What's new in the updated breast pathology guidelines?

Rahul Deb
Consultant Histopathologist/Breast MDT Lead
University Hospitals of Derby & Burton

Overview

- **Continued with "back to basics" approach of previous version (common practical problems)**
- **Aligned ourselves in line (or not) with new WHO/ASCO-CAP/ICCR guidance.**
- **Added new sections but also simplified text where necessary**
- **Low ER/Low HER2 status (not discussed here)**

“Back to basics”- Fixation

- **Dissection issues (Fixation in MxT)**
  - **Specimen sent immediately to the lab with an ideal cold ischaemic time of less than an hour**
  - **If impossible to send the fresh state, by mutual agreement, incision(s) by the surgeon from the posterior aspect of large specimens can be helpful**
  - **Vacuum packing/refrigeration can be useful if either not available.**

"Back to basics"- Radioactivity

- **Dissection issues (Radioactivity)**
  - **No requirement to delay handling of radioactive specimens (low radiation exposure risk)**
  - **Lab staff handling these specimens DO NOT need to be registered as radiation workers**
  - **Local radiation protection office/officer should be able to provide advice if required (but also refer to this guidance)**

"Back to basics"- Dissection general principles

- **Dissection issues (General principles of sampling)**
  - **In WLE/lumpectomy, margin closest to nipple should be sampled (esp if DCIS)**
  - **Anterior margin in skin-sparing mastectomy should be sampled, if close**
  - **Nipple area of a nipple sparing mastectomy should be sampled (constitutes a true margin)**

"Back to basics"- Dissection of additional specimens

- **Dissection issues (Additional specimens)**
- **A range of specimens with different terminologies are used in different depts – "bed biopsies/cavity shave/shave re-excision/re-excision"**
  - ***Cavity shave*** **- small portions of tissue, often taken as routine from multiple radial margins at the same time as the main Sx**
  - ***Immediate re-excision*** **- larger portions of tissue submitted, usually from a one or two aspects, taken at the same time as main Sx**
  - ***Delayed re-excision – specimens*** **taken at subsequent operation.**

Cavity Shaves

- **Weighed & measured, particularly thickness**
- **Embed in total, usually one block, without slicing**
- **If orientated, new margin placed face-down for histology.**
- **Not possible to assess the distance to margins (report states tumour present or absent)**
- **Sufficient to comment if disease is present (or absent) on histology**

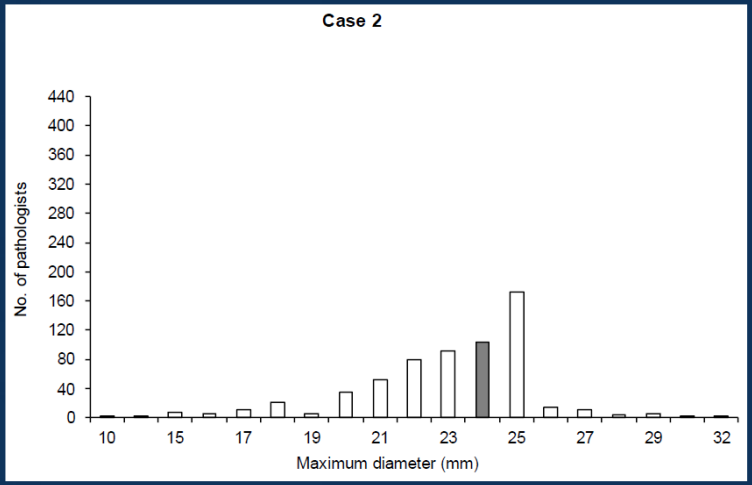
Immediate/Delayed Re-excision

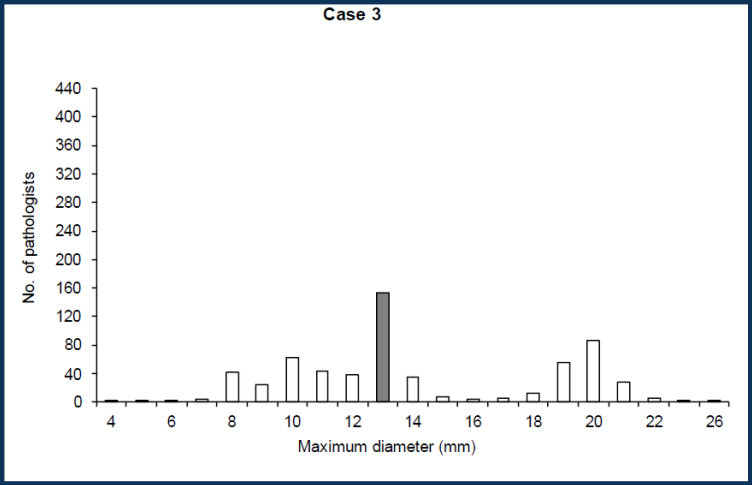
- **Weighed & measured, particularly thickness**
- **New margin inked**
- **Inking with multiple colours (like WLE) not routinely necessary**
- **‘Shave’ approach to the new margin is not recommended**
- **Smaller specimens (<30mm) should be sampled entirely**

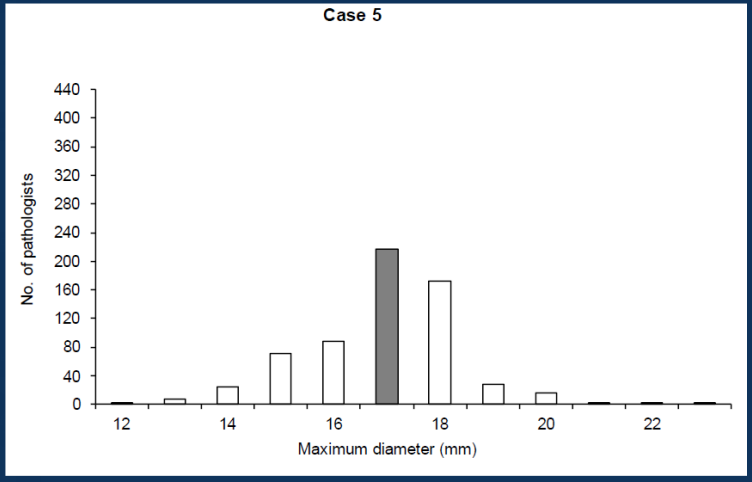
Immediate/Delayed Re-excision

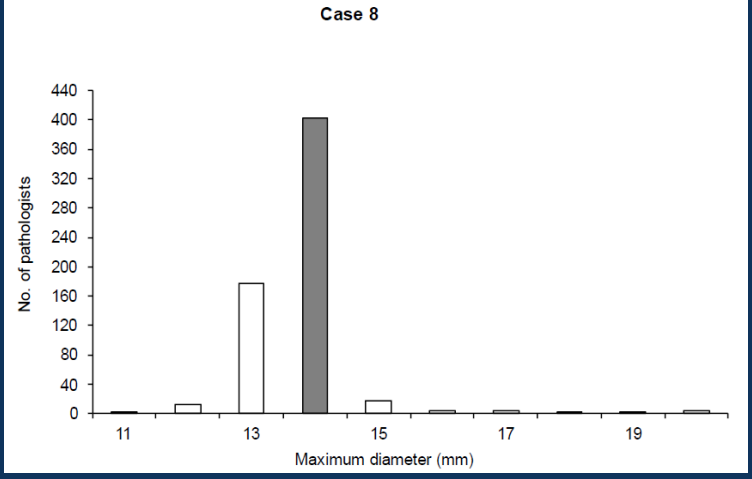
- **Larger specimens- be pragmatic!**
  - **Examine for any macroscopic suspicious areas & sample accordingly, if found**
  - **Alternate or 3rd slice, dependent on size of specimen**
  - **Nature of underlying lesion may also help, DCIS in main specimen, close to margin may be sampled more extensively than a discrete mass**
  - **Not necessary to embed each slice in a separate block**

“Back to basics”- Tumour size measurement









ABP 4th Annual meeting, Oct 2021; Webinar

Circulation 62 (2021/1) – 627 participants

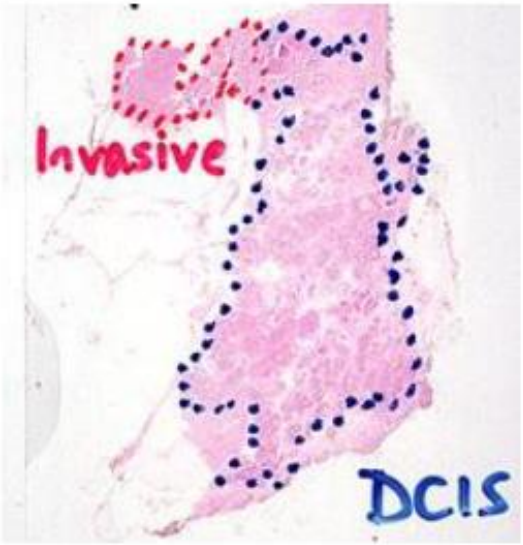


Figure 38: **Marking the microscope slide can aid size measurement**

a)

b)

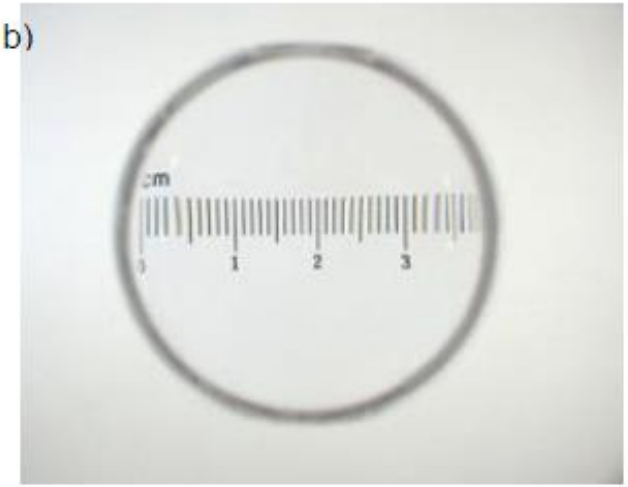
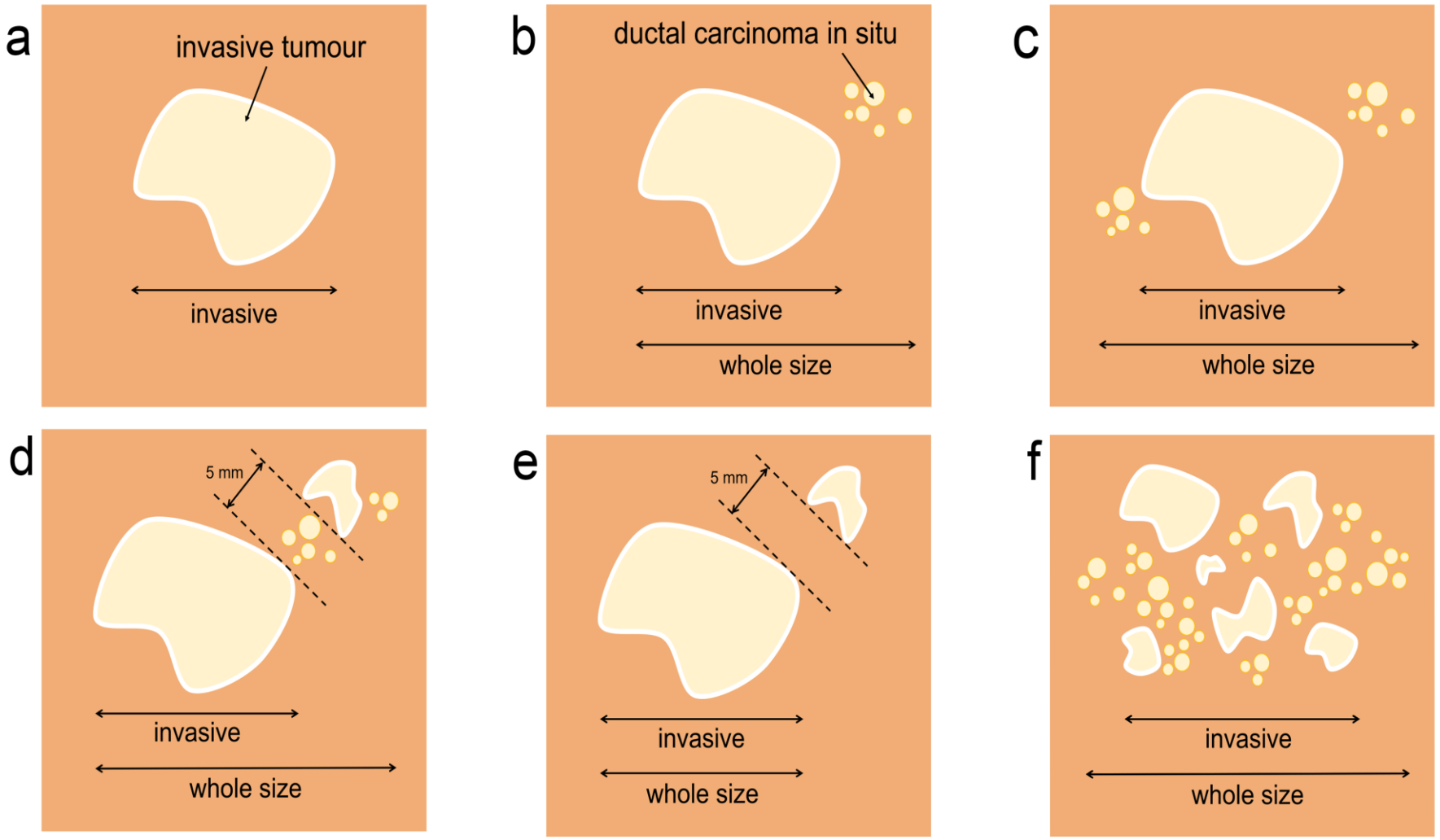
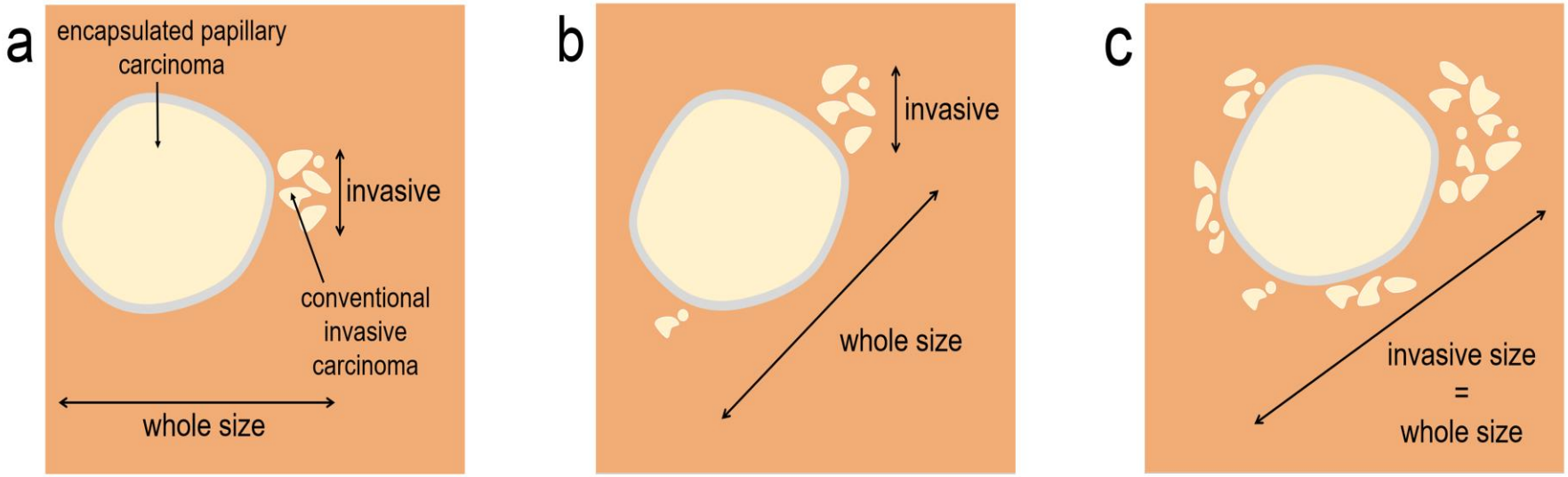


Figure 39: A simple lens measuring device can aid size measurement


a
invasive tumour
invasive
b
ductal carcinoma in situ
invasive
whole size
c
invasive
whole size
d
5 mm
invasive
whole size
e
5 mm
invasive
whole size
f
invasive
whole size


a
encapsulated papillary carcinoma
invasive
conventional invasive carcinoma
whole size
b
invasive
whole size
c
invasive size
=
whole size

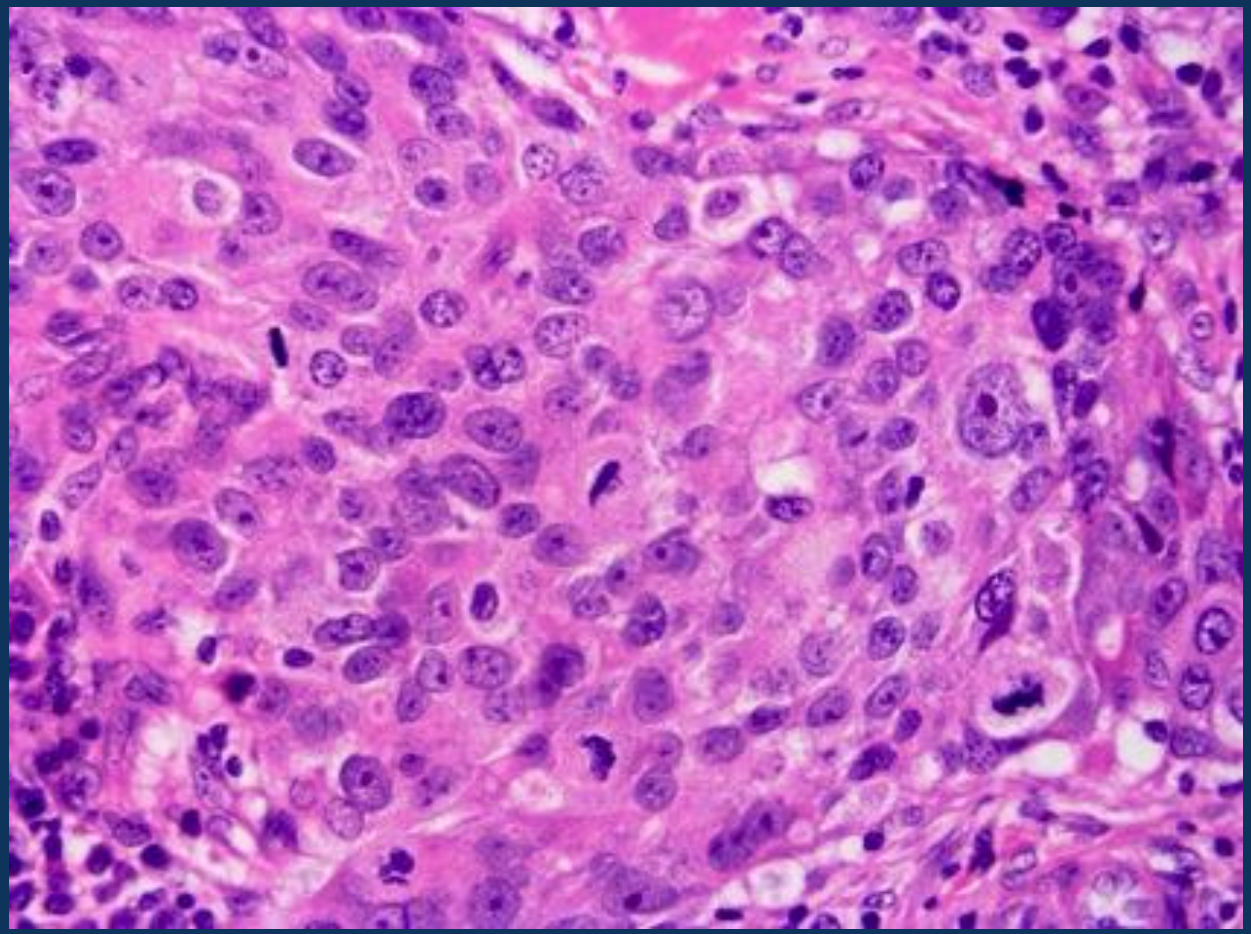
No tumour in resection specimen

- **Cancer removed at core**
  - **Review NCB/VAB/VAE to confirm diagnosis**
  - **Complete MDS items (including tumour size) based on biopsy findings**

- **Pathological complete response (pathCR) foll NACT**
  - **Biopsy size likely to be a significant underestimate**
  - **Defer to other modalities using the following hierarchy**
  - **Micro<Macro<MRI<Ultrasound<MMG<Clinical**

ASSOCIATION OF BREAST PATHOLOGY

"Back to basics"- counting mitosis



ABP 4th Annual meeting, Oct 2021;
Webinar

"Back to basics"- counting mitosis

		Number of mitoses corresponding to		
Field diameter (mm)	Field area (mm^2)	Score 1	Score 2	Score 3
0.40	0.126	up to 4	5 to 9	10 or more
0.41	0.132	up to 4	5 to 9	10 or more
0.42	0.139	up to 5	6 to 10	11 or more
0.43	0.145	up to 5	6 to 10	11 or more
0.44	0.152	up to 5	6 to 11	12 or more
0.45	0.159	up to 5	6 to 11	12 or more
0.46	0.166	up to 6	7 to 12	13 or more
0.47	0.173	up to 6	77to 12	13 or more
0.48	0.181	up to 6	7 to 13	14 or more
0.49	0.189	up to 6	7 to 13	14 or more
0.50	0.196	up to 7	8 to 14	15 or more
0.51	0.204	up to 7	8 to 14	15 or more
0.52	0.212	up to 7	8 to 15	16 or more
0.53	0.221	up to 8	8 to 16	17 or more
0.54	0.229	up to 8	8 to 16	17 or more
0.55	0.238	up to 8	9 to 17	18 or more
0.56	0.246	up to 8	9 to 17	18 or more
0.57	0.255	up to 9	9 to 18	19 or more
0.58	0.264	up to 9	10 to 19	20 or more
0.59	0.273	up to 9	10 to 19	20 or more
0.60	0.283	up to 10	10 to 20	21 or more
0.61	0.292	up to 10	10 to 21	22 or more
0.62	0.302	up to 11	12 to 22	23 or more
0.63	0.312	up to 11	12 to 22	23 or more
0.64	0.322	up to 11	12 to 23	24 or more
0.65	0.332	up to 12	13 to 24	25 or more
0.66	0.342	up to 12	13 to 24	25 or more
0.67	0.353	up to 12	13 to 25	26 or more
0.68	0.363	up to 13	13 to 26	27 or more
0.69	0.374	up to 13	13 to 27	28 or more
0.70	0.385	up to 13	14 to 27	28 or more

“Back to basics”- counting mitosis (alternative table)

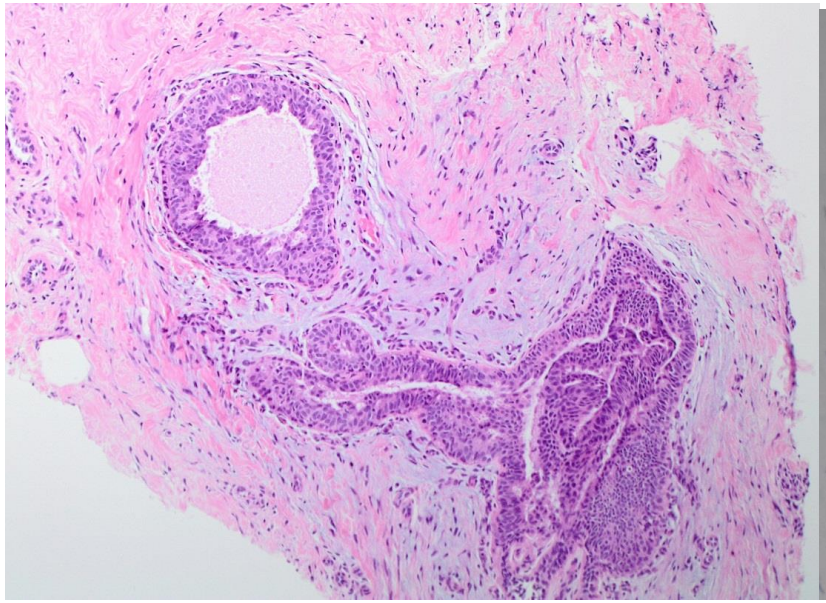
	Number of mitoses corresponding to		
Standard area (mm^2)	Score 1	Score 2	Score 3
2	up to 7	8-14	15 or more
3	up to 11	12-22	23 or more
4	Up to 14	15-29	30 or more

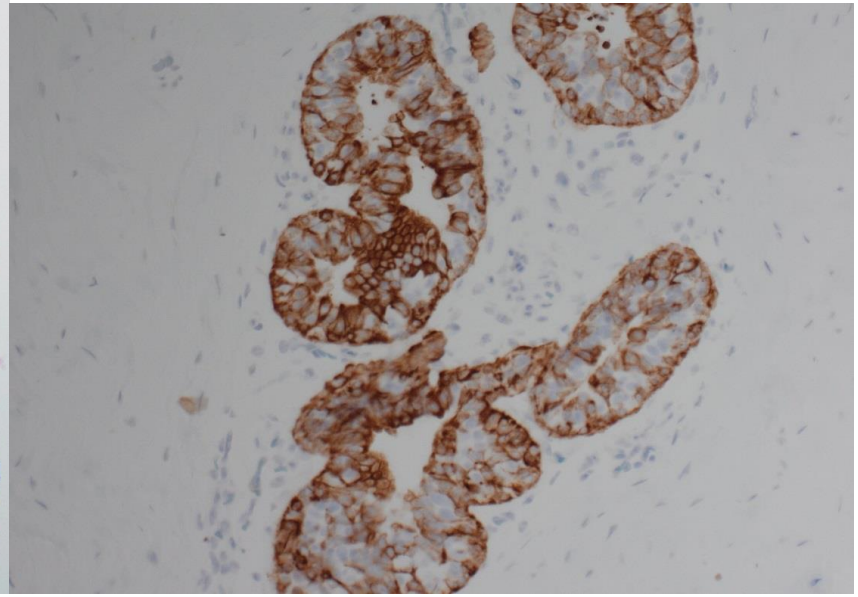
Male breast lesions

—

separate chapter

- **Gynaecomastia**
  - **CK pattern different to UEH in female breast**
  - **trilayered pattern of inner and outer basal layers (CK5, CK14 positive) enclosing a middle layer of luminal cells**





Male Breast lesions- separate chapter

- **Male Breast cancer**
  - **All men with breast cancer are eligible for a genetic testing (BRCA2)**
  - **GATA3 is less frequently expressed in male breast cancer (small series 6 of 19 (31.6%) male vs 135 of 164 (82.3%) female carcinomas** (**ref** Gonzalez, R.S., et al., *GATA-3 expression in male and female breast cancers: comparison of clinicopathologic parameters and prognostic relevance.* Hum Pathol, 2013. **44**(6): p. 1065-70)
  - **Conflicting data on prognosis but SEER data (1973-2005) would suggest that even after controlling for other factors, the risk of death was 43% greater than in women**

Common practical problems

Histological feature	Fibroadenoma	Benign PT	Borderline PT	Malignant PT
Outline	Well defined	Well defined	Well defined, may be focally infiltrative	Infiltrative
Stromal cellularity	Variable, usually uniform	Cellular, usually mild, may be focal or diffuse	Cellular, usually moderate, may be focal or diffuse	Cellular, usually marked and diffuse
Stromal atypia	None	Mild or none	Mild or moderate	Marked
Mitotic activity	None or low	Low (<2.5/mm^2 or <5/10HPFs)	Frequent (2.5-5/mm^2 or 5-10/10HPFs)	Abundant (>5/mm^2 or >10/10HPFs)
Stromal overgrowth	Absent	Absent	Absent or very focal	Often present
Malignant heterologous elements	Absent	Absent	Absent	May be present
Distribution relative to other breast tumours	Common	Uncommon	Rare	Rare
Relative % of all phyllodes tumours	N/A	60-75%	15-26%	8-20%

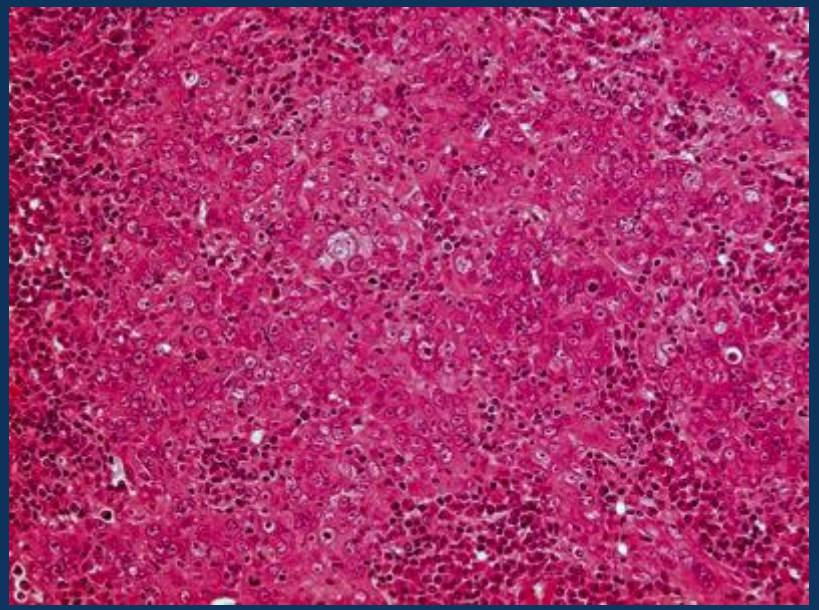
Columnar cell change	Columnar cell hyperplasia	Flat epithelial atypia	Atypical ductal hyperplasia
TDLUs with variably, usually mildly, dilated acini. Irregular internal contour	TDLUs with variably dilated, usually irregularly shaped, acinar contour	TDLUs dilated. Usually bluer than normal at low power. Typically smooth internal contour to acini	TDLUs may be dilated. Usually bluer than normal at low power due to increased cell numbers
Acini lined by one to two cell layers	Acini lined by more than 2 layers of cells; may form tufts, but no complex architectural patterns	Acini lined by one or more layers of cells with a flat growth pattern (no complex architectural patterns)	Acini lined by one or more layers of cells. Complex architectural pattern
Lining cells bland, columnar in shape, with uniform ovoid to elongated nuclei oriented perpendicular to basement membrane	Lining cells bland, columnar in shape, similar to those in columnar cell change, with uniform ovoid to elongated nuclei oriented perpendicular to basement membrane. Nuclei may appear crowed and overlap	Acini lined by cells with low-grade (monomorphic) cytological atypia; cells most often resemble those seen in low-grade DCIS. Nuclei typically round, but may be ovoid in some cases	Low-grade (monomorphic) cytological atypia. Nuclei typically round, evenly-spaced
Normal nuclear to cytoplasmic ratio	Normal nuclear to cytoplasmic ratio	Increased nuclear to cytoplasmic ratio	Increased nuclear to cytoplasmic ratio
Nucleoli absent or inconspicuous	Nucleoli absent or inconspicuous	Nucleoli may or may not be prominent	
Cells polarised	Cells polarised	Cells typically lack polarity, not regularly oriented perpendicular to basement membrane; however, in some cases, stratified, atypical, ovoid nuclei are arranged perpendicular to basement membrane (resembling pattern seen in colonic adenomas)	Cells polarised around architecturally atypical features, such as micropapillae and cribriform spaces
Luminal secretions may be present but are usually not prominent. Calcifications may be present	Luminal secretions may be present and prominent; calcifications often present may be psammomatous	Luminal secretions may be present and prominent; calcifications often present may be psammomatous	Luminal secretions may be present but are usually not prominent. Calcifications may be present
Mitoses infrequent	Mitoses infrequent	Mitoses infrequent	Mitoses infrequent

Histological features	Usual ductal hyperplasia	Atypical ductal hyperplasia	Low nuclear grade DCIS
Size	Variable size but rarely extensive unless assoc-iated with other benign processes such as papilloma or radial scar	Usually small (< 2 mm) and/ or incomplete duct space involvement	At least 2 mm and/or 2 complete duct spaces
Cellular composition	Mixed epithelial cell and spindle shaped cells* present. Lymphocytes and macrophages may also be present. Myoepithelial hyperplasia may rarely occur around the periphery	A uniform cell population, which may merge with areas of usual type hyperplasia within the same duct space.	Single uniform cell population.
Architecture	Variable	Micropapillary, rigid epithelial bridges and roman arches or solid pattern.	Well developed micropapillary, cribriform or solid patterns
Lumina	Irregular, often ill defined peripheral slit like spaces are common and a useful distinguishing feature	May be distinct, well formed rounded spaces in cribriform type. Irregular, ill defined lumina may also be present	Well delineated, regular punched out lumina in cribriform type. Micropapillae are of classical appearance, with thinner necks and more bulbous tips.
Cell orientation	Often a streaming pattern with the long axes of nuclei arranged in parallel to direction of cellular bridges, which often have a 'tapering' appearance	Cell nuclei may be at right angles to bridges in cribriform type, forming 'rigid' structures	Micropapillary structures with indiscernible fibrovascular cores or smooth, well delineated geometric spaces. Cell bridges 'rigid' in cribriform type with nuclei orientated towards the luminal space
Nuclear spacing	Uneven	Even	Even
Epithelial/ tumour cell character	Small and ovoid, but showing variation in shape	Small uniform or medium sized monotonous population present at least focally	Small uniform monotonous population
Nucleoli	Indistinct	Single small	Single small
Mitoses	Infrequent; no abnormal forms	Infrequent; abnormal forms rare	Infrequent; abnormal forms rare
Necrosis	Rare	Rare	If present, confined to small particulate debris/ secretion in cribriform and/or luminal spaces
Immunohisto-chemistry **ER** **High MW cyto-keratins (e.g. CK5, 5/6,14,17)**	Heterogeneous/mosaic Heterogeneous/mosaic	Homogeneous usually strong Negative	Homogeneous usually strong Negative

Features	Papilloma	Papilloma with atypia/DCIS	Papillary DCIS	Encapsulated papillary carcinoma
Periphery of the lesion	Peripheral myoepithelial cell layer present	Peripheral myoepithelial cell layer present	Peripheral myoepithelial cell layer present	Circumscribed, frequently surrounded by a thick 'capsule' Peripheral myoepithelial cell layer absent
Fibrovascular cores	Usually broad and extend throughout lesion	Usually broad and present in benign papilloma component.	Variable, usually fine	Very variable, usually fine. May be lacking in at least part of the lesion
Cells covering papillae	Two cells types. Myoepithelial layer always present. Single layer of regular luminal epithelium OR features of regular usual type hyperplasia.	Two cell types present in benign papilloma component. Myoepithelial cell layer evident in benign papilloma component. For a low grade epithelial proliferation within a papilloma, 3mm extent is used to differentiate between ADH (<3mm) and low grade DCIS (≥3mm). A diagnosis of intermediate or high grade DCIS within a papilloma is made regardless of extent.	One cell type. Myoepithelial cells absent within the lesion One or more layers of atypical epithelial cells. Nuclei may be hyperchromatic.	Usually one cell type. Myoepithelial cells absent within and around the lesion Epithelial cells often taller and more monotonous with oval nuclei, the long axes of which lie perpendicular to the stromal core of the papillae. Nuclei may be hyperchromatic. Epithelial multi-layering is frequent, often producing cribriform and micropapillary patterns overlying the papillae or lining the wall.
Mitoses	Infrequent, no abnormal forms	May be present within atypical foci or DCIS	More frequent, abnormal forms may be seen	More frequent, abnormal forms may be seen
Apocrine metaplasia	Common	May be seen within the benign papilloma component	Not seen	Rare
Adjacent tissue	Benign changes may be present, including usual epithelial hyperplasia	Surrounding tissue may show varied histological change including atypia and/or DCIS	Surrounding ducts may bear DCIS	Surrounding ducts may bear DCIS
Necrosis and haemorrhage	May be present.	Necrosis within atypical proliferation suggests DCIS	May be present	May be present
Periductal and intra-lesional fibrosis	May be present	May be present	May be present	Usually present

WHO blue book – alignment with tumour types

- Previously discussed at this meeting (not repeated here)
- Medullary carcinoma now a Ductal, NST variant
  - circumscribed or pushing border
  - syncytial growth pattern
  - high-grade vesicular nuclei with prominent nucleoli
  - prominent lymphoid infiltration



Writing Group

- **Dr Rahul Deb (Chair)**
- **Prof Sarah E Pinder (Deputy)**
- **Dr C Boyd**
- **Prof G Callagy**
- **Dr P J Carder**
- **Dr AHS Lee**
- **Dr Y Mir**
- **Dr E Provenzano**
- **Prof C Quinn**
- **Prof E Rakha**
- **Prof A Shaaban**
- **Dr B Tanchel**

Writing Group

- **Dr Rahul Deb (Chair)**
- **Prof Sarah E Pinder (Deputy)**
- **Dr C Boyd**
- **Prof G Callagy**
- **Dr P J Carder**
- **Dr AHS Lee**
- **Dr Y Mir**
- **Dr E Provenzano**
- **Dr C Quinn**
- **Prof E Rakha**
- **Prof A Shaaban**
- **Dr B Tanchel**

What's new in the updated UK guidelines

- **"Back to basics" approach (Dissection)**
  - **New detailed guidance on handling additional specimens (cavity shaves, immediate and delayed re-excisions)**
  - **Re-emphasised importance of rapid fixation**

- **"Back to basics" approach (Tumour size)**
  - **New guidance on dealing with size measurement in encapsulated carcinoma**

- **"Back to basics" approach (mitosis)**
  - **To enable DP, also provided area for mitotic counts**

What's new in the updated UK guidelines

- **Helpful tables to deal with commonly encountered diagnostic problems**
- **Aligned tumour types in line with WHO guidance**
- **New chapter on male breast lesions**
- **Guidance on ER/HER2 testing (not discussed today)**

- **AND A LOT MORE!**

Thank You!