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ANATOMICAL PATHOLOGY

Evaluation of pathology review at gynaecological oncology multidisciplinary team meetings: a 5-year prospective analysis of cases with major diagnostic discordance

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Summary

Multidisciplinary team meetings (MDTs) play an essential role in the management of patients with newly diagnosed and recurrent cancers, and often include review of pathology specimens that were initially assessed in external departments. Many studies have demonstrated a low but significant rate of diagnostic disagreement following such review but the pathological findings have seldom been detailed. We present a prospective 5-year study of all external cases reviewed at the Western Australian Gynaecological Oncology MDT focusing upon those cases with major diagnostic discordance likely to impact patient management. In total, 1275 cases were reviewed of which 132 (10.4%) were considered discordant including 48 (3.8%) with major discordance. Different interpretation of the presence and/or extent of tumour invasion accounted for a significant proportion of cases and in particular some adenocarcinoma and squamous carcinoma variants were initially reported to show only *in situ* or minimally invasive disease. Endometrial high-grade serous carcinoma was under-recognised and on occasion reassignment of tumour origin including metastasis to the gynaecological tract was facilitated by additional clinical information and supported by appropriate immunohistochemistry. This study supports the role of pathology review at MDTs and highlights problematic lesions that may merit a low threshold for additional opinion and ancillary studies.

Key words: Pathology; review; multidisciplinary meeting; gynaecological; MDT.

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INTRODUCTION

In many countries multidisciplinary team meetings (MDTs), also referred to as tumour board meetings or tumour conferences, have become an established part of the standard of care in patients with cancer.[1,2] In particular, MDTs provide a centralised forum that concentrates expertise from all relevant medical and non-medical specialties involved in the diagnosis and management of patients with new or recurrent malignancies. However, they also serve a wider educational purpose which includes the explanation or clarification of diagnostic findings and the provision of relevant updates, such as information on potentially targetable developments in tumour molecular analysis or the availability of clinical trials.[3]

MDTs are typically held in tertiary cancer centres and they often include a requirement to review anatomical pathology specimens (histological and/or cytological) that were initially assessed in 'outside' non-specialist pathology laboratories. Many studies, whether encompassing a broad range of specimens[4–10] or cases restricted to sub-speciality areas such as gynaecological oncology,[11–20] have demonstrated that such reviews lead to a revision of the initial pathological diagnoses in a significant minority of cases, often resulting in altered patient management. While these studies have provided support for the role of pathology review in the MDT setting, details of those cases causing diagnostic discrepancy (potential misdiagnoses) have generally received less attention.

In Western Australia (WA), >95% of gynaecology oncology patients undergoing treatment in both the public and private sectors are referred to a single state-wide gynaecology oncology MDT. Pathology specimens initially reported in external laboratories are requested for review at the state gynaecological cancer centre, King Edward Memorial Hospital (KEMH) prior to MDT discussion. The purpose of this study is to document the proportion and nature of diagnostic discrepancies encountered over a 5-year period at KEMH, with discussion of the lesions that most commonly led to discordant pathological assessment.

MATERIALS AND METHODS

A prospective study was performed of all external histopathology and cytopathology specimens reviewed at KEMH from patients referred to the WA Gynaecological Oncology MDT during the 5-year period from January 2013 to December 2017. The majority of cases were obtained from other WA pathology departments but some were submitted from inter-state or overseas laboratories. While most samples were derived from gynaecological organs, relevant specimens from other sites, for example biopsies of lymph node metastases or cytology preparations from pleural fluids, were included where appropriate. The site of origin of the specimens (vulvo-

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vaginal, cervical, uterine corpus, tubo-ovarian, cytology and 'other'/miscellaneous), and the final diagnostic grouping (benign, atypical, borderline, or malignant), were recorded. The borderline group specifically comprised borderline ovarian tumours while the atypical group comprised histological and cytological cases from any anatomical site where a specific diagnosis could not be reached due to limited material, concurrent inflammatory changes or biopsy artefact. In cases with multiple specimens, the sample considered most relevant to the principal diagnosis was used for assessment.

In general, all external cases were initially assessed by one experienced gynaecological pathologist based at KEMH and selected slides were subsequently presented and discussed at a weekly multiheader microscope review session prior to the MDT meeting. Typically, five or six gynaecological pathologists attended each meeting and a consensus diagnosis was achieved in each case, albeit sometimes noting the requirement for further sampling or the necessity of correlation with the clinical and/or radiological findings.

Following the pathology review, and occasionally taking into account additional information made available at the MDT, the initial pathological diagnosis in each case was considered to be concordant or discordant, with the latter further divided into minor and major discrepancies.[21] It is accepted that there is some subjectivity in the latter sub-classification, but in general a minor discordance was considered to be an interpretative variation that was unlikely to have any immediate management implication. Examples include disagreement in the assessment of excision margins (positive or negative) in high-grade squamous intraepithelial lesions (HSIL) involving the vulva, vagina or cervix, or variations in the histological subtyping of a high-grade endometrial carcinoma. Conversely, a revised pathological diagnosis that potentially affected patient management or prognosis was considered a major discordance. Examples include altered tumour grading or subtyping that could influence the type of surgery or adjuvant therapy, differences in designated tumour origin, or major changes to lesion classification (benign/atypical to malignant, or vice versa). Cases with diagnostic agreement but in which the initial pathology report lacked specific information relevant for management [for example depth of tumour invasion in a vulval biopsy showing squamous cell carcinoma (SCC)] were not considered discordant in this study. All cases considered to have a major diagnostic discrepancy were independently assessed by a gynaecological oncologist (author YCL).

Whenever possible, follow-up pathological and/or clinical data were sought to determine whether the original diagnosis or the review diagnosis was more accurate. The KEMH review diagnosis was documented in all cases and a copy of the review report was sent to the original reporting pathologist as well as the oncology department at KEMH.

RESULTS

In total 1275 external cases were reviewed during the study period. The anatomical sites and final diagnostic categories are summarised in Table 1. The most common specimen sites, accounting for approximately half of all cases, were uterine corpus and cervix, and almost two-thirds of cases had a final malignant diagnosis. Following review, there were 132 (10.4%) diagnostic discrepancies of which 84 (6.6%) were considered minor and 48 (3.8%) were considered major; 46 of the latter comprised histology specimens while two were cytology samples. The cases with major discordant diagnoses are summarised in Table 2.

Table 1 Summary of anatomical location and final diagnosis in 1275 reviewed cases

	n	%
Site		
Vulvo-vaginal	138	10.8
Cervix	266	20.9
Uterine corpus	396	31.1
Tubo-ovarian	104	8.2
Cytology	231	18.1
Other	140	11.0
Diagnosis		
Benign	327	25.6
Atypical	71	5.6
Borderline	41	3.2
Malignant	836	65.6

The majority of major diagnostic discrepancies could be categorised as 'down-grades' or 'up-grades' following review (21 cases each), and these are considered in greater detail below. In six cases the diagnostic amendment was principally related to the anatomical site of tumour origin (Cases 1–6, Table 2). Four of these cases involved the cervix and on three occasions the review led to a different assignment of primary endocervical versus primary endometrial neoplasia; in one of these cases, an endometrial high-grade serous carcinoma (HGSC) involving the cervix was initially reported as endocervical adenocarcinoma *in situ* (ACIS). Another case was initially interpreted to be a primary endocervical adenocarcinoma with endometrial involvement but the diagnosis was amended after review to metastatic colorectal carcinoma involving both sites (Fig. 1). The revised diagnosis was supported by appropriate immunohistochemical studies and a history of prior colonic carcinoma was obtained subsequently. There was also one patient presenting with a vulval lesion reported as a primary cutaneous (sweat gland) adenocarcinoma that upon review was considered to be more suggestive of metastatic HGSC (Fig. 2); a history of prior endometrial HGSC was confirmed at the MDT.

Cases down-graded after review

Five cases initially reported as atypical endometrial hyperplasia were considered to be non-hyperplastic/neoplastic following review (Cases 7–11, Table 2). In three cases the revised diagnosis was benign endometrial polyp while in one case shedding changes with glandular 'pseudo-crowding' created diagnostic difficulty. There were also six cases with an initial diagnosis of high-grade squamous intraepithelial lesion (HSIL) with suspected or definite superficial stromal invasion (SSI) (sometimes termed 'microinvasion' or 'early' stromal invasion) where the review diagnosis was *in situ* neoplasia only (Cases 12–17). Three of these cases involved the cervix and demonstrated prominent expansile endocervical crypt involvement by HSIL [cervical intraepithelial neoplasia, grade 3 (CIN 3)] (Fig. 3). In the vulval and perianal cases, tangential sectioning ('cross-cutting') sometimes raised concern for invasion.

Five tumours (Cases 18–22) were revised from high-grade to low-grade malignancies. These included one lymph node fine needle aspirate cytology specimen that was initially reported as HGSC but subsequently interpreted to be low-grade serous carcinoma. Another serous neoplasm with predominant peritoneal involvement was also reported as HGSC but upon review the appearances were favoured to represent a primary peritoneal borderline serous neoplasm without definite invasive carcinoma. Additional immunohistochemistry performed on both cases demonstrated wild-type p53 expression and in the former case there was a history of ovarian borderline serous tumour, a finding more consistent with the spectrum of low-grade serous neoplasia than HGSC.

Two endometrial biopsy specimens were amended from grade 3 to grade 2 or grade 1 endometrioid carcinoma (EAC); in the latter case, a 'solid' component of corded and hyalinised tumour was initially interpreted to represent high-grade carcinoma. One mesenchymal tumour in a hysterectomy specimen reported as high-grade endometrial stromal sarcoma (ESS) was revised to low-grade ESS. This tumour was initially interpreted to be oestrogen and progesterone receptor (ER/PR) negative on immunohistochemistry but repeat analysis at KEMH demonstrated diffuse hormone receptor staining as well as, in our opinion, characteristic morphology of low-grade ESS.

The remaining down-graded cases included three cases of high grade intraepithelial neoplasia/*in situ* carcinoma that were subsequently considered to be negative or demonstrate only reactive/low-grade epithelial changes (Cases 23–25). One of these cases was initially reported to be serous tubal intraepithelial carcinoma (STIC) but histological review and subsequent immunohistochemical analysis [demonstrating wild-type p53 and low (<10%) Ki67 expression] were more consistent with reactive epithelial changes (Fig. 4). There was one ovarian serous neoplasm initially reported as borderline that was reviewed as benign (Case 26). Finally, a detached fragment of basaloid carcinoma present in one section of an otherwise mature cystic teratoma was favoured to represent specimen contamination rather than genuine malignant transformation (Case 27).

Cases up-graded after review

The most common source of discordance related to the presence of, or the extent of, invasion in the setting of high-grade intraepithelial neoplasia involving the cervix (8 cases) or vagina (2 cases) (Table 2, Cases 28–37). There were four cases initially reported as cervical ACIS with or without SSI that upon review were considered to represent invasive adenocarcinoma. The difficulty in these cases was mainly related to the interpretation of lobular tumour growth and/or papillary architecture in the absence of overt destructive stromal invasion. However, upon review the complexity and 'non-anatomical' distribution of the neoplastic elements was considered incompatible with ACIS alone (Fig. 5). Similarly, there were four cases in which the initial diagnosis was HSIL with possible SSI in which review favoured frankly invasive SCC. Three of these tumours showed features of papillary squamous/squamo-transitional cell carcinoma while one had a CIN 3-like growth pattern (Fig. 6 and 7). In two further cases there was discordance regarding the presence or multifocality of SSI associated with CIN 3.

Two cervical punch biopsies reported to show CIN 3 were found on review to show both CIN 3 and ACIS (Cases 38 and 39); one of these cases demonstrated features of stratified mucin-producing intraepithelial lesion (SMILE) rather than conventional ACIS.

Seven endometrial specimens (Cases 40–46) were upgraded including two cases where the presence of atypical hyperplasia was under-estimated. One of these cases had been modified by hormonal therapy prior to biopsy, and subsequent hysterectomy demonstrated grade 1 EAC. In the second case, an atypical endometrial mucinous proliferation was initially misinterpreted to be contaminant endocervical tissue. There were five high-grade endometrial adenocarcinomas that were initially reported to be low-grade (grade 1 or 2) EAC (Fig. 8). Notably, three of these cases were amended to HGSC on review, and all high-grade diagnoses were confirmed at hysterectomy.

There was only one mesenchymal neoplasm among the upgraded major discordances (Case 47), this being a myometrial tumour initially interpreted to be a cellular epithelioid leiomyoma. However, review including additional immunohistochemistry favoured an endometrial stromal neoplasm with at least limited stromal invasion, and additional sampling was required to exclude more extensive myometrial invasion and vascular invasion (therefore low-grade ESS could not be excluded). The final case was an ovarian tumour that was reported as a borderline mucinous tumour but favoured to be a seromucinous carcinoma upon review (Case 48).

Follow-up data

Clinical and pathological follow-up data for the major discordant cases were obtained whenever possible. However, this did not always clarify whether the initial or the review diagnosis was more accurate, and such cases were considered 'not determined' regarding diagnostic accuracy (Table 2). For example, negative follow-up in a case of HSIL with disagreement regarding the presence of SSI would be unlikely to have discriminatory value given the excellent prognosis of both scenarios (HSIL alone versus HSIL plus SSI). Similarly, many patients who had revised non-neoplastic or low-grade findings did not undergo further histological sampling. Nonetheless, relevant follow-up information was available in 30 cases and in our opinion supported the review diagnosis in 29 of these (summarised in Table 2). The exception was a patient with an initial diagnosis of atypical endometrial hyperplasia that was revised upon review to a benign polyp who then had confirmed atypical hyperplasia on repeat biopsy 12 months later suggesting that the initial biopsy interpretation may have been correct (Case 10, Table 2).

DISCUSSION

In this study we have assessed externally reported pathology specimens that were reviewed following patient referral to the WA gynaecology oncology MDT over a 5-year period. The majority of cases were derived from vulvo-vaginal, cervical and endometrial sites with relatively few tubo-ovarian specimens. This probably reflects the typical distribution of 'community' gynaecological specimens since many patients with suspected tubo-ovarian neoplasia are likely to be referred to and initially managed in specialist centres. It should be noted that specimens that were directly referred to KEMH from pathologists based in other laboratories because of perceived diagnostic difficulty ('opinion' cases) during the study period were excluded, as were cases where review was requested by gynaecologists because of an apparent discrepancy between the clinical findings and the initial pathology report. Thus, all cases in this study had been issued an initial definitive diagnosis. Even so, we found a 10.4% diagnostic discordance rate and there was a potentially significant impact on patient management or prognosis in more than one-third of these cases.

Our findings are broadly similar to other evaluations of pathological review in the general pathology setting,[4–10] or in

Table 2 Summary of cases with major diagnostic discordance

Case	Specimen site	Initial diagnosis	Review diagnosis	Additional history, investigation and/or follow-up	Favours review diagnosis
Amended tumour origin					
1	Cervix/lower segment	Adenocarcinoma cervix	Adenocarcinoma endometrium (lower segment)	Previous subtotal hysterectomy, IHC and HPV testing favour endometrial primary	Yes
2	Cervix/lower segment	Adenocarcinoma endometrium (villoglandular and ? HGSC)	Adenocarcinoma cervix (usual type)	Previous subtotal hysterectomy, subsequent surgery confirmed endocervical adenocarcinoma	Yes
3	Cervix and endometrium	Adenocarcinoma cervix	Metastatic colorectal carcinoma	History of colorectal carcinoma, IHC consistent with colonic origin	Yes
4	Cervix	ACIS	Endometrial HGSC invading cervix	Endometrial HGSC at hysterectomy	Yes
5	Ovary	Primary mucinous adenocarcinoma	Metastatic adenocarcinoma	Appendiceal primary at hemicolectomy	Yes
6	Vulva	Primary sweat gland carcinoma	Metastatic HGSC	Subsequently obtained history of endometrial HGSC	Yes
Down-graded on review					
7	Endometrium	Atypical hyperplasia	Shedding endometrium	None	ND
8	Endometrium	Atypical hyperplasia	Disordered proliferative endometrium	None	ND
9	Endometrium	Atypical hyperplasia	Polyp	None	ND
10	Endometrium	Atypical hyperplasia	Polyp	Biopsy one year later showed atypical hyperplasia	No
11	Endometrium	Atypical hyperplasia	Polyp	None	ND
12	Cervix	CIN 3, ACIS and ?SSI	CIN 3 and ACIS, no invasion	Negative follow up cytology	ND
13	Vulva	VIN 3, SSI and suspicious of LVSI	VIN 3	Subsequent biopsy VIN 3 only	Yes
14	Vulva	VIN 3 and invasion >1 mm	VIN 3	Subsequent biopsy VIN 3 only	Yes
15	Vulva/anal	AIN 3 and SSI	AIN 3	None	ND
16	Cervix	CIN 3 and SSI	CIN 3	None	ND
17	Cervix	CIN 3, ACIS and ?SSI	CIN 3 but no ACIS or SSI	Subsequent biopsy negative	Yes
18	Lymph node (fine needle aspirate)	HGSC	LGSC	Ovarian borderline serous tumour 12 years earlier, p53 wild type, later surgery LGSC	Yes
19	Peritoneum	HGSC	Borderline serous tumour	None	ND
20	Endometrium	G3 EAC	G2 EAC	G2 EAC at hysterectomy	Yes
21	Endometrium	G1 and G3 EAC	G1 EAC with corded and hyalinised pattern	G1 EAC at hysterectomy	Yes
22	Myometrium	High-grade endometrial stromal sarcoma	Low-grade endometrial stromal sarcoma	None	ND
23	Vagina	HSIL (cytology)	Reactive changes/VAIN 1	Follow up cytology and histology low-grade/ negative	Yes
24	Fallopian tube	STIC	Reactive changes	None	ND
25	Cervix	ACIS	Reactive/metaplastic changes	None	ND
26	Ovary	Borderline serous tumour	Serous cystadenoma	None	ND
27	Ovary	Teratoma with basaloid carcinoma	Contaminant tissue	None	ND
Up-graded on review					
28	Cervix	ACIS	Adenocarcinoma	Negative hysterectomy	ND
29	Cervix	ACIS and CIN 3	Adenocarcinoma	Clinical stage 1B1 carcinoma, at least 12×6 mm on subsequent biopsy	Yes
30	Cervix	CIN 3, ACIS ? invasion	CIN 3, adenocarcinoma	Negative radical hysterectomy and lymph node dissection	ND
31	Cervix	ACIS ?invasion	Adenocarcinoma	Adenocarcinoma on radical hysterectomy and lymph node dissection	Yes
32	Vagina	VAIN 3	Papillary SCC	Clinical cancer with parametrial spread, 3 cm tumour on imaging	Yes
33	Vagina	VAIN 3	Papillary SCC	Sarcomatoid SCC on vaginal bx 1yr later	Yes
34	Cervix	CIN 3 and SSI	Papillary SCC	Clinical stage IIB cancer	Yes
35	Cervix	CIN 3 and SSI	SCC with CIN 3-like pattern	SCC at radical hysterectomy and lymph node dissection	Yes
36	Cervix	CIN 3 and focus of SSI	CIN 3 and multifocal SSI	Negative cone biopsy and hysterectomy	ND
37	Cervix	CIN 3	CIN 3 and SSI	None	ND
38	Cevix	CIN 3	CIN 3 and ACIS	CIN 3 and ACIS on LLETZ biopsy	Yes
39	Cervix	CIN 3	CIN 3 and ACIS (SMILE)	CIN 3 and ACIS on LLETZ biopsy	Yes
40	Endometrium	Mild atypical hyperplasia	At least severe atypical hyperplasia modified by therapy	G1 EAC at hysterectomy	Yes
41	Endometrium	G1 EAC	G2/3 EAC	G3 EAC at hysterectomy	Yes
42	Endometrium	G2 EAC	HGSC	IHC supportive of HGSC. Later vault biopsy HGSC	Yes
43	Endometrium	G1 EAC	HGSC	Stage IV HGSC at hysterectomy	Yes
44	Endometrium	G2 EAC	HGSC	Stage IV HGSC at hysterectomy	Yes
45	Endometrium	G2 EAC	G3 EAC	G3 EAC at hysterectomy	Yes

Table 2 (*continued*)

Case	Specimen site	Initial diagnosis	Review diagnosis	Additional history, investigation and/or follow-up	Favours review diagnosis
46	Endometrium	Endocervical tissue	Atypical hyperplasa with mucinous differentiation	Focal G1 EAC at hysterectomy	Yes
47	Myometrium	Epithelioid leiomyoma	Endometrial stromal neoplasm	None	ND
48	Ovary	Borderline mucinous tumor	Seromucinous carcinoma	Subsequent sigmoid and lung metastases	Yes

ACIS, adenocarcinoma *in situ*; AIN, anal intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia; EAC, endometrioid adenocarcinoma; G, grade; HGSC, high-grade serous carcinoma; IHC, immunohistochemistry; LGSC, low-grade serous carcinoma; LLETZ, large loop excision of transformation zone; LVSI, lymph-vascular space invasion; ND, not determined; SCC, squamous cell carcinoma; SMILE, stratified mucin producing intraepithelial lesion; SSI, superficial stromal invasion; VAIN, vaginal intraepithelial neoplasia; VIN, vulval intraepithelial neoplasia.

gynaecological oncology specifically,[11–20] where most studies have recorded minor diagnostic discordances in 10–20% of cases and major discordances in 2–8% of cases. However, it should be noted that criteria for defining discordance/error have varied significantly in these studies. Indeed while there is agreement that slide review or second opinion constitutes one important facet of quality assurance in surgical pathology,[22] there is no clear consensus on how 'error' should be defined.[6,21,23,24] It must also be acknowledged that there are limitations in accepting the centralised pathological review as being necessarily the 'gold standard' in studies such as this, and that in some cases follow-up data may prove more supportive of the initial diagnosis than the review assessment.[6–8] Ideally, determination of accurate pathological diagnosis would be based upon patient outcomes but in practice this is often not possible since many confounding variables affect management and prognosis. Furthermore, some diagnostic scenarios such as HSIL with discordant interpretation regarding the presence of SSI will almost certainly have a benign clinical course even though the presence of SSI would often mandate more radical excisional surgery (such as cone biopsy in the cervix) to ensure adequate clearance and the exclusion of more significant invasive neoplasia. For such reasons, it has been suggested that diagnostic consistency (precision) is a more appropriate measurement of accurate pathological assessment than clinical outcome.[21,22] Despite these accepted limitations, we believe that available follow-up data in the current series

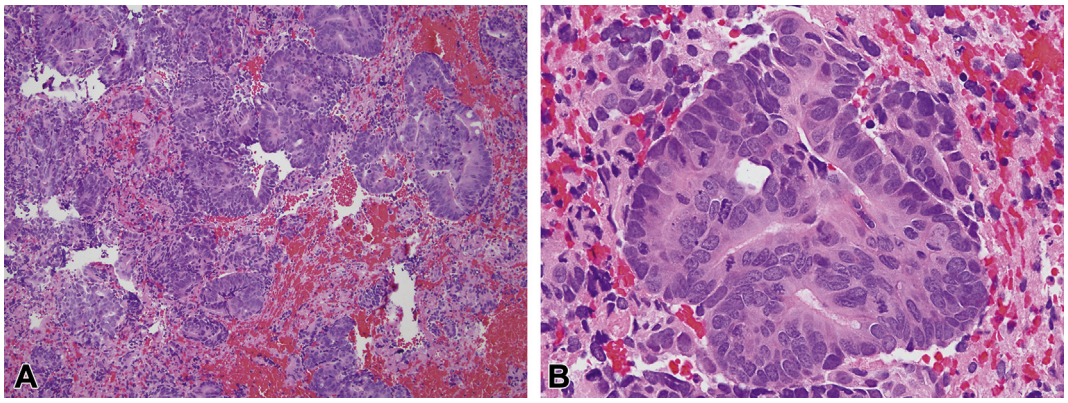

Fig. 1 Colorectal carcinoma metastatic to the endometrium. (A) The biopsy includes neoplastic glands against a background of blood and necrosis. (B) The glands are lined by columnar cells showing conspicuous mitotic activity.

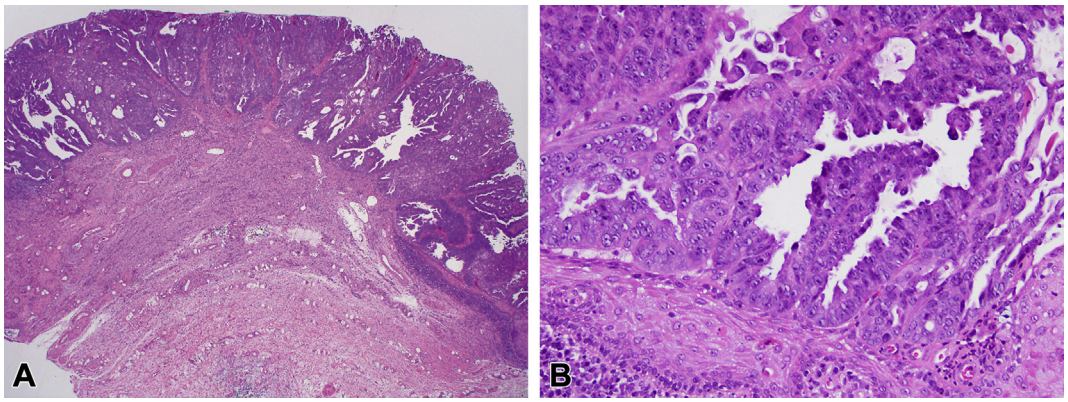

Fig. 2 Vulval biopsy showing metastatic endometrial high-grade serous carcinoma. (A) The tumour involves the epidermis and dermis and exhibits papillary and glandular architecture. (B) Higher magnification showing high-grade tumour morphology. Residual epidermis is present adjacent to the tumour (lower).

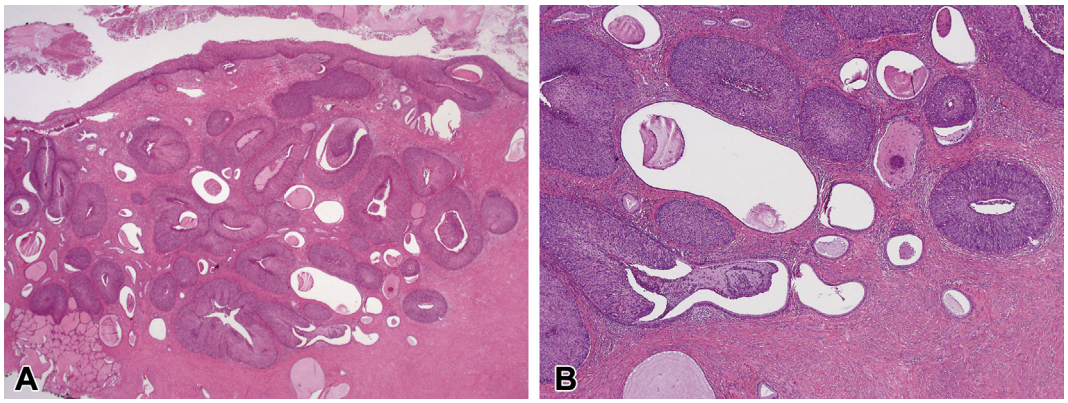

Fig. 3 Loop excision biopsy of cervix. (A) Extensive cervical intraepithelial neoplasia, grade 3 (CIN 3) with expansile endocervical crypt involvement is concerning for invasion at low magnification. (B) Higher magnification shows focal continuity of the CIN with endocervical epithelium and the presence of benign glands towards the deep aspect (lower).

supported the review diagnosis in the great majority of cases (29/30 cases, Table 2).

The pathological issues creating review disagreement at MDTs have seldom been specified or discussed in detail but in this study we found that a relatively small number of diagnostic situations accounted for the majority of cases that we encountered. Commonly, these involved the assessment of invasion in the context of *in situ* neoplasia involving the cervix, vagina or vulva. In many cases the discordance reflected conflicting assessment of the presence of SSI ('microinvasion'). This is an area of accepted diagnostic difficulty and subjectivity, and in particular it has been reported that the histological distinction of ACIS and superficially invasive adenocarcinoma of the cervix may not be possible in up to 20% of cases.[25–28] However, perhaps more significantly, we encountered a number of cervical and vaginal specimens that were initially interpreted to show mainly HSIL or ACIS with varying degrees of concern

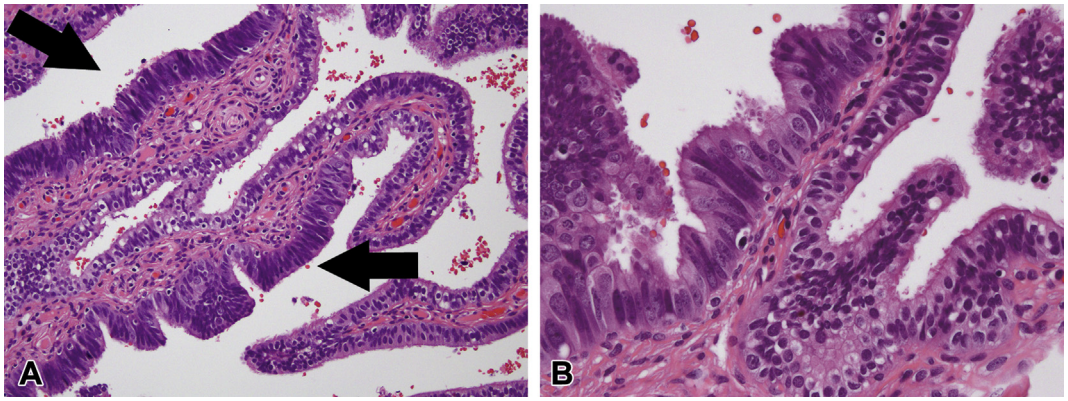

Fig. 4 Fallopian tube. (A) In areas the lining epithelium appears more stratified and monomorphic with nuclear hyperchromasia (arrows). (B) Comparison of atypical epithelium (left) and normal tubal epithelium (right). However there is no cellular dyscohesion or mitotic activity and immunohistochemistry did not support serous tubal intraepithelial carcinoma.

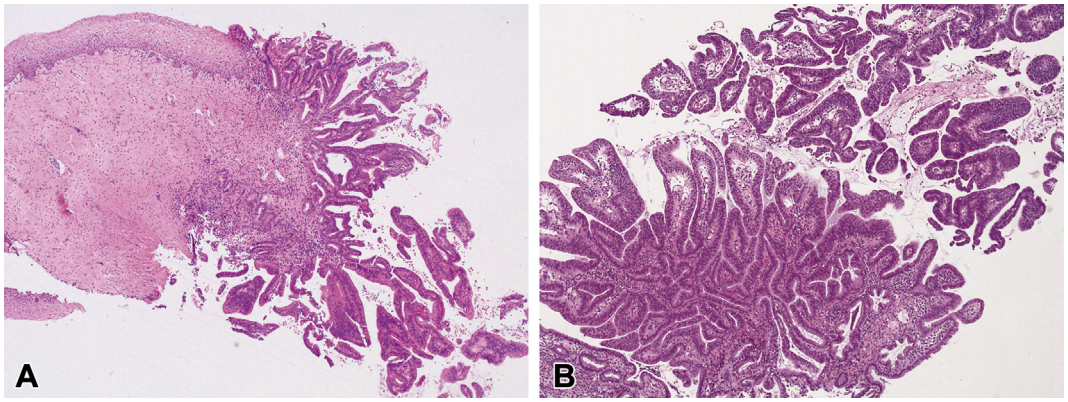

Fig. 5 (A,B) Small cervical biopsies initially reported as adenocarcinoma *in situ*. No stromal invasion is seen in this superficial material but in our opinion the complex papillary architecture is indicative of adenocarcinoma (confirmed on subsequent excisional specimens).

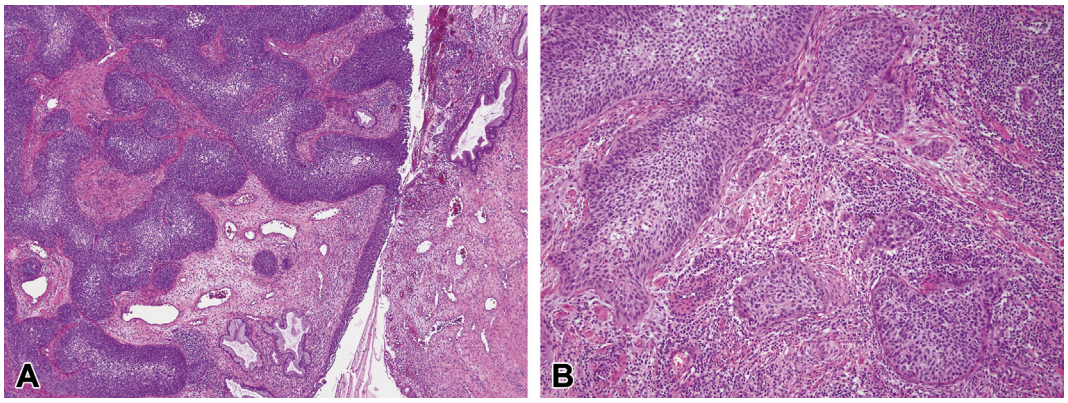

Fig. 6 Loop excision biopsy of cervix with cervical intraepithelial neoplasia, grade 3 (CIN 3)-like squamous cell carcinoma. (A) The left field shows anastomosing, well-demarcated cords of neoplastic squamous epithelium that superficially resemble endocervical crypt involvement by CIN 3. However, the complexity and 'non-anatomical' distribution of the epithelium indicates an invasive process. (B) Higher magnification from the deep aspect resembles superficial stromal invasion associated with CIN. However, based on tumour distribution all of the neoplastic epithelium in this image is considered invasive.

regarding SSI that we believed upon review to demonstrate frankly invasive carcinoma. The review assessment, supported in most cases by subsequent clinicopathological findings, was based upon the architectural complexity and 'non-anatomical' distribution of the neoplastic epithelium even in the absence of demonstrable destructive stromal invasion or desmoplastic reaction. In this regard, two potentially under-recognised variants of SCC are worthy of note, namely those showing papillary architecture (sometimes referred to as squamo-transitional carcinoma),[29,30] and those exhibiting a CIN 3-like growth pattern.[31] Although there was only one case of the latter in this series, in our routine diagnostic experience these tumours are often misinterpreted as HSIL with only SSI on biopsy,[32,33] often prompting a request for review since the clinical findings are suspicious of cancer.

Five endometrial carcinomas in this series were initially 'under-graded' on biopsy (4 cases) or hysterectomy (1 case) with all initially being reported as grade 1 or grade 2 EAC. Two of these were considered to be grade 3 EAC after review while three were reclassified as HGSC. The diagnostic difficulty in the latter cases appeared related to the architectural pattern of these tumours which predominantly comprised rounded glands with relatively smooth luminal borders thus mimicking EAC.[34,35] This is also a well-recognised pitfall in the context of tubo-ovarian neoplasia where many tumours previously interpreted to be intermediate or high-grade endometrioid carcinomas would now be reclassified as HGSC.[36,37] Despite their 'pseudo-endometrioid' appearances, all up-graded cases in this series demonstrated high-grade cytological features and the characteristic immunoprofile of HGSC, including mutation-pattern p53 staining and diffuse p16 expression; two tumours were also ER/PR negative which would be unusual in low-grade EAC. One additional endometrial HGSC in this study was initially misclassified as a primary endocervical adenocarcinoma and it should be noted that immunohistochemistry may be misleading in this situation since both tumours are typically diffusely p16 positive.[27,38] However, primary HPV-related ('usual type') cervical adenocarcinomas rarely, if ever, demonstrate mutation-pattern p53 expression and the clinical findings including patient age and tumour localisation usually facilitate the distinction of such cases. One further case of endometrial HGSC metastatic to the vulva was initially reported to be a primary sweat gland carcinoma but on review, with additional immunohistochemical analysis, was considered to be more consistent with metastatic HGSC. Subsequent information obtained at the MDT revealed that the patient had a history of endometrial HGSC 2 years earlier. These cases illustrate the importance of relevant clinical history but also indicate that endometrial HGSC is probably

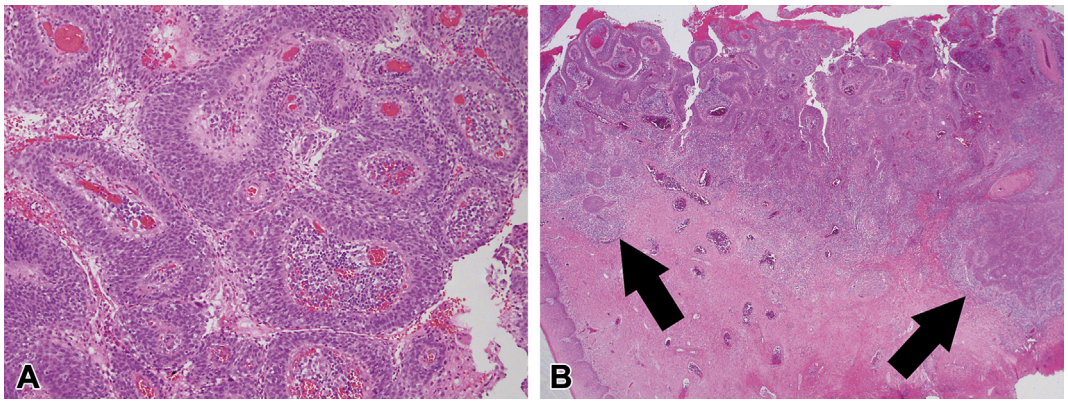

Fig. 7 Papillary squamous cell carcinoma of cervix. (A) A superficial biopsy shows transversely sectioned fibrovascular stromal cores lined by neoplastic squamous epithelium. (B) Hysterectomy specimen shows papillary tumour architecture at the mucosal surface (upper field) with foci of conventional invasive carcinoma in the underlying stroma (arrows).

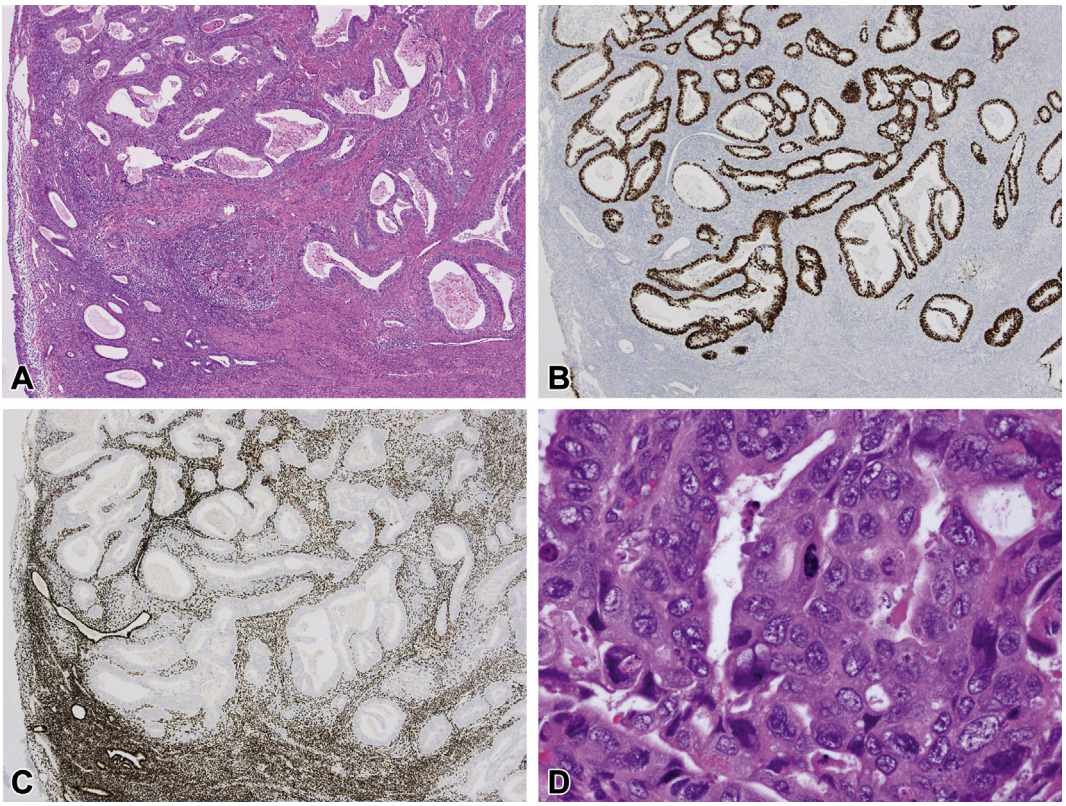

Fig. 8 Endometrial serous carcinoma invading the myometrium (right). (A) The tumour shows well-formed glands with smooth luminal borders resembling an endometrioid carcinoma. (B) Immunohistochemistry shows mutation-pattern p53 staining and (C) loss of ER expression in the tumour cells. (D) High-grade cytological abnormality is evident at higher magnification.

under-recognised, suggesting that there should be a low threshold for second opinion and ancillary immunohistochemical analysis in uncertain cases.

In addition to the two cases of endometrial HGSC noted above, there were four additional tumours where histological review led to an amendment of tumour origin, two of which involved a reversal of endocervical versus endometrial origin. It is well-recognised that the distinction of primary endocervical and endometrial adenocarcinoma can be difficult, even with the use of ancillary techniques such as immunohistochemistry, and often clinical and radiological correlation is required to achieve a definitive diagnosis.[38] The two cases described herein were further complicated in that both patients had previously undergone subtotal hysterectomy making anatomical localisation of the tumour more problematic. However, accurate identification of tumour origin remains important considering the different management of endocervical and endometrial carcinomas, as well as different aetiological factors (for example, the potential association of endometrial carcinoma with Lynch syndrome). The two final cases with misclassified tumour origin were ultimately determined to be of metastatic origin comprising an appendiceal adenocarcinoma metastatic to the ovary and a colorectal carcinoma involving the endometrium and cervix. In the latter case, the initial reporting pathologist was not aware of the history of colorectal carcinoma but in our opinion there were morphological features that might have at least suggested metastatic origin.[35,39] The difficulty presented by tumours metastatic to the ovaries is well-documented and the present case illustrates the requirement to consider and exclude extra-ovarian origin, particularly in cases of mucinous adenocarcinoma.[40,41]

There were a smaller number of cases in this series where diagnostic discord probably reflected unfamiliarity with less common entities. In one such case the presence of a spindled, corded and hyalinised pattern within an otherwise conventional grade 1 EAC was interpreted to represent solid tumour growth and hence grade 3 carcinoma.[42] Two cases of ACIS concurrent with HSIL were overlooked on biopsy, one of which showed only a subtle stratified mucin producing lesion ('SMILE').[43] Both patients underwent large loop excision of the transformation zone for HSIL rather than cone biopsy which would have been standard management of ACIS in our institution during the study period.

In summary, a 5-year review of 1275 external cases reviewed at a gynaecological oncology MDT revealed a low but significant number of cases with major diagnostic discordance. Different interpretation of the presence or extent of invasion accounted for many disagreements, and there were also cases where tumour origin was not correctly assigned. Failure to identify specific tumour subtypes was an issue in some cases, and in particular under-recognition of endometrial HGSC was a relatively common event. The importance of relevant clinical history is emphasised and could have pre-empted some diagnostic errors, particularly regarding the interpretation of metastasis presenting in the gynaecological tract. This study supports the policy of pathological review in the gynaecological oncology MDT setting.

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