

What we could do now: molecular pathology of gynaecological cancer

C S Herrington

Abstract

Gynaecological tumours exemplify many of the molecular paradigms of carcinogenesis. The clinical value of many of the molecular abnormalities present is now being tested and it is likely that the identification of at least some of these will become routine in the near future. This may help to refine diagnosis and guide treatment—for example, therapeutic vaccination for human papillomavirus related disease.

(*J Clin Pathol: Mol Pathol* 2001;54:222–224)

Keywords: gynaecology; cancer; papillomavirus

There is a large literature examining the molecular pathology of tumours of the female genital tract. However, much of the information has limited, if any, diagnostic value. Before considering some of the details, it is useful to identify those features that would be of clinical value.¹ There are three basic categories; namely, diagnostic markers, prognostic markers, and markers of therapeutic response. With regard to diagnostic markers, these need to distinguish two or more different diagnoses, each of which would lead to different clinical management. From a prognostic point of view, the marker needs to be an independent prognostic factor in such a way that the prognostic difference alters treatment, and cost benefit analysis must support the introduction of such a marker. These criteria are rarely satisfied, partly because diagnostic and prognostic markers fail to distinguish lesions requiring altered management strategies and partly because many of the studies that have been performed have insufficient power or rigour to assess the value of the markers analysed.

Ovarian tumours

Most available data deal with epithelial ovarian tumours and there are clear examples—for example, ovarian carcinomas arising in hereditary cancer syndromes, where molecular testing may identify “at risk” individuals.^{2,3} The data available on sporadic ovarian tumours are less clearly clinically applicable. For example, it would be extremely useful to identify early stage disease, thus allowing definitive early treatment, and to help with the accurate distinction between benign, borderline, and invasive tumours. However, no molecular markers are capable of consistently achieving either of these aims. Although it has been suggested that ploidy might have a role in the assessment of ovarian tumours, there is debate regarding whether this is the case.^{1,4} There are numerous molecular studies analysing loss of

heterozygosity and clonality among other parameters, but these give little information that satisfies the criteria enumerated above.

Mesenchymal tumours of the uterus

Most of these tumours are benign smooth muscle tumours (leiomyomas) and the traditional approach of assessment of smooth muscle tumours of the uterus based on pleomorphism, coagulative necrosis, and mitotic count is adequate to identify most of these tumours as benign. It would be useful if atypical smooth muscle tumours could be stratified using molecular approaches, but no data currently exist to support this. For example, cytogenetic changes have been described in benign uterine leiomyomata,⁵ and hence the identification of chromosome abnormalities per se is not helpful. Whether specific cytogenetic abnormalities are of use—for example, in the diagnosis of uterine sarcomas,^{6,7} remains to be established.

Endometrial neoplasia

There is currently debate regarding the classification of endometrial hyperplasia, with the suggestion that atypical hyperplasia should be considered neoplastic receiving considerable support. In such a system, non-invasive atypical endometrial lesions would be characterised as endometrial intraepithelial neoplasia and viewed as a continuum with well differentiated endometrial carcinoma. However, these morphological refinements rely to some extent on subjective assessment, and molecular adjuncts would be helpful—for example, in predicting those patients with myoinvasive disease. Some stratification of endometrial tumours is possible on the basis of morphology.⁸ For example, papillary serous carcinoma has a poor prognosis, predominantly related to its greater propensity for early spread, and high amounts of p53 protein are typically found in this tumour. This contrasts with endometrioid carcinoma and its preinvasive counterpart endometrioid hyperplasia, which does not express p53 but, in a proportion, shows microsatellite instability,^{9,10} and/or PTEN mutation,¹¹ and/or ras mutation.¹² However, despite these molecular differences, the distinction between these two tumour types is generally easily made on morphological grounds alone, and it is not clear whether the identification of molecular abnormalities affords any additional benefit. The identification of low grade, low stage, endometrioid carcinomas that behave aggressively would be clinically useful because adjuvant treatment could be offered early. However, no molecular differences that fulfil the appropriate criteria have been identified.

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Accepted for publication 15 March 2001

Cervical neoplasia

Human papillomavirus (HPV) DNA is now known to be present in almost 100% of invasive cervical carcinomas.^{13 14} Moreover, HPV infection, particularly if persistent and of high risk type, confers an increased risk of developing high grade disease.¹⁵ Therefore, HPV testing is being considered as an adjunct to histological and cytological assessment of cervical disease. Molecular approaches to the assessment of cervical disease can be considered in the context of cervical screening, and also in the context of the diagnostic and prognostic assessment of established lesions.

HPV typing has little application in the context of histopathology but, in cytopathology, it shows considerable promise as an adjunctive methodology.¹⁶⁻¹⁸ With regard to cervical screening, it has been suggested that HPV testing might provide a useful adjunct to cervical cytology in the detection of preinvasive disease.

From a histopathological point of view, HPV typing does not distinguish HPV infection from HPV associated cervical intraepithelial neoplasia (CIN), nor does it assist in the grading of CIN. It could be argued that the distinction between low and high risk HPVs could help to assess the risk of lesion progression but, practically, this is unlikely to be of value. Although there is some evidence that HPV-18 associated invasive carcinomas have a worse prognosis than those containing other HPV types, the size of this increased risk is small.¹⁹ No role has been identified for HPV typing in the detection of metastatic disease or in the prediction of recurrence.²⁰

It has been suggested that HPV testing could be used in place of cervical cytology for population screening. However, in settings where cervical cytology is already established, it is more likely that HPV testing will be used as an adjunctive methodology.¹⁸ There is more support for the introduction of HPV testing in the context of specific patient groups, in particular women with low grade cytological abnormalities, women over 30–35 years of age (because the prevalence of HPV in the population is significantly lower in this age group), and immunosuppressed patients.^{16 17} However, before HPV testing can be introduced in any context, robust data must be collected regarding the diagnostic performance of the test, in addition to its cost effectiveness and consideration of practical implementation. Well established methods are now available for HPV typing—for example, using hybrid capture or the polymerase chain reaction. These methods can be semiautomated and hence practical implementation is less of an issue. More problematic is the fact that the diagnostic performance of HPV testing is closely dependent upon the nature of the population being analysed. For example, high sensitivity for the detection of high grade intraepithelial disease (CIN 2, CIN 3) can be achieved, but this is often at the expense of specificity and relatively low positive predictive values. This is particularly true in populations containing women under the age of 30, and underlies the suggestion that HPV

testing may be particularly useful in women over the age of 30–35, in whom sensitivity and specificity can be optimised more easily. These considerations have also prompted the suggestion that the absence of HPV DNA may be more useful in a clinical setting than its presence.²¹ This is because the negative predictive value of HPV testing is extremely high and is less population dependent. However, the duration of protection of a negative HPV test is not known, and further work is required to evaluate the effect of potentially extending the screening interval in patients who are HPV negative and have normal cervical smears. The combination of HPV testing and cervical cytology also introduces a group of women who have a negative cervical smear but are HPV positive. It is not entirely clear what the appropriate management is in this situation, although clearly two options include increasing the frequency of cytological surveillance and referral for colposcopy.

Conclusion

Neoplastic lesions of the female genital tract exemplify many of the molecular paradigms of carcinogenesis. Molecular pathological approaches have contributed greatly to our knowledge of this group of diseases, but the clinical value of much of this information remains to be determined. The most notable exception to this is the potential use of HPV testing for the detection of neoplastic cervical disease. In the next few years, it is likely that large amounts of information will be generated using RNA and protein profiling techniques, but it is important that such information is interpreted in the context of clinically relevant criteria for information that is truly useful in the diagnosis and management of disease in patients.

- 1 Silverberg, SG. Molecular diagnosis and prognosis in gynaecologic oncology. *Arch Pathol Lab Med* 1999;123:1035–40.
- 2 Duncan JA, Reeves JR, Cooke TG. BRCA1 and BRCA2 proteins: roles in health and disease. *J Clin Pathol: Mol Pathol* 1998;51:237–47.
- 3 Kasprzak L, Foulkes WD, Shelling AN. Hereditary ovarian carcinoma. *BMJ* 1999;318:716–19.
- 4 Braly P. DNA content and S-phase fraction in epithelial ovarian cancer: what information do they really add? *Gynecol Oncol* 1998;71:1–2.
- 5 Mantovani MS, Neto JB, Philbert PMP, et al. Multiple uterine leiomyomas: cytogenetic analysis. *Gynecol Oncol* 1999;72:71–5.
- 6 Packenham JP, du Manoir S, Schrock E, et al. Analysis of genetic alterations in uterine leiomyomas and leiomyosarcomas by comparative genomic hybridisation. *Mol Carcinog* 1997;19:273–9.
- 7 Iliaszko M, Mandahl N, Brozek K, et al. Cytogenetics of uterine sarcomas: presentation of eight new cases and review of the literature. *Gynecol Oncol* 1998;71:172–6.
- 8 Burton JL, Wells M. Recent advances in the histopathology and molecular pathology of carcinoma of the endometrium. *Histopathology* 1998;33:297–303.
- 9 Sakamoto T, Murase T, Urushibata H, et al. Microsatellite instability and somatic mutations in endometrial carcinomas. *Gynecol Oncol* 1998;71:53–8.
- 10 Esteller M, Levine R, Baylin SB, et al. MLH1 promoter hypermethylation is associated with microsatellite instability phenotype in sporadic endometrial carcinomas. *Oncogene* 1998;16:2413–17.
- 11 Levine RL, Cargile CB, Blazes MS, et al. PTEN mutations and microsatellite instability in complex atypical hyperplasia, a precursor lesion to uterine endometrioid adenocarcinoma. *Cancer Res* 1998;58:3524–8.

- 12 Mutter GL, Wada H, Faquin WC, *et al.* K-ras mutations appear in the premalignant phase of both microsatellite stable and unstable endometrial carcinogenesis. *J Clin Pathol: Mol Pathol* 1999;52:257-62.
- 13 Herrington CS. Do HPV-negative cervical carcinomas exist? Revisited. *J Pathol* 1999;189:1-3.
- 14 Walboomers JM, Jacobs MV, Manos MM, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12-19.
- 15 Burk RD. Pernicious papillomavirus infection. *N Engl J Med* 1999;341:1687-8.
- 16 Cuzick J, Sasieni P, Davies P, *et al.* A systematic review of the role of human papillomavirus testing within a cervical screening programme. *Health Technol Assess* 1999; 3:1-196.
- 17 Cuzick J, Sasieni P, Davies P, *et al.* A systematic review of the role of human papilloma virus (HPV) testing within a cervical screening programme: summary and conclusions. *Br J Cancer* 2000;83:561-5.
- 18 Cuzick J. Human papillomavirus testing for primary cervical cancer screening. *JAMA* 2000;283:108-9.
- 19 Rose BR, Thompson CH, Simpson JM, *et al.* Human papillomavirus deoxyribonucleic acid as a prognostic indicator in early-stage cervical cancer: a possible role for type 18. *Am J Obstet Gynecol* 1995;173:1461-8.
- 20 Herrington CS. Cervical pathology. *Curr Opin Obstet Gynecol* 1997;9:57-62.
- 21 Meijer CJLM, Walboomers JMM. Cervical cytology after 2000: where to go? *J Clin Pathol* 2000;53:41-3.

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Mol Path 2001 54: 222-224

doi: 10.1136/mp.54.4.222

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