

Gynaecological Pathology reporting. What *really* matters - When and Why

Abstracts and References Monday 16 October 2017

Introduction: Rationale of the course
Dr Murali Varma, Cardiff

Please see separate handout at back of document

Pathology of the ovary and fallopian tube
Dr Naveena Singh, London

Learning points

- Correct disease categorisation as benign, borderline or malignant, accurate diagnosis of histological type and correct clinicopathological staging underpin optimum patient management.
- The following vary for different tumours and are dependent on correct diagnosis: Surgical vs non-surgical treatment; fertility preservation; ovary conservation; extent of surgery: initial or completion; adjuvant therapy (including targeted) and hereditary cancer screening
- Pathologists must be aware of changes to disease classification in WHO 2014.
- Pathologists must be aware of the 2013 FIGO staging system including sub-stages.
- The ICCR dataset clearly defines reporting parameters for ovarian cancer reporting.
- Pathologists must be aware of the role and limitations of immunohistochemistry in diagnosis of ovarian neoplasia.

The diagnosis of ovarian neoplasms as benign/borderline/malignant and accurate staging of borderline and malignant tumours are essential for treatment decisions and optimal patient management. The 5 major ovarian carcinoma histotypes can be readily distinguished from each other, usually on routine morphological assessment and, when required, with a relatively small immunohistochemistry panel that is readily available in most laboratories in the UK. In cases of high grade serous carcinoma, optimal tubal sampling, categorisation of primary site, and evaluation of the pathological response to chemotherapy are all relatively recently defined additional requirements. Low grade serous carcinoma is currently diagnosed based on the presence of invasion within the ovary or at extra-ovarian sites (previously termed 'invasive implants'). Between 3% and 10% of serous borderline tumours recur and about 4% develop into carcinoma, both these adverse outcomes sometimes occurring many years after initial diagnosis. Disease stage is the strongest predictor of outcome in serous borderline tumours; on the other hand, owing to the overall indolent nature of the disease in the majority of cases, fertility conservation with close follow-up and delayed completion surgery are acceptable alternatives. Other, less common, epithelial tumour histotypes and non-epithelial tumours have specific management implications which will be addressed.

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Small diagnostic biopsies: handling and reporting issues

Dr Varsha Shah, Newport

Learning points

- Consider embedding core biopsies in multiple cassettes and either examining a single superficial section of each block or retaining multiple unstained spares upfront for potential immunohistochemistry.
- No need to measure each biopsy in 3 dimensions: largest dimension is sufficient.
- Description of biopsy specimens (colour, consistency etc) generally of little clinical utility.
- Prioritise choice of immunostains rather than shot-gun standard large immunopanel approach
- Try not to exhaust block; retain some material for IHC/mol testing in future (may be several years later)
- The biopsy sample may not be representative of the tumour due to intratumoral morphological and biological heterogeneity

Small diagnostic biopsies and curettings pose special problems for histopathologists due to limited amount of tissue available, tissue fragmentation precluding orientation, sampling error and uncertain topography. Moreover, the clinical requirements from biopsy pathology are often very different from that from resection specimens.

The diagnosis of even common tumours may be challenging in limited material when only non-typical areas may be represented while rare tumour type or variant may be difficult to identify even with more generous sampling. Unlike resection specimens where the origin of the tissue is usually obvious, there may be uncertainty in endometrial biopsies whether the tissue is of endometrial or endocervical origin. Moreover, due to intratumoral morphological and biological heterogeneity, the biopsy sample may not be truly representative of the tumour.

Pathologists must be acutely aware of issues dealing with small amount of tissue obtained by invasive procedures and optimise handling techniques to optimise the use of limited material for diagnostic and prognostic assessment. Since biopsy material may require extensive immunohistochemistry one should consider processing needle cores separately and examining a single superficial level of each block for initial assessment while retaining sufficient tissue in the block for subsequent immunohistochemistry.

Peritoneal/omental pathology and cytology

Dr Tony Williams, Brighton

Learning points

- Histology is preferred for diagnosis of tubo-ovarian malignancy.
- Duplication of diagnostic immunopanel on biopsy and cytology specimens provides little clinical value unless a second diagnosis is suspected.
- Peritoneal cytology specimens should be correlated with concurrent resection specimens and reported together
- Peritoneal washings specimens are seldom indicated in the investigation of benign conditions.
- Ovarian cysts aspirates have low sensitivity and are seldom therapeutic. Aspiration of malignancy risks iatrogenic upstaging.



Peritoneal cytology forms an important part of investigation and staging of malignancy of the fallopian tubes and ovaries. Historically it has also been used in the staging of endometrial cancer: Although it no longer appears in the current FIGO staging system it may assume some importance in prognosis and management and should be reported.

Abdominopelvic peritoneal washings are of limited sensitivity in the identification of peritoneal disease and a variety of benign lesions may fall into the differential diagnosis of malignant involvement.

Ovarian cyst aspirates are discouraged in the investigation and management of ovarian cysts. This is an insensitive investigation in the evaluation of malignancy, is seldom therapeutic and in the presence of malignancy risks iatrogenic upstaging of disease.

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Endometrial pathology

Professor Glenn McCluggage, Belfast

Endometrial specimens, especially small biopsies, are amongst the commonest specimens in many surgical pathology laboratories. Practical and personal (others may disagree) tips for more efficient reporting of benign endometrial biopsies are:-

1. In general, performing of levels is of limited or no value and this does not need to be done routinely.
2. Don't routinely ask for or suggest repeat endometrial biopsies in scant specimens.
3. Don't worry about dating of endometrial biopsies.
4. Endometrial biopsies do not need to be scrutinised at high power to look for plasma cells (indicative of endometritis) unless there are low power clues to raise the possibility of endometritis.
5. Artefacts are common- don't stress about them.

Regarding reporting of endometrial carcinomas, parameters which are important are those which are needed for patient management, tumour staging and assessment of prognosis. The following are practical and personal (others may disagree) tips:-

1. The distinction between atypical hyperplasia and grade 1 endometrioid adenocarcinoma on a biopsy is almost always clinically unimportant.
2. The distinction between grade 1 and 2 endometrioid adenocarcinoma is clinically unimportant.
3. Extensive sampling of a grossly normal cervix does not need to be performed in hysterectomy specimens of endometrial carcinoma.
4. Don't worry about extensive sampling of grossly normal omentum in cases of endometrial carcinoma.
5. The distinction between intraendometrial carcinoma and carcinoma exhibiting superficial myometrial involvement is subject to significant interobserver variability and is clinically unimportant.
6. Don't waste time searching for lymphovascular space invasion in endometrial carcinomas if extrauterine metastasis is present.



Learning points

- Diagnosis of CIN2 - Use of p16
- Handling a loop – top hat, open loop, fragmented loop and end slices
- Identifying invasion in squamous and glandular lesions
- Difficulties in measuring cervical carcinomas
- Trachelectomy and hysterectomy for cervical carcinomas – approach to trimming

The lecture will attempt to capture practical aspects of reporting cervical pathology from biopsies to cancer excision specimens and examine evidence, the clinical perspective and difficulties in converting theory into practice.

This will include importance of CIN2 diagnosis, use of p16, use of levels, handling of loops, identification of invasion, difficulties encountered in measuring cervical cancers, unifocal vs multifocal carcinomas, important aspects of reporting of cervical resection specimens.

References

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Learning points

- Gross examination of specimens is an integral part of the diagnosis of mesenchymal tumours of the uterus. The characteristic whorled appearance on cross section is reassuring. Deviation from this pattern requires thorough sampling. Colour and consistency are important factors to take into consideration.
- Clinical history is vital particularly any hormonal drug history, previous embolization or any other process that might confound the diagnosis.
- The distinction of endometrial stromal vs smooth muscle lesions requires an assessment of the gross morphology together with histological features. Beware putting too much emphasis on a CD10 positive result as it can be misleading if not used as part of a panel of antibodies.
- One of the most problematic areas is the diagnosis of a leiomyosarcoma especially when confronted with a leiomyoma variant. Whilst we rely on the trivariate classification system proposed by Bell, Hendrickson and Kempson proposed in 1994, do not underestimate the value of judicious sampling at the tumour/ myometrial junction where myometrial infiltration and lymphovascular space permeation are conspicuous especially in myxoid leiomyosarcoma where judicious sampling is always rewarded by the presence of LVSI at the tumour/ myometrial interphase.
- Endometrial stromal sarcomas arise in extrauterine sites within endometriosis. This MUST be considered when dealing with an unusual sarcoma that appears low grade and is ER and PR positive. FISH for JAZF1 can be very helpful in these cases.



- There are no reliable markers of prognostication or of diagnostic value in the distinction of leiomyoma variants from leiomyosarcoma. Cell cycle regulatory markers such as P16 and p53 and hormone receptors have not been found to be valuable and studies reporting their discriminatory value in this regard have been conflicting.

The importance of the distinction of endometrial stromal vs smooth muscle tumours is emphasised particularly with regard to their prognosis. Their management and clinical behaviour is addressed.

The distinction of leiomyoma variants from leiomyosarcoma is discussed with features that require attention and those that you need not bother with.

Finally the importance of making the distinction of LGESS from HGESS is discussed as they may have overlapping histological features.

The role of immunohistochemistry and prognostic markers and their place with regard to diagnosis is considered. When should you worry about using molecular techniques. Special criteria for the diagnosis of myxoid and epithelioid smooth muscle lesions is considered.

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Vulval and vaginal pathology

Dr Asma Faruqi, London

Learning points

- Importance of including prognostic points in the report
- Handling specimens- dataset points
- Implications of HPV-dependant and independent cancers
- Discussion on SLN
- Vulvovaginal cysts
- Mesenchymal tumours may be site-specific but non-site specific lesions should be kept in mind

The vulval cancer report should include prognostic factors that impact on further treatment (size, site, type and grade, depth of invasion/thickness, LVSI, perineural (intraneural) invasion, VIN – dVIN vs. uVIN. Optimal handling of lymph nodes, specially sentinel nodes is important as groin recurrence carries a poor prognosis. HPV-independent cancer has a worse prognosis and effort should be made to identify and separate this group from HPV-dependent cancer. This is discussed together with use of adjunct immunohistochemistry.

Most benign vulvovaginal cysts can safely be reported as Mullerian or non-Mullerian as there is usually insufficient clinical information available for further subtyping.

Important site specific mesenchymal lesions are discussed.

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Gynaepathology reporting

What really matters

When and Why

Murali Varma

University Hospital of Wales
Cardiff

RCPATH 2017

Histopathology reporting practice

A critical re-appraisal

Outline

- **Why** do we collect data?
- **Who** do we collect data for?
- **What** data do we collect?
- **How** do we collect data?
- **Do** we need to change?
- **How** do we change?

Why do we collect data?

1. Patient management
 - Treatment
 - Follow-up
2. Clinical Trials entry/exclusion
3. Epidemiology
4. Current research
5. Potential future research
6. Audit of surgeons performance
7. "Part of complete pathology report"

Who do we collect data for?

- **Treating clinicians**
 - Local clinicians
 - Outside clinicians
- **Researchers**
- **Epidemiologists**
- **Nobody!**
 - Size of specimen incl fat, size of bladder
 - 3 dimensions of tumour
 - Lengths of ureter, fallopian tube

How do we collect data?

- **Same data in all cases**
 - **One size fits all**
 - Vascular invasion in patients with distant mets!!
- **Precise data**
 - *mm or %*
 - amount of tumour, tumour components etc
 - *Pseudo-precision?*

Pathology measurements: *Examples*

- **Lengths**
 - Specimen size
 - Tumour size (Macro and Micro)
 - Distance to margins
- **Percentages**
 - % tumour in needle core
 - % tumour in radical prostatectomy
 - % tumour components: bladder, testis ...
 - % necrosis in RCC
 - % sarcomatoid change in RCC

Biopsy tumour size *What should we collect?*

- In **section**?
- In **slide**?
- In **tissue block**?
- In **specimen**?
- In **patient**?

It's what's in the patient that counts

All others are surrogate estimates

Pathology measurements *Causes of variation*

- **In slide**
 - Difference between sections (levels)
 - Temperature of water bath
- **In block**
 - Unexamined material in block
- **In specimen**
 - Specimen distortion
 - Fixation
 - Plane of section
 - Sampling error of biopsy

Debunking percentage estimation

- **% tumour in needle core**
 - More benign tissue makes tumour better?
- **% tumour in organ (eg. prostate)**
 - Tumour more aggressive in small glands?
- **% tumour components, necrosis, sarcomatoid change**
 - **Depends on sampling protocol**
 - % will depend on number of sections taken from areas of necrosis, fleshy white areas etc

Measurements *Perfect precision not required*

- **Percentages**
 - **Eyeball estimate sufficient**
 - 10% vs. 50% relevant
 - 10% vs. 20% irrelevant

Measurements: *Perfect precision not required*

- **Size/distances (mm)**
 - **To nearest mm (or <1mm)**
 - "2.1mm" is meaningless
 - May be different in other levels or blocks
 - Cannot eyeball distinguish 2.1 for 2.3mm so would require measuring multiple levels/blocks!
 - **Well clear margins: >5mm/>10mm sufficient?**
 - **Use field diameter of objective lenses?**
 - x5 objective: approx. 5mm, x10: approx. 2mm, x20: approx. 1mm, x40: approx. 0.5mm

Borderline measurements

A pragmatic approach

- **Tumour size/depth of invasion**
 - Round up: ?1mm ?2mm = 2mm
 - Measurement is minimum size/depth
 - May be more in deeper levels
- **Distance from margin**
 - Round down: ?1mm ?2mm = 1mm
 - Measurement is maximum clearance
 - May be less in deeper levels

“x blocks per cm max diameter”

What is a “block”?

- **Block of tissue or paraffin block?**
- **2 pieces of tissue in 1 cassette**
 - 2 tissue blocks
 - 1 paraffin block

“x blocks per cm max diameter”

- **Re-define as “x cm² tissue per cm max diameter?”**
- **Number of block too simplistic?**
 - Sampling macroscopically different areas more important than number of blocks
 - Need fewer blocks for grossly homogeneous tumours?
- **Are such requirements pertinent for cystic lesions?**
 - Size of cystic lesion depends on amount of fluid

Tumour grading/staging

- **Arbitrary cut-offs in a morphological and *clinical* continuum**
- **>50% myometrial invasion = stage 1B**
 - No studies comparing outcome of 40/50/60% invasion
 - 50% cut-off chosen only for convenience
 - 60% invasion not different from 40% invasion

Why grade tumours?

- **Groups of patients**
 - **Clinical trials**
 - Groups have to be comparable
 - **Survival analysis**
 - Surgeons, Areas (eg. Wales vs. England)
- **Individual patient**
 - Prognosis
 - Management

Tumour grading

Principles

- **Groups of patients**
 - Borderline grades cancel out as randomly distributed across adjacent grades
 - Interobserver reproducibility less important
 - Fewer tiers better
 - More cases in each group
 - Easier statistics

Tumour grading

Principles

- Reproducibility issues (inter-observer and intra-observer) would not impact studies of outcome on cohorts
- Reproducibility issues would seriously impact individual patient's management

Tumour grading

Principles

- **Individual patient**
 - Arbitrary lines in continuum
 - Inter-observer reproducibility critical
 - More tiers the better

Tissue sampling

- **All specimens only partially examined**
- **"All embedded" = 0.2% examined microscopically**
 - 5 micron section from every 3-4mm tissue block
- **Is submission of representative blocks from grossly normal, clinically benign specimens a form of cancer screening (without informed consent)?**

Clinical data
VS.
Pathology data

Clinical vs. histology data

- **Clinical**
 - Single window of opportunity
 - Unrecorded data (clinical examination or investigation) lost for ever
- **Histological**
 - Slides stored "indefinitely"
 - Data can be retrieved if necessary
 - No need to record every potentially useful data item

Macroscopy data
VS.
Microscopy data

Macroscopic vs. microscopic data

▪ Macroscopy

- **Single window of opportunity**
 - Unrecorded data may not be retrievable
 - Under-sampling may not be correctable

▪ Histological

- **Slides stored “indefinitely”**
 - Data can be retrieved if necessary
 - Retrospective immunohistochemistry feasible

Macroscopic vs. microscopic data

- Accurate and complete collection of macroscopic data more critical than microscopic data?
- Yet macroscopy often delegated to junior trainees and advanced practitioners with very limited guidance/supervision!

Clinical management vs. Pathology reporting

Clinical management

- **Based on clinical scenario and perceived cost-effectiveness**
 - **Eg. bone scans for prostate cancer patients**
 - Only for patients with intermediate/high risk of mets: eg. Gleason 7 or PSA >20
 - Rare Gleason 6 / low PSA patients may have bone mets but not cost-effective to do bone scan

Pathology reporting

- Proforma based “one size fits all” approach
- **Search and report for vascular invasion in patients with distant mets!!**
- **Some path data even if “effective” may not be cost-effective to collect**
 - Data that shows statistically significant prognostic difference may not be clinically significant
 - More important to improve turnaround time and reduce patient anxiety?

Communication gaps

Clinicians and Pathologists

- Most clinicians have limited understanding of path data
 - Clinicians do not need to be able to interpret histology slides (unlike radiology material)
 - Clinicians must be able to interpret reports and understand its limitations
- Many pathologists have limited understanding of the clinical utility of path data

Communication gaps

Expert pathologists and Practicing pathologists

- Experts do not always explain how to collect data
 - eg. degree of precision required
 - Percentage tumour in prostate bx recommended to reduce workload (eyeball guesstimation)
 - Some pathologists increased their workload by measuring both tumour and core lengths and calculating %!

We need to change!!

Drivers for change

- **Increasing workload**
- **Ever lengthening cancer datasets**
- **Increasing other commitments**
 - Management, EQA
- **Human constraints**
 - Time , concentration span
- **No increase in resources**
 - Manpower, finance

Risks of current practice

- **Waste of resources**
 - Time and money
- **Information overload**
 - Significant findings missed by clinicians
- **Stressed pathologist**
- **Risk of errors**
 - Missing data due to excess redundant data
 - Transcription error missed in unduly long report
 - Interpretation errors due to “rushed” pathologist

Examples of wasteful practice?

- **Routine histology review for MDT meetings**
 - Focus on getting it right the first time around?
- **Routine double reporting of cancers**
- **Use of standard immunohistochemical panels**
 - Select markers based on clinical and morphological differential
 - Size of panel should be determined on degree of uncertainty
 - Blunderbuss approach wasteful and often misleading
- **Detailed pre-MDT work-up of metastatic carcinoma of unknown primary**
 - Work-up should be based on clinical and morphological differential

How do we change?

- **Consider patient management**
 - All differentials are not equally important
 - All dataset items not equally important
- **More focussed approach**
 - Tailor report to clinical scenario
 - **While still meeting RCPATH requirements**

Why change?

- **More interesting**
- **More satisfying**
- **More efficient**
 - Less work
 - Less stress
 - Fewer errors
- **Improve image**
 - Able to discuss with clinicians as equals
 - Able to question unjustified demands

Categorising pathology data

RCPATH *Data categorisation*

- **Core**
 - “Required for cancer staging, optimal patient management and prognosis”
 - “Supported by robust published evidence”
- **Non-core**

Clinically orientated data categorisation

- **Critical**
 - Presence of cancer
 - Prognostic/predictive factors affecting treatment
- **Important**
 - Prognostic factors affecting follow-up
- **Less important**
 - Prognostic factors that do not affect management
- **Unimportant**
 - Size of prostate/fallopian tube ...

Clinically orientated data categorisation

- **Based on clinical scenario rather than path diagnosis**
 - A core data item may be either critical, important or unimportant in different clinical scenarios

1mm Gleason 3 + 3 prostate cancer in a needle bx

- **Man with raised PSA**
 - Critical
- **Man on active surveillance**
 - Irrelevant
 - Benign, suspicious and low volume 3+3 cancer managed in identical manner
 - Continue active surveillance
 - Grade and amount of cancer critical

Why clinically categorise data?

- **Identify where to focus time, money, energy**
- **Recognise clinically significant cut-offs**
 - **Cytology**
 - Urine: U2/U3 vs U4/U5
 - Thyroid: Thy 4 vs Thy 5
 - **Histology**
 - Bladder: grade 2 vs grade 3
 - Cervix: CIN1 vs CIN 2/CIN3

Why clinically categorise data? (2)

- **Recognise clinical implications of diagnosis**
 - **U4 vs. U5 in voided urine:** limited clinical significance
 - Both lead to further investigations
 - **Thy 4 vs. Thy5 in thyroid FNA:** May be critical
 - Thy4: lobectomy
 - Thy5: total thyroidectomy following by lifelong thyroxine replacement.
 - **G3Ta TCC or CIS: first presentation**
 - BCG Rx
 - **G3Ta TCC or CIS: following BCG Rx**
 - Cystectomy

Clinically orientated data categorisation

Critical caveats

- **Subjectivity in categorisation**
- **May change with time**
- **Would change with local practice**
- **Principles may differ between cancers**
 - Grade irrelevant in muscle invasive or metastatic TCC
 - Grade important in metastatic ovarian serous carcinoma
- **All RCPATH core data items MUST be collected**
- **If in doubt: err on side of critical/important**

How to effect change?

- **More discussion with clinicians**
 - What do they use?
 - What is redundant?
- **Annual pathology study day for surgery and oncology trainees?**
 - Should be mandatory part of their training programme?

RCPATH datasets

Change?

- **More scrutiny (esp. non-core data items)**
 - Eg. specimen measurements
- **More guidance**
 - How to collect data
 - Degree of precision required
 - Clinical significance of path data

RCPATH datasets

Change?

- **Change reporting options?**
 - **Vascular invasion:** Seen/not seen/not assessed
- **Change the way we audit data?**
 - Focus on accuracy rather than completeness
 - Evaluate clinical significance of missing data
 - Vascular invasion missing in patients with known LN metastasis may be less important