

EIN and WHO94

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Considering the classification of endometrial hyperplasia

Endometrial hyperplasia is a common disease (at least 120 000 new cases each year in the European Union). The wide range of histological presentations of endometrial hyperplasia is accompanied by high intraobserver and interobserver variability in diagnostic classification. The overall risk of progression of hyperplasia to cancer is 5–10%, but this may vary substantially between individual patients according to the histological pattern. Unreliable diagnosis of hyperplasia translates into inappropriate treatment, either as a result of the undertreatment of high risk lesions or the overtreatment of low risk lesions, which leads to unnecessary suffering and high treatment costs.

Many different classification systems for endometrial hyperplasia have been proposed and used over the past few decades. Before 1985, such terms as “mild, moderate, and severe hyperplasia” were often used in the USA, whereas “cystic” and “adenomatous hyperplasia” was more fashionable in Europe. By 1982, confusion in terminology and disagreement in criteria between experts, even within the same country, became painfully clear.^{1,2} In 1994, the World Health Organisation proposed its classification for endometrial hyperplasia (WHO94). This was based upon a seminal study,³ which correlated the presence of cytological atypia with heightened cancer risk, and had the effect of standardising terminology world wide. The WHO94 classification uses two criteria: glandular complexity and nuclear atypicity. This resulted in four categories: simple (SH), complex (CH), simple atypical (SAH), and complex atypical hyperplasia (CAH), which have different progression risks of <1%, 3%, 8%, and 29%, respectively.³

“The World Health Organisation 1994 classification uses two criteria: glandular complexity and nuclear atypicity”

WHO94 was substantially advanced at the time because it incorporated newly documented histological correlates of clinical outcome, rather than

being a simple reworking of old nomenclature. However, the interpretation of the essential microscopic features was still subjective and subsequent international studies have independently shown that the WHO94 classification is not very reproducible.^{4–6} Moreover, the value of a four class system (SH, CH, SAH, and CAH) was limited from the beginning. Such a four class classification does not, in practice, match with discrete therapeutic options (observation, hormonal treatment, or hysterectomy). Many gynaecologists use atypia as an indication to perform hysterectomy, based upon a highly significant predictive value of cytological atypia versus non-atypia in the original report of 170 cases.³ CAH is the worst prognostic subgroup, but the incidence is relatively low, and even in CAH cancer progression risk is not higher than 29%.^{3,7} The small number of available simple atypical hyperplasias (n = 13)³ made it difficult to separate as a prognostic group different from CAH. The overall progression risk of SAH and CAH hyperplasia with atypia combined is around 20%. Emphasis on cytological atypia is of particular concern in light of several recent studies showing this to be poorly reproducible by pathologists.^{4–6}

Since the WHO94 classification was defined, molecular genetic endpoints for disease classification have emerged as an adjunctive tool to clinical outcome in establishing functional subclasses of disease. The WHO 2003 book⁸ also includes a new section on the genetics of endometrial precancers which, together with morphometrical and clinical outcome studies, is presented as the basis for EIN classification.^{9,10} Genetic and morphometric approaches have now independently identified an overlapping group of endometrial lesions likely to progress to cancer. These genetic methods are informative in a research setting, but are of little clinical value as routine diagnostic tests. Clonal analysis is too laborious and expensive, and biomarkers such as inactivation of the PTEN tumour suppressor gene have poor sensitivity and specificity in the detection of high risk EIN lesions. This has refocused interest on the appearance of high risk EIN lesions in routine

haematoxylin and eosin (H&E) stained slides.

The data clearly show that computerised morphometry has the best clinical predictive value and reproducibility for EIN diagnosis. Less certain is the range of institutions able to purchase and deploy the necessary equipment. Limited experience in implementation of the subjective EIN diagnostic schema, and uncertainty about the best way to combine objective morphometrical and subjective pathologist diagnosis, are concerns that precluded formal endorsement by the WHO at this time. Less contentious is the agreement that WHO94 is not fulfilling current clinical needs and is due for replacement. This review will provide an update of the status of these issues, and the authors' opinion of how they might be resolved.

EIN: A DIFFERENT APPROACH

The new EIN classification, originally proposed by the International Endometrial Collaborative Group,¹⁰ is based on integrated morphological, genetic molecular, cell biological, and prognostic morphometrical studies. Three disease categories are discerned:

- (1) Benign hyperplasia (a hormone dependent diffuse lesion, which is polyclonal).
- (2) Endometrial intraepithelial neoplasia (at the beginning a localised “clonal” proliferation, which is monoclonal and neoplastic. With advanced stage, it may become a more diffuse lesion).
- (3) Cancer.

Table 1 summarises the nomenclature, topography, functional category, and treatment of each category. The three different categories are each defined in morphological, clinical, and biological terms. Diagnosis and treatment are based on these features.

EIN is a clinically relevant diagnosis that is intended to direct treatment.¹⁰ Its prognostic value resides in a combination of easily measured H&E morphometrical features used to calculate the D-score. The D-score has been developed from the onset in the early 1980s not to mimic subjective WHO94 diagnostic classes, but as a prognostic test in predicting future or concurrent carcinoma.¹¹ The three essential D-score features are of an architectural (volume percentage stroma, and outer surface density of the glands) and cytological (standard deviation of the shortest nuclear axis) nature. These features have been selected from a total of 47 features studied as being independently informative in predicting cancer outcomes, using multivariate regression

Table 1 Functional, diagnostic, and therapeutic aspects of the endometrial intraepithelial neoplasia (EIN) classification

EIN nomenclature	Topography	Functional category	Treatment
Benign architectural changes of unopposed oestrogens (endometrial hyperplasia)	Diffuse	Oestrogen effect	Hormonal treatment
EIN	Focal, later diffuse	Precancer	Hormonal or surgical
Carcinoma	Focal, later diffuse	Cancer	Surgical, stage based

analysis of a large group of other quantitative features. Because the D-score is not widely available, it is fortunate that a simple assessment of the percentage stroma (VPS) in the lesion is a good alternative. Lesions with less than 55% stroma fulfilling the other EIN criteria are equivalent to EIN, whereas those above 55% are reactive hyperplasias. Other variables such as DNA ploidy and nuclear arrangement are also important, but are overshadowed by the three original features of the D-score.¹² Later, three retrospective studies in the USA,¹³ the Netherlands,⁷ and Norway¹⁴ confirmed the prognostic value of the D-score. Moreover, a recent 10 year prospective, routine, multicentre study has shown that the prognostic value of the D-score in relation to cancer progression also holds during a protracted follow up interval, greatly exceeding that of the WHO94.¹⁵ The D-score has been successfully implemented as a routine diagnostic and therapeutic decision making pathology test in several laboratories in the Netherlands and Norway.¹⁶

“Because the D-score is not widely available, it is fortunate that a simple assessment of the percentage stroma in the lesion is a good alternative to diagnose a lesion as EIN or not”

Genetic clonality studies using X chromosome inactivation (HUMARA assay) and altered microsatellites (microsatellite instability) showed that most hyperplasias were polyclonal, although some were monoclonal and displayed distinctive genetic changes that were conserved in subsequent cancers.^{17–20} These findings are consistent with experience in multiple epithelial systems that premalignant lesions are benign monoclonal neoplasms prone to malignant transformation. Attempts were made to establish the relations between WHO94 hyperplasia subclasses and clonality. A comparison of the WHO94 diagnoses of four expert gynaecopathologists, molecular genetic clonality, and the D-score showed that the D-score correlated much more strongly

with clonality than did the experts' WHO94 diagnosis (fig 1).¹⁹ The D-score was also much more reproducible than WHO94.^{7, 19} Nearly all cases with a D-score > 1 (or VPS > 55%) are polyclonal, whereas many (but not all) cases with a D-score < 1 (or VPS < 55%) are monoclonal. Most of the endometrial samples classified as “polyclonal” that have a D-score < 1 (VPS < 55%) probably result from technical errors in which contaminating normal polyclonal tissues diluted the monoclonal component.

The PTEN gene is the most commonly inactivated gene in endometrioid

endometrial cancer,^{8, 21} in contrast to papillary serous type cancers, which rarely show inactivation of PTEN, although p53 abnormalities are often seen.²² Functional inactivation of PTEN results in the upregulation of proliferation and its association with endometrial hyperplasia and cancer has been confirmed in knockout mice.²³ Recently, the monoclonal antibody 6h2.1 has been used for routine immunohistochemical evaluation of PTEN activity, confirming that up to 83% of endometrioid-type endometrial cancers, and 63% of EIN lesions are aberrantly PTEN null.²¹ Loss of PTEN function is not a very useful biomarker for clinical diagnosis, however, because its inactivation precedes all histological changes evident by light microscopy. Rare PTEN null glands occur in almost half of routine curettings of “normal” proliferative endometrium from endogenously cycling premenopausal women.²¹ Progression to EIN from this earliest “latent” stage, detectable only with biomarker studies, is extremely inefficient. Because PTEN null glands are

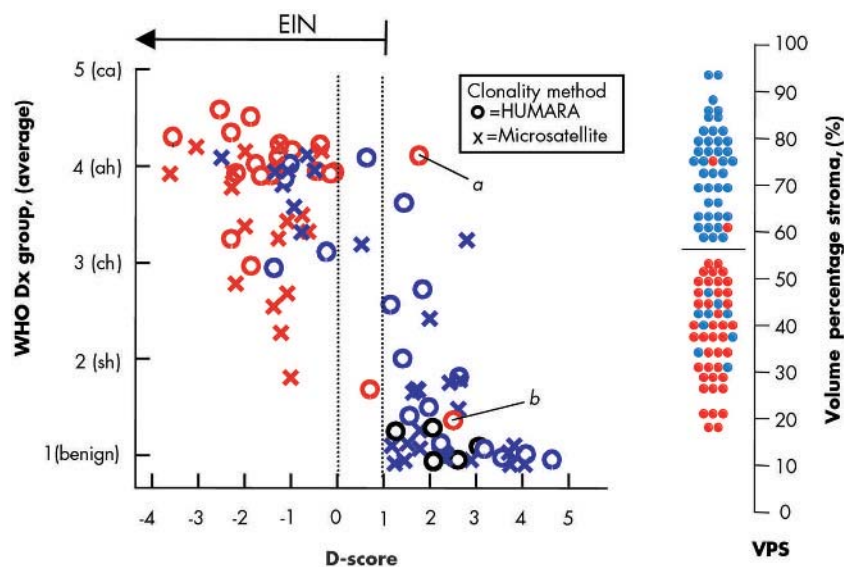


Figure 1 Morphometry and WHO94 diagnosis of endometria, by clonal result (modified from Mutter *et al*).¹⁹ Left hand section: putative endometrial precancers (red crosses, monoclonal) and polyclonal non-neoplastic tissues (blue circles, polyclonal) were delineated in haematoxylin and eosin stained glass histopathological sections and assigned to one of five diagnostic groups (ca, carcinoma; ah, atypical hyperplasia; ch, complex non-atypical hyperplasia; sh, simple non-atypical hyperplasia; and benign, non-hyperplastic endometrium) by four gynaecological pathologists, and a D-score computed by computerised morphometrical analysis. The vertical axis shows the average of four diagnosing pathologists. The dotted lines delineate a zone of computer ascertained high risk lesions on the left (D-score < 1; endometrial intraepithelial neoplasia) from low risk lesions on the right (D-score > 1). Worrying morphologies scored as polyclonal (circles in upper left quadrant) may be explained by false negative results in the genetic detection of monoclonality caused by contaminating polyclonal stroma. Note that non-atypical hyperplasias in the mid-horizontal region can be monoclonal or polyclonal, and these are well segregated by D-score. Specimen “b” is not a precancer, because the inactivated X chromosomes copy differed from resultant cancer. Tissue “a” had only a few neoplastic glands diluted by more widely distributed normal glands (precancer missed by morphometry as a result of sampling error). The right hand side shows the 55% volume percentage stroma cutoff threshold between monoclonal (blue dots) and polyclonal (red dots) endometria.

common in many “normal” endometria, and at least a third of EIN lesions continue to express the PTEN protein, PTEN immunohistochemistry is neither a specific nor sensitive single test for the identification of those endometrial lesions likely to progress to cancer. However, these PTEN data do give insight into the progression from normal endometrium through EIN to cancer.

“Thus, EINs are those WHO94 “hyperplasia” cases with a D-score < 1 or volume percentage stroma < 55%”

Thus, EINs are those WHO94 “hyperplasia” cases with a D-score < 1 (see below) or VPS < 55%. These are truly neoplastic monoclonal lesions by nature; if left alone it is only a matter of time before many will progress to cancer. In contrast, WHO94 “hyperplasias” with a D-score > 1 are non-neoplastic, polyclonal, non-progressive lesions, which are oestrogen induced and should be regarded as harmless and treated accordingly. It is important to recognise that there is not a rigid translation of WHO94 hyperplasia categories to EIN diagnoses, because differing criteria are used in each system. Two to five per cent of simple hyperplasias, 40% of CHs, and 59% of atypical hyperplasias are reclassified as EIN. Discrete localising lesions are sometimes misdiagnosed in WHO94 according to the dominant or background pattern, whereas recognition of their monoclonal origin in an EIN model supports basing a diagnosis on the “worst area”. The EIN system interprets cytology quite differently from WHO94. Although altered cytology is a consistent feature of those glands that comprise an EIN lesion, the manner of change varies substantially between patients and is not identical to “atypia” in the WHO94 classification. In bona fide EIN, architecture and cytology change coordinately within a common population of lesional glands. Cytomorphological changes in epithelial glands are usually most evident in nuclear morphology, but may involve the cytoplasmic compartment also.

SUBJECTIVE AND OBJECTIVE APPROACHES TO EIN DIAGNOSIS

EIN diagnostic schemes might be implemented using either quantitative (D-score) or subjective (table 2) diagnostic modalities, each with its advantages and disadvantages. Whichever method is used, in practice, the accurate diagnosis of EIN lesions always requires subjective input by the pathologist. If formal morphometry is to be performed for

the calculation of a D-score, it is necessary to select the “worst” area for measurement, and exclude a line up of mimics that may include hypersecretory endometrium, menstrual endometrium, or artifactually disrupted fragments. Endometrial polyps are a particular problem, because benign polyps have a wide range of D-scores; nonetheless, EIN lesions are still a possibility. D-scores are also not capable of distinguishing between EIN and carcinoma, although other morphometrical approaches can.^{24–26}

Subjective diagnostic criteria for EIN that do not require formal morphometry have been proposed for routine H&E slides (table 2).^{10 27 28} These explicitly define several subjective elements, which are already components of successful D-score measurement, such as exclusion of mimics and carcinoma. Other criteria were developed from individual D-score variables (the VPS variable is described in qualitative threshold fashion as “area of glands exceeds that of stroma in EIN”), or the sample size required for accurate D-score measurement (diameter of lesion exceeds 1 mm).

SUBJECTIVE EIN DIAGNOSIS

The diagnosis of EIN is often possible without morphometry. Table 2 shows the most important daily practice “eyeball” diagnostic criteria to classify an endometrial hyperplastic lesion as EIN. Note that all criteria must be met in a single grouping of glands.

Architectural and cytological EIN diagnostic requirements can be assessed progressively during screening of an endometrial specimen at the microscope. Low magnification is best to recognise those architectural changes characteristic of EIN: crowding of glands to a point where the area of glands exceeds that of stroma. In many cases, the crowded architectural focus defines a localising lesion, obvious from a regular background of more loosely distributed glands. Once identified at low power by architecture, higher magnification should be used to examine

the cytological appearance of those glands within the crowded focus relative to neighbouring uncrowded glands.

The subjective interpretation of EIN cytology uses criteria that are quite different from the atypia of WHO94 and mathematical calculation of the standard deviation of the shortest nuclear axis in the D-score. Compact gland clusters that present as localising EIN lesions always have a different cytology to the background, but the nature of the change differs between patients. The cytological changes of EIN can include alteration in nuclear shape and size, nuclear stratification and orientation, chromatin texture, nucleoli, in addition to cytoplasmic differentiation. The appearance in an individual patient can vary with hormonal state. In some EIN lesions, the nuclei become elongated; in others they are more rounded. For those EIN lesions that have spread throughout the endometrial compartment, a relative standard is no longer accessible, but these later stage cases tend to have an obviously abnormal cytology that is not a particular diagnostic problem.

“The subjective cytological changes of endometrial intraepithelial neoplasia can include alteration in nuclear shape and size, nuclear stratification and orientation, chromatin texture, nucleoli, in addition to cytoplasmic differentiation”

The exclusion of mimics is the most difficult part of EIN diagnosis, because there are many entities that fulfil some, but not all, EIN criteria. These are usually recognised by experienced pathologists at a glance, but pose greater difficulties with less experienced pathologists and trainees, who may not be familiar with the broad range of presentations of common endometrial findings. Carcinoma should be diagnosed when the lesion is no longer composed of individual glands, which is the case with intricate maze-like or “rambling” lumens that interconnect extensively, or lesions with solid neoplastic epithelium.

Table 2 Subjective histological EIN criteria. All criteria must be fulfilled for a diagnosis of EIN to be made

EIN criterion	Comments
Architecture	Area of glands exceeds that of stroma
Cytology	Cytology differs between architecturally crowded focus and background
Diameter > 1 mm	Maximum linear dimension of the lesion exceeds 1 mm
Exclude mimics	Benign conditions with overlapping criteria: basalis, secretory, polyps, repair, etc
Exclude cancer	Carcinoma if maze-like meandering glands, solid areas, or appreciable cribriforming

The epithelium of EIN lesions is generally not cribriform, and cancer should be considered if this feature is prominent. Invasion is not usually helpful in diagnosing carcinoma from biopsy material, because myometrial invasion will not be evident in the usual superficial sample, and the assessment of endometrial stromal invasion is not very reproducible and is of dubious biological relevance.

OBJECTIVE DIAGNOSIS BY D-SCORE

The morphometrical diagnosis of EIN uses the D-score to replace subjective assessments of gland architecture and cytology. The practical EIN diagnosis procedure guidelines using morphometry and D-score are as follows:

- (1) With the first subjective impression, exclude a mimic and confirm that the case is a possible EIN or EH. Exclude cancer.
- (2) Examine the maximal diameter of the lesion. If it is smaller than 1 mm, classify the lesion as a hyperplasia with low cancer progression risk.
- (3) If greater than 1 mm, carefully demarcate the lesion, excluding non-hyperplastic areas, and perform morphometrical D-score measurement in the selected area.
- (4) If the D-score is < 1 , diagnose EIN. If the D-score is > 1 , the lesion is benign and should be diagnosed as benign EH.

The EIN classification as implemented by morphometry (D-score) is well reproducible, as shown by replicate evaluations.¹⁴⁻¹⁹ The retrospective studies⁷⁻¹¹⁻¹⁴ and one longterm prospective multicentre routine application of the D-score have shown that it is prognostically superior to WHO94 (table 3).¹⁵ A recent international survival analysis of 674 patients with up to 18 years follow up has again shown the over-riding prognostic value of the D-score based EIN (Baak *et al*, submitted 2004).

DISTINCTION OF EIN FROM WELL DIFFERENTIATED CARCINOMA

It is often clinically important to distinguish EIN from well differentiated carcinoma. Kurmand and Norris²⁹ found that endometrial stromal invasion, increased degrees of nuclear atypia, mitotic activity, cellular stratification, and epithelial necrosis in curettings were associated with a greater likelihood of carcinoma of the uterus. Of these, stromal invasion was the most important feature. A multicentric European study³⁰ also found that for discriminating atypical hyperplasia from well differentiated adenocarcinoma, stromal alteration was a useful feature, but intraobserver and interobserver agreements were poor. Solid areas of epithelium, cribriform glands, interconnected "meandering" (confluent) lumina are also useful criteria to identify carcinoma. We have previously described an objective, well reproducible morphometric classifier for the distinction of atypical hyperplasia and carcinoma.²⁴⁻²⁵ With routine use of that classification rule in 148 cases of endometrial hyperplasia or carcinoma, the quantitative microscopically assigned grades of carcinomas in curettings correlated significantly with the depth of invasion in the myometrial wall, whereas the grade routinely indicated by eight pathologists did not.²⁶ The accurate prediction of which endometrial neoplasias are associated with deep myometrial invasion can be therapeutically useful.

TREATMENT OF EIN AND BENIGN HYPERPLASIAS

Clinical management in the EIN classification system will depend on whether the endometrium is interpreted as altered secondary to an abnormal hormonal environment of unopposed oestrogens (D-score, > 1 ; "benign reactive EH"), or a premalignant lesion, EIN (D-score, < 1). These diagnoses might be rendered using either subjective (table 2) or objective morphometrical (D-score, see above) methods. Common

treatment options are shown below according to diagnostic category.

- (1) EH (unopposed oestrogen effect, benign hyperplasia) is often treated symptomatically with short term progestins, follow up ultrasonography, and/or tissue resampling.
- (2) EIN cases are high cancer risk lesions that require treatment. Hysterectomy is the most reliable method of ruling out a coexisting carcinoma at the time of EIN diagnosis, and is definitive in reducing future cancer risk. Younger women who wish to retain their fertility, or older women who are poor surgical risks or otherwise have contraindications for hysterectomy, may, in consultation with their gynaecologist, elect to undergo a trial of hormonal treatment. In these instances, the gynaecologist must have an adequate pretreatment endometrial sample so that carcinoma can be reasonably excluded. After completion of hormonal treatment (the formulations and administration schedules of progestins vary widely) intended to treat an EIN lesion, the patient should be allowed several weeks to complete endometrial shedding before re-biopsy. Premature biopsy may detect residual lesion in the process of involution, leading to the false conclusion of an EIN treatment failure. The interpretation of biopsies while still under active progestin treatment is severely compromised by pseudo-decidual expansion of the stromal compartment, which distorts the architectural features characteristic of EIN.³³ If EIN persists, further treatment is indicated.³¹
- (3) Equivocal or ambiguous diagnoses of EIN need to be managed according to the source of interpretive difficulty and the active differential diagnosis. Severely fragmented or poorly preserved specimens can be followed up by re-biopsy, and scanty Pipelle specimens may be more abundant if sampled by curettage. If interpretation is compromised by exogenous hormonal treatment, cessation of hormones and re-biopsy is indicated. There is no fixed formula of how to handle all equivocal cases.

Table 3 Sensitivity, specificity, and positive and negative predictive values of EIN diagnosed by histomorphometry (D-score) in different studies

Study	Sensitivity	Specificity	Positive PV	Negative PV	No of patients
Delft (1988) ¹⁰	100	63	40	100	39
Philadelphia (1996) ¹²	100	71	67	100	54
Tromsø (2000) ¹⁴	100	78	58	100	68
Multicentre prospective study AJSP (2001) ¹⁵	100	82	38	100	132
Average	100	74	51	100	293*

*Total number of patients.
EIN, endometrial intraepithelial neoplasia; PV, predictive value.

THE FUTURE OF EIN IMPLEMENTATION

The use of EIN criteria for the diagnosis of endometrial precancers will provide benefits for the patient as a result of more consistent and appropriate

management of disease, but it will also present special challenges for pathologists. The combined body of molecular, formal morphometrical, and clinical outcome data provides a compelling argument for the translation of EIN into everyday practice as soon as is practical. Despite the high technology tools used to define EIN as a discrete entity, the bottom line is paradoxically simple: all of the information necessary to stratify patients according to cancer risk for triaging into therapeutic groups can be garnered from an H&E slide.

“The use of endometrial intraepithelial neoplasia criteria for the diagnosis of endometrial precancers will provide benefits for the patient as a result of more consistent and appropriate management of disease, but it will also present special challenges for pathologists”

What distinguishes EIN from many new proposals are the diverse options for implementation, which can be illustrated by the current clinical practices of the two authors of this paper.

One approach is to extract from the combined morphometry and molecular experience revised diagnostic criteria that may be applied in existing settings without the need for specialised equipment. Essentially, pathologists are retrained to diagnose using those criteria that had previously been discovered by objective means. Although subjective diagnosis can never match the excellent reproducibility of computer generated D-scores, key diagnostic elements such as VPS (which is the best single predictive variable of the D-score) and initial focal distribution of lesions with architecture and cytology differing from background (radial growth from a clonal point of origin) are intuitive concepts that pathologists can readily incorporate into their diagnostic repertoire. Readily accessible teaching tools such as online tutorials that illustrate concordance between morphometrically and subjectively diagnosed EIN lesions²⁸ may further assist in standardising the diagnostic practices of pathologists across differing backgrounds and practice settings. Multicentre studies to assess the reproducibility of subjective EIN assessments are not yet available, but a first reproducibility study gave encouraging results.³²

Alternatively, one can directly emulate in practice those exact methods proved to correlate with outcome in published clinical trials (morphometrical D-score). This is enabled by the purchase of a morphometry workstation (estimated price, €50 000), including a

highly automated microscope (practical but not essential). The total costs for a non-automated morphometry unit alone, without microscope, is around €14 000, with direct costs for each case averaging €20. The initial capital outlay of €50 000 for a highly automated morphometry workstation is compensated for by a lower running cost, of approximately €25 for each case (approximately 30 minutes of technician time and 20 minutes of pathologist time for each case) to perform the analysis itself. These expenses would naturally fall within the operational budget of the host pathology department. In the Netherlands⁷ and Norway (JPA Baak, unpublished results, 2004), use of the D-score to triage women into treatment groups has standardised the therapeutic decision making process and reduced the frequency of over and under treatment of diseased endometria, which would have been inconsistently or incorrectly diagnosed under WHO94. The benefit to patients, and savings in unnecessary surgery, more than compensates for the increased pathology costs. Therefore, although cost effective overall, the programme would require increased fiscal support of pathology departments in anticipation of gains to be seen elsewhere. Once the morphometrical equipment has been installed and is in use, a large number of non-endometrial morphometrical applications immediately become possible at minimal added cost and effort.³³⁻³⁴ Each of these applications would improve diagnostic reproducibility and appropriate treatment of other disease entities. Regional variation in health care planning and accounting practices will thus instil differing levels of enthusiasm for the introduction of morphometry.

CONCLUSIONS

The WHO94 endometrial hyperplasia classification system will continue to play an active role in the daily practice of many pathologists, but is plagued by poor diagnostic reproducibility, suboptimal prognostic prediction, and the lack of a solid statistical foundation and biological and therapeutic context. These factors combine to raise concerns about the appropriateness of previous patient management decisions, dampen enthusiasm for its use in current patient treatment decisions, and limit its usefulness for the future. WHO94 is a system that needs improvement, which will probably take the form of an entirely new approach rather than minor revision. This is the main message of the new WHO Bluebook on the subject.

The EIN classification system is the best documented alternative, based on extensive morphological, genetic molecular, and clinical outcome data. Implementation of EIN diagnosis by morphometrical determination of the D-score or VPS offers a highly standardised and clinically verified method to manage endometrial disease in affected women. Although quantitative EIN diagnostic procedures have been extrapolated to subjective diagnostic criteria, more experience is needed to evaluate the everyday performance of retrained pathologists in diverse practice environments. Quantitative and subjective approaches need not be mutually exclusive, however. Individual practices may choose between options based on local practice conditions. The hard objective diagnostic standard of D-score or VPS calculation will certainly have a central role in standardisation, whether applied in a local site, reference laboratory, or teaching setting.

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