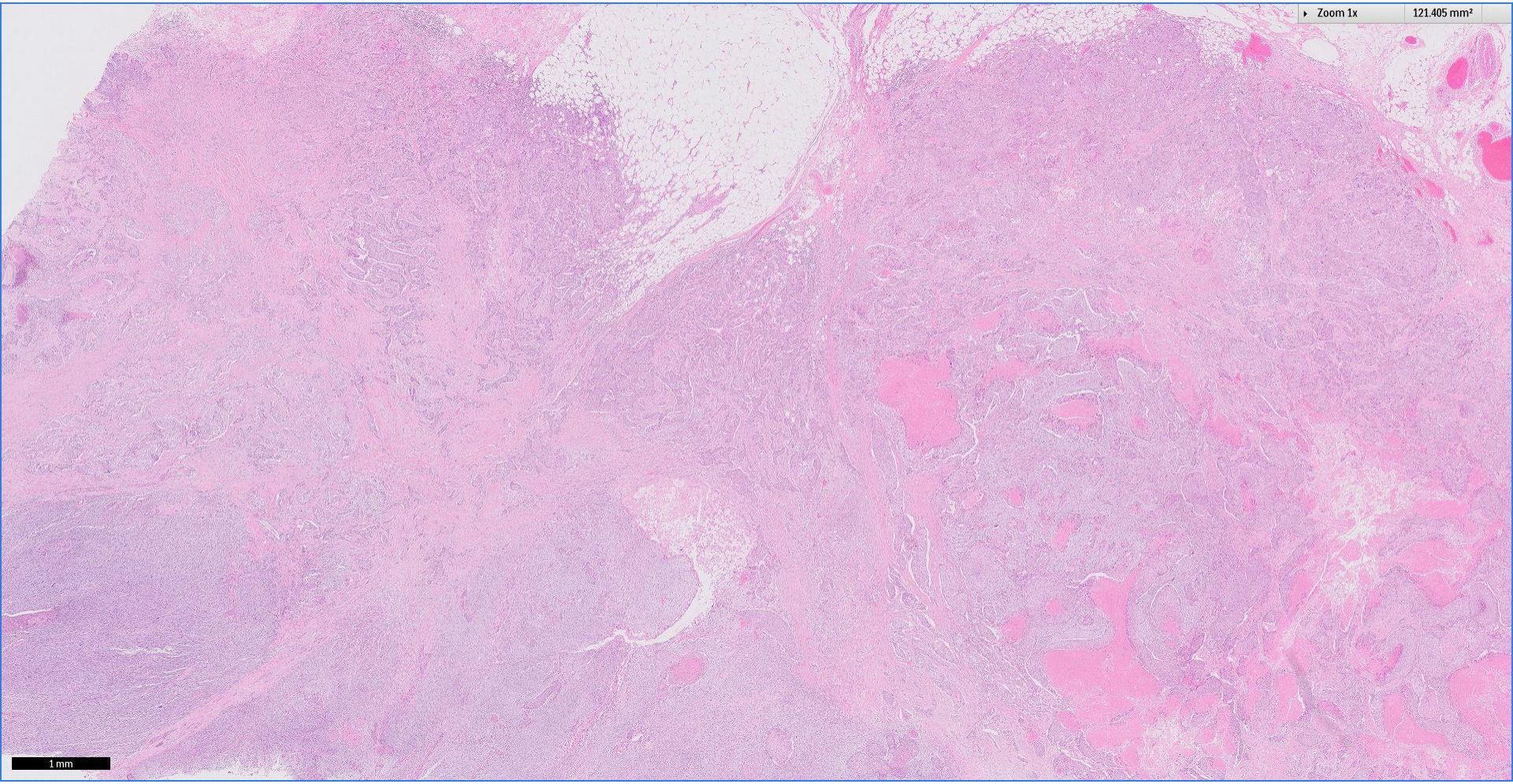
# *Case 5*

41 year old Burmese female.
Materials of 'left breast and axillary lymph nodes' submitted for histological review.
Section provided of the left breast tumour.

Division of Pathology
Singapore General Hospital

SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

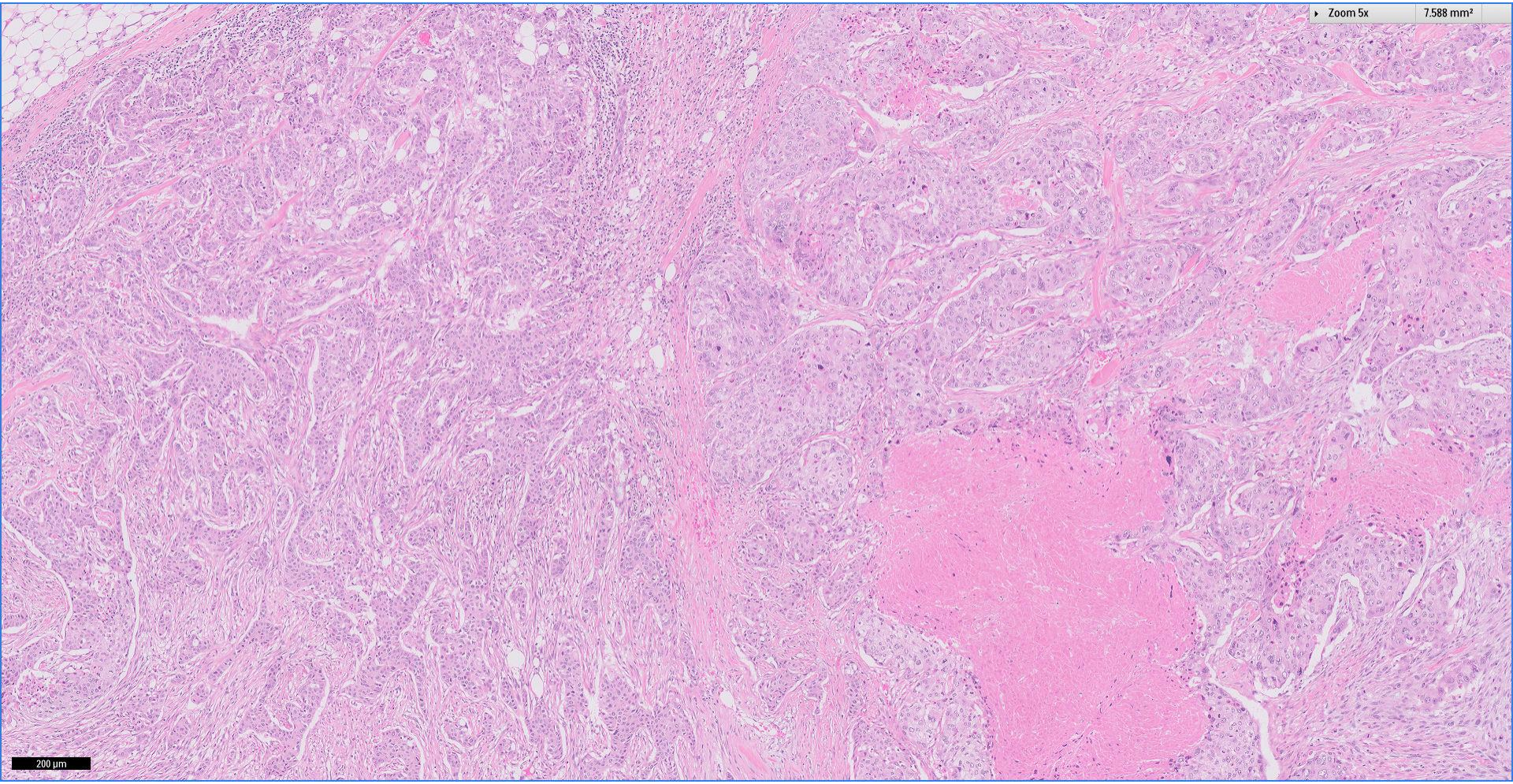
IAP
International Academy of Pathology
Singapore Division




Division of Pathology
Singapore General Hospital

SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

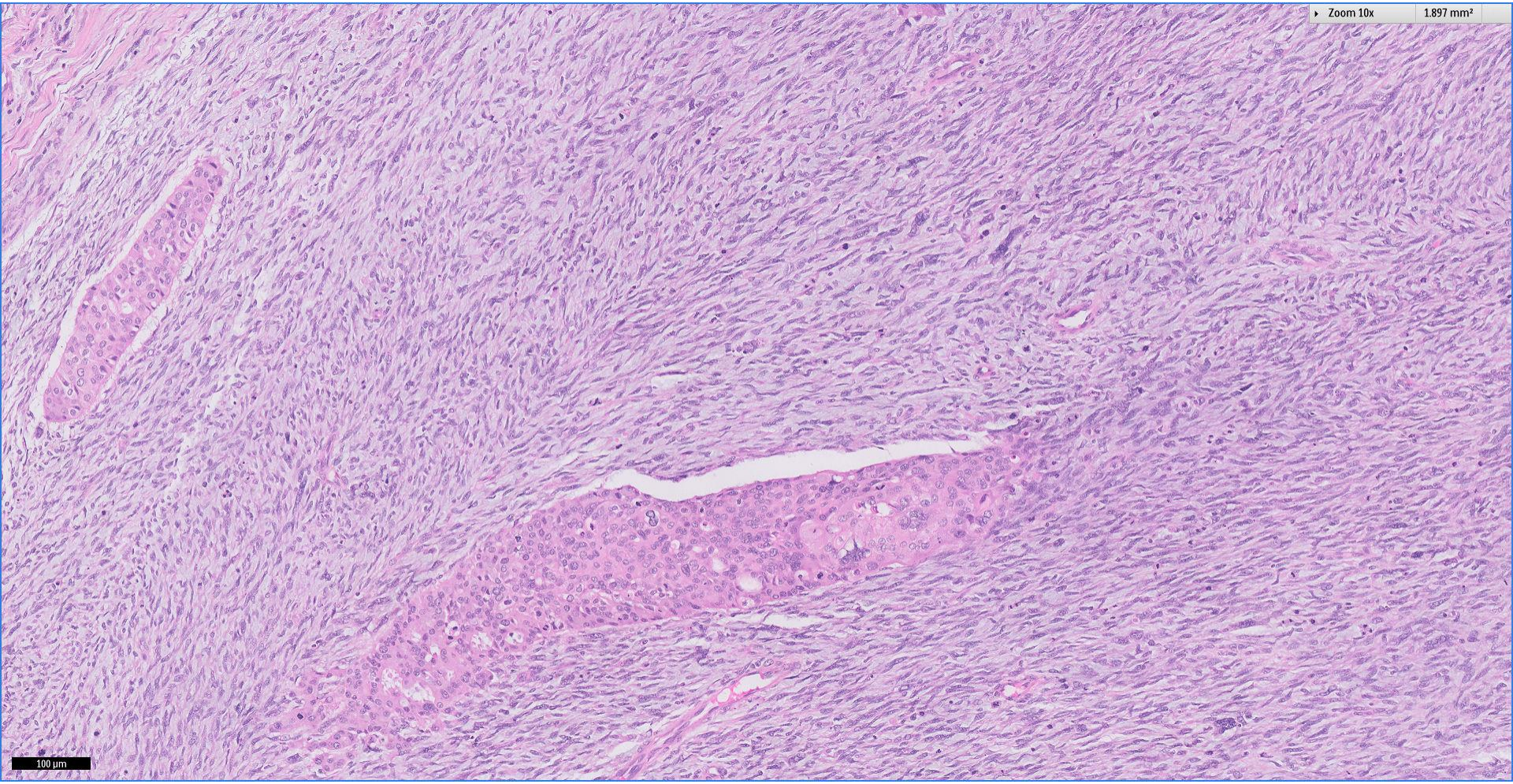
IAP
International Academy of Pathology
Singapore Division




Division of Pathology
Singapore General Hospital

SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

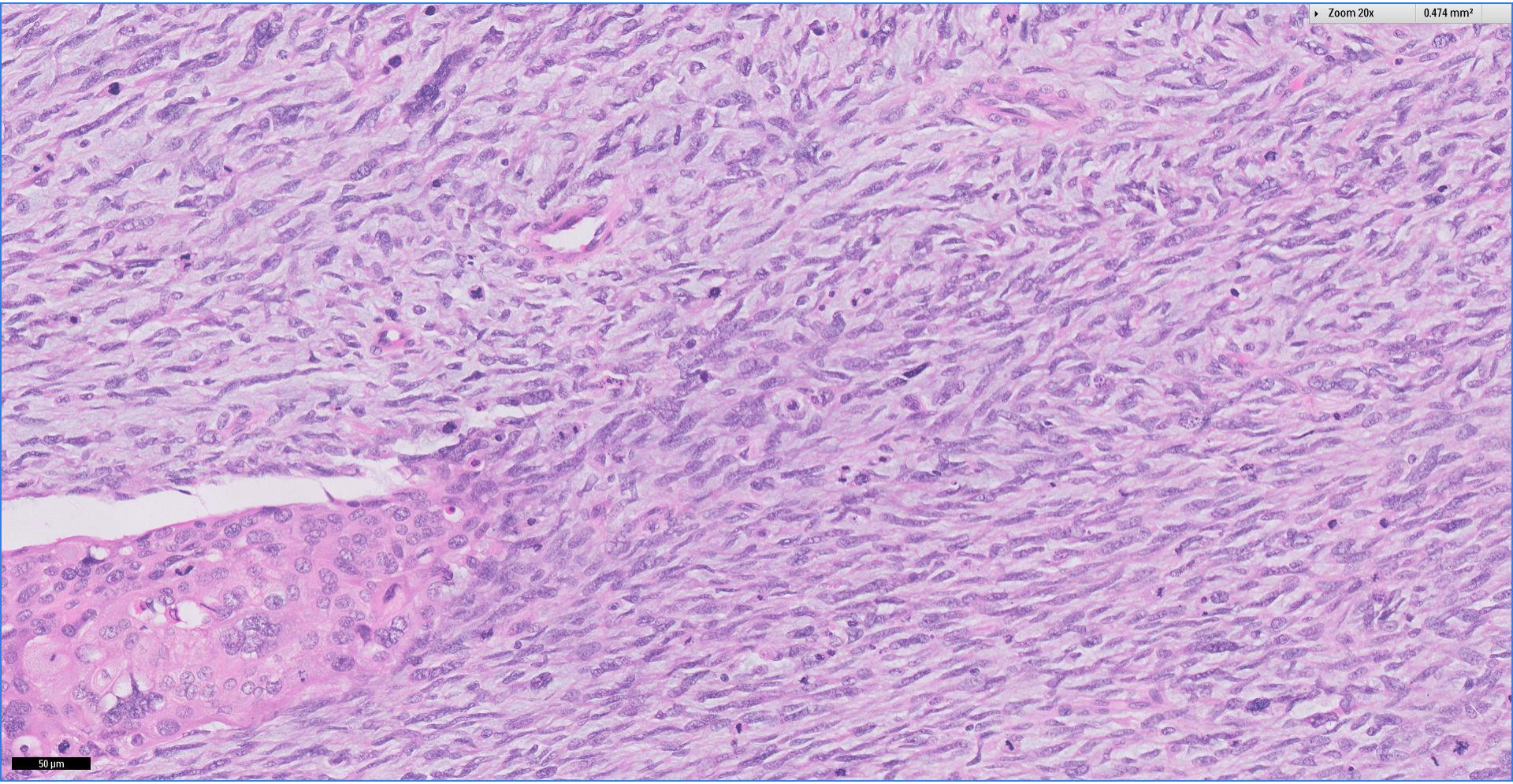
IAP
International Academy of Pathology
Singapore Division




Division of Pathology
Singapore General Hospital

SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

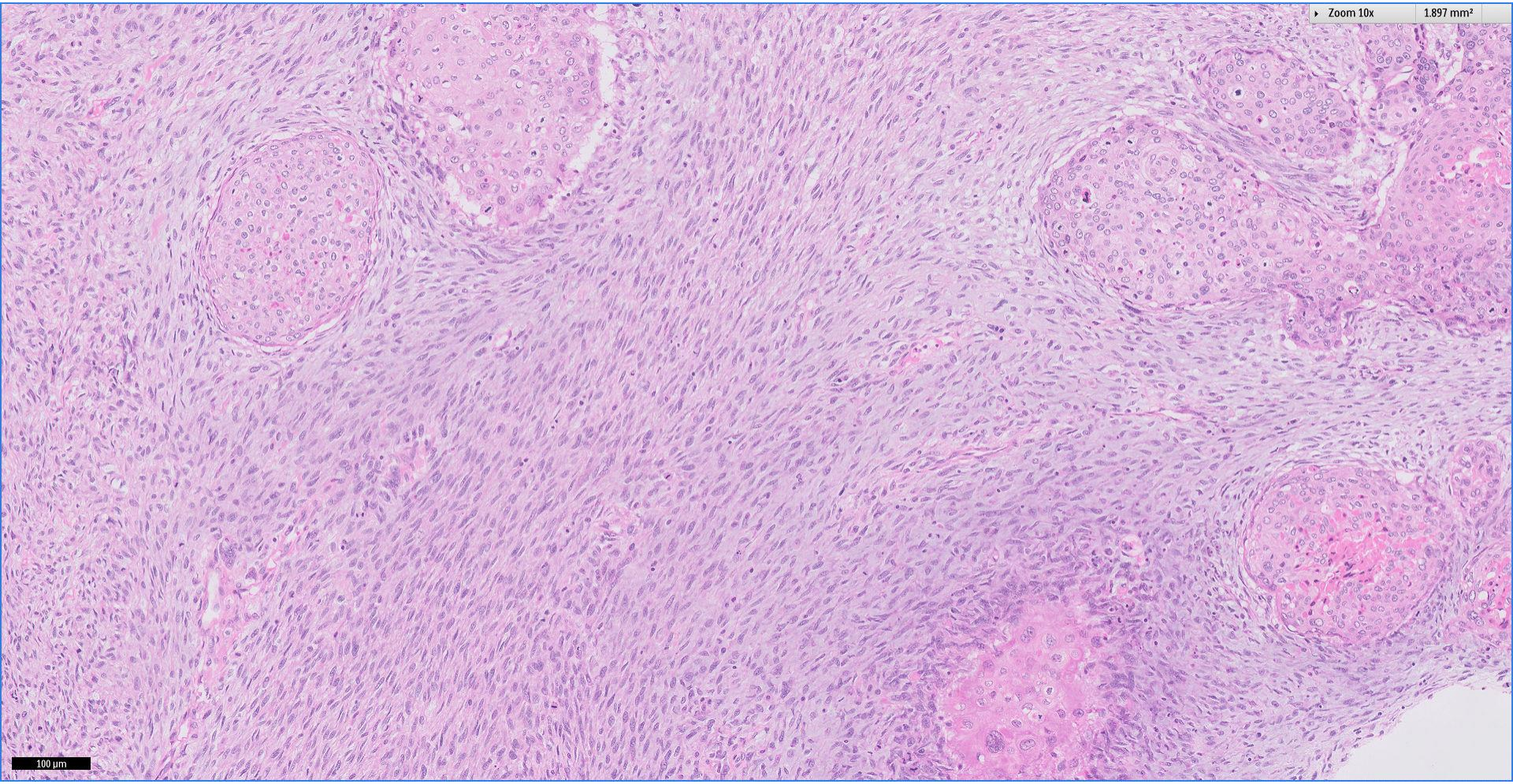
IAP
International Academy of Pathology
Singapore Division




Division of Pathology
Singapore General Hospital

SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

IAP
International Academy of Pathology
Singapore Division



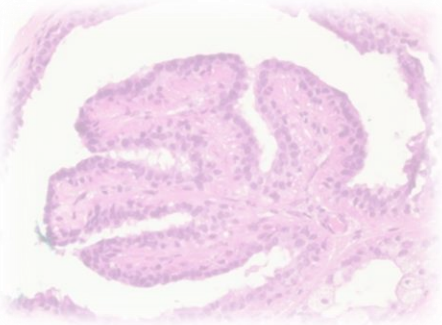

Division of Pathology
Singapore General Hospital

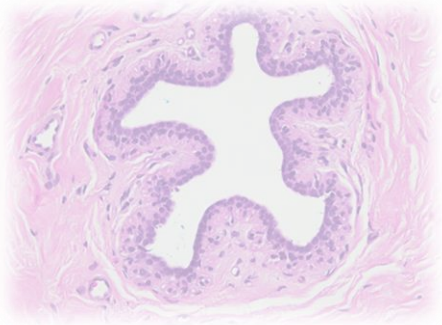
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

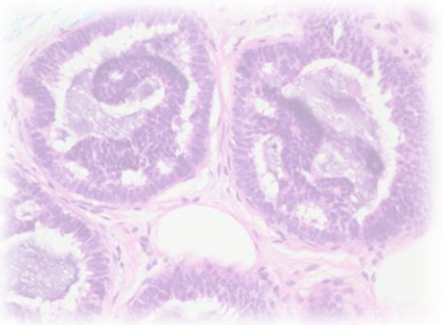
IAP
International Academy of Pathology
Singapore Division

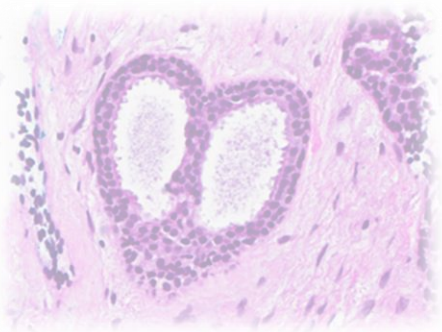
Breast Pathology Course 2019

# Additional pictures





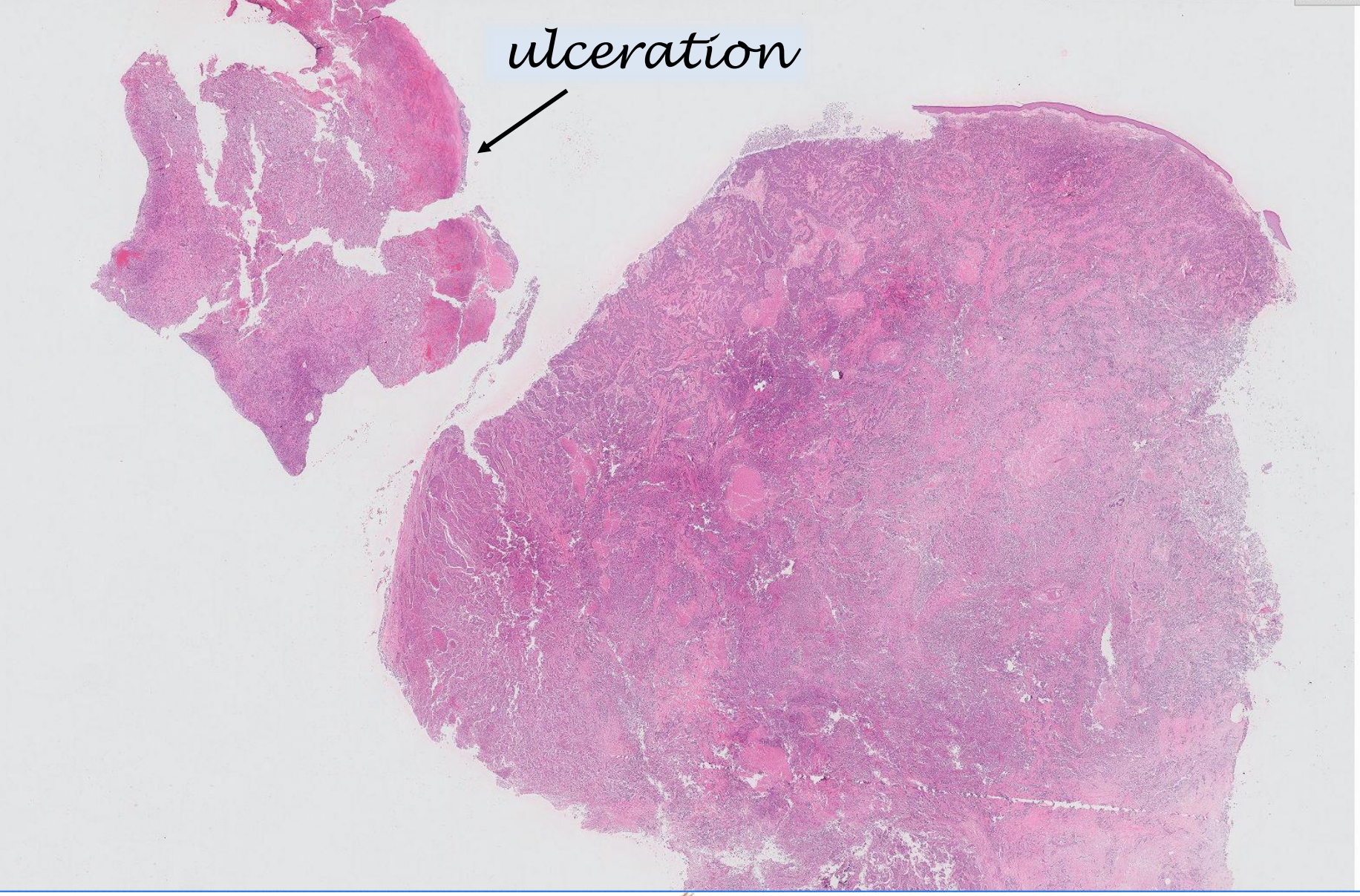




Division of Pathology
Singapore General Hospital

SingHealth DukeNUS ACADEMIC MEDICAL CENTRE
PATHOLOGY

IAP
International Academy of Pathology
Singapore Division


ulceration

# Diagnosis, case 5

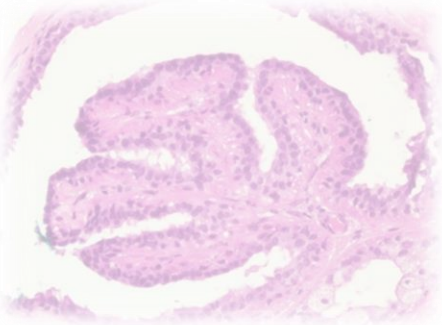
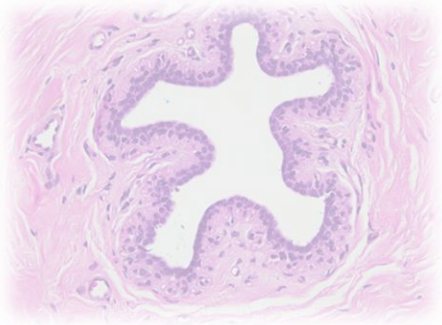
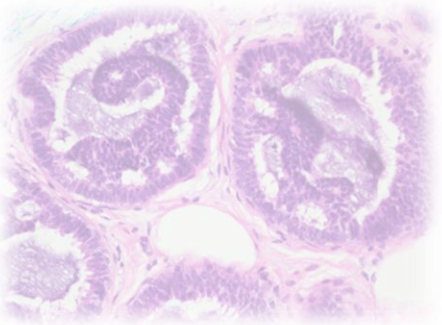
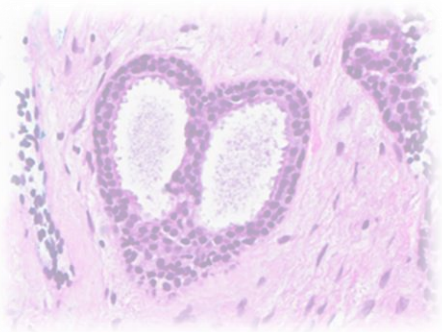
- Left breast and axillary lymph nodes, submitted materials:

  Metaplastic carcinoma with ductal, spindle and squamous differentiation, grade 3, 70mm.

  ER+, PR+, cerbB2- (ER+/PR+ in the ductal component).

  Tumour ulcerates skin with dermal lymphovascular emboli.

  9 out of 11 lymph nodes show metastatic carcinoma.

# Metaplastic carcinoma

- Heterogeneous group of invasive breast carcinomas (IBCs) characterized by differentiation of the neoplastic epithelium towards squamous cells and/or mesenchymal-looking elements, including but not restricted to spindle, chondroid, and osseous cells.

**WHO 2019**

# Metaplastic carcinoma

- **Localisation ~** **WHO 2019**
  - Any anatomical area of the breast.
- **Clinical features ~**
  - Similar to those of ER-negative IBC of no special type (NST).
  - Metaplastic carcinomas are more likely to present at an advanced stage.
  - Most cases (85%) present with a palpable lump and are detected as a mass lesion on ultrasonography (100%) or mammography (78%).
  - Calcifications are uncommon (17%); when present, they are often associated with ductal carcinoma in situ and/or osseous differentiation.

# Metaplastic carcinoma

WHO 2019

- **Epidemiology ~**
  - Accounts for 0.2–1% of all IBCs.
- **Etiology ~**
  - Multifactorial, and it appears not to differ from that of IBC-NST (in particular of the triple-negative subtype).

Breast Pathology Course 2019

# Metaplastic carcinoma ~ pathogenesis

- Heterogeneous group of tumours with distinctive morphological characteristics and marked intertumoural and intratumoural heterogeneity.
- Genetic studies support a monoclonal origin of the heterogeneous components of metaplastic carcinomas.
- Some authors support the concept of a late-step change of tumour dedifferentiation rather than an origin from a basal-like stem cell.
- Unknown whether somatic mutations cause the differentiation that allows for metaplastic carcinoma subtypes.
- No specific pathognomonic mutations for metaplastic carcinomas have yet been identified.

**WHO 2019**

Breast Pathology Course 2019

# Metaplastic carcinoma ~ pathogenesis

- Genes frequently mutated include *TP53* and *PIK3CA*.
- Overexpression and mutations of *EGFR*, as well as p63 immunopositivity, have been reported in metaplastic carcinomas with squamous metaplasia and spindle cell morphology.
- Other genetic abnormalities include losses of *PTEN* and *CDKN2A*.
- Stem cell–like phenotype, with positivity for CD44 and negativity for CD24.
- Characterized by low expression of *GATA3*-regulated genes and the genes that are responsible for epithelial–mesenchymal transition and cell–cell adhesion, with upregulation of vimentin and E-cadherin repressor molecules (SNAI1 [SNAIL], SNAI2 [SLUG], TWIST) and downregulation of E-cadherin.
- These molecular features suggest that metaplastic carcinomas arise from a breast epithelial precursor that is relatively chemoresistant.

**WHO 2019**

# Metaplastic carcinoma ~ macroscopic appearance

- Often not distinctive.
- Well-circumscribed masses or display indistinct, irregular borders.
- Cystic degeneration is not uncommon, in particular in metaplastic carcinomas with squamous cell carcinoma.
- Pearly, white-to-greyish, and glistening cut surfaces can be seen in areas of squamous and chondroid metaplasia, whereas the cut surface of areas of osseous metaplasia can be gritty and hard.
- Compared with IBC-NST, metaplastic carcinomas tend to be larger, with a mean size of 3.9 cm, ranging from 2 to > 10 cm.
- Thorough sampling of the lesion is strongly advised.

**WHO 2019**

Breast Pathology Course 2019

# Metaplastic carcinoma ~ histopathology

**WHO 2019**

- Group of histopathologically distinct patterns with different outcomes, although there is often overlap.
- Given the heterogeneity of metaplastic carcinomas, the WHO Classification of Tumours Editorial Board has maintained a **descriptive classification system**, based on the type of the metaplastic elements.
- Metaplastic carcinomas can be **monophasic** (with only one metaplastic component) or **biphasic** (with two or more components).
- The two components can both be of metaplastic histology, such as squamous and/or spindle cells with a mesenchymal/matrix-producing component, or there can be one metaplastic component and one adenocarcinoma component (most frequently IBC-NST).
- **If more than one component is identified, it is suggested to note each component and its approximate percentage within the tumour.**
- On the basis of histological pattern, metaplastic carcinomas can also be classified into **epithelial-only carcinomas** (with low-grade adenosquamous carcinoma [LGASC], high-grade adenosquamous carcinoma, or pure squamous cell carcinoma), **pure (monophasic) sarcomatoid (spindle cell or matrix-producing) carcinomas**, and **biphasic epithelial and sarcomatoid carcinomas**.
- **Some IBC-NSTs may have only a very focal metaplastic component, and this should be noted in the report.**

Breast Pathology Course 2019

# Metaplastic carcinoma ~ cytology

**WHO 2019**

- Biphasic tumour cells on FNA of the breast with atypical spindle cells, squamous carcinoma cells, osteoclast-like giant cells, and/or matrix with or without a component of adenocarcinoma cells may provide clues for diagnosis of metaplastic carcinomas.
- Cytology of matrix-producing metaplastic carcinoma shows abundant myxoid matrix along with cellular clusters composed of monotonous cellular populations, ***overlapping with the cytology of pleomorphic adenoma***.
- Cytological diagnosis of metaplastic carcinomas may not be possible in all cases because of selective sampling of various pathological elements.

Breast Pathology Course 2019

# Metaplastic carcinoma ~ diagnostic molecular pathology

**WHO 2019**

- Vast majority (> 90%) of metaplastic carcinomas lack expression of ER, PR, and ERBB2 (HER2).
- Majority express high-molecular-weight cytokeratins (CK5/6 and CK14), p63, and EGFR (HER1).
- A subset of EGFR (HER1)-positive metaplastic carcinomas display EGFR gene amplification.
- EGFR-activating somatic mutations appear to be vanishingly rare in these tumours.
- Identification of epithelial differentiation in metaplastic breast carcinomas requires the use of a panel of immunohistochemical markers.
- Usual markers are keratins – in particular AE1/AE3 and MNF116 (positive in 75–85% of cases); 34βE12, CK5/6, and CK14 (in 70–75%); and p63 (in 77%).
- Low-molecular-weight cytokeratins such as CK8/18, CK7, and CK19 are positive in a lower proportion of cases (36–61%).
- Myoepithelial markers, including SMA, CD10, and maspin, are also frequently positive (in 50–70% of cases).

# Metaplastic carcinoma ~ diagnostic molecular pathology

**WHO 2019**

- Negative for CD34 (in 100% of cases).
- Often lack expression of desmin (in 18%) and SMMHC (in 11%).
- E-cadherin may be aberrantly expressed within squamous foci.
- β-catenin may also be aberrantly expressed.
- Metaplastic carcinoma with LGASC pattern has a biphasic composition: the epithelial layer in gland-like structures is positive for luminal and occasionally basal cytokeratins, and the myoepithelial/basal cells display varying levels of expression of basal cytokeratins and p63, with staining ranging from complete to incomplete to absent.

Breast Pathology Course 2019

# Metaplastic carcinoma ~ diagnostic molecular pathology

- Transcriptomically, these tumours are classified as basal-like or claudin-low subtype using the intrinsic gene classification, or as basal-like or mesenchymal-like using the classification proposed by Lehmann et al.
- Whole-exome and targeted sequencing analyses demonstrate complex landscapes of gene copy-number alterations and a repertoire of somatic mutations including mutations affecting *TP53*, *RB1*, and chromatin-remodelling genes (i.e. *ARID1A* and *KMT2C*), as well as genes related to the PI3K pathway (i.e. *PIK3CA, PIK3R1, and PTEN*), the *MAPK* pathway (i.e. *NF1, KRAS, and NRAS*), and the WNT pathway (i.e. *FAT1 and CCN6 [WISP3*]).
- Evidence suggests that *TP53* mutations may be less frequently found in spindle cell carcinomas than in other forms of metaplastic carcinomas and in LGASC.
- Compared with other forms of triple-negative breast cancer, metaplastic carcinomas more frequently display mutations affecting PI3K pathway–related genes than do basal-like cancers, but at a frequency similar to that found in luminal AR triple-negative disease.
- Similar to phyllodes tumours, metaplastic carcinomas were reported to harbour *TERT* gene promoter mutations in 25% of cases in one study, but these mutations were not detected in others.
- Further analysis to define the frequency of *TERT* promoter mutations in metaplastic breast cancers is needed.

**WHO 2019**

# Metaplastic carcinoma

**WHO 2019**

## Essential criteria ~

- An IBC with atypical squamous, spindle cell, and/or mesenchymal/matrix-producing differentiation.
- In metaplastic carcinomas lacking ductal carcinoma in situ or conventional-type mammary carcinoma components, direct evidence of epithelial differentiation by immunohistochemistry, based on unequivocal expression of (high-molecular-weight) cytokeratins and/or p63.

Breast Pathology Course 2019

# Metaplastic carcinoma

**WHO 2019**

## ❑ Staging ~

- Similar to other IBCs.

## ❑ Prognosis & prediction ~

- Lymph node metastases are found significantly less frequently in metaplastic breast cancers than in IBC-NST of similar size and grade.
- Distant metastases (preferentially affecting the brain and lungs) occur in the absence of lymph node metastases.
- No prognostic markers or predictive markers of therapeutic response supported by level 1 evidence.
- Fibromatosis-like carcinomas and LGASCs are associated with more-indolent behaviour.
- High-grade spindle cell, squamous cell, and high-grade adenosquamous carcinomas are associated with the worst prognosis.
- Matrix-producing carcinomas are associated with a better prognosis.
- Higher numbers of morphologies within mixed metaplastic carcinomas correlate with a worse outcome.
- Prognostic value of histological grade in metaplastic breast carcinomas is uncertain.

# Metaplastic carcinoma

WHO 2019

## ❑ Prognosis & prediction ~

- 3-year, 5-year, and 10-year overall survival rates are 77%, 62%, and 53%, respectively.
- No difference in 5-year survival was found between hormone-positive and hormone-negative metaplastic carcinomas.
- Rare forms of HER2-positive metaplastic carcinoma may be associated with a better outcome than triple-negative metaplastic carcinomas.
- Radiotherapy provides a survival benefit.
- As a group, metaplastic breast cancers are reported to have lower response rates to conventional adjuvant chemotherapy and a worse clinical outcome after chemotherapy than other forms of triple-negative breast carcinomas.

Breast Pathology Course 2019

# Thank You

Division of Pathology
Singapore General Hospital

SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

IAP
International Academy of Pathology
Singapore Division