Journal of Cellular Biochemistry, Supplement 23:137-146(1995)

The Role of Computerized Morphometric and Cytometric Feature Analysis in Endometrial Hyperplasia and Cancer Prognosis

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Abstract In our hospital, quantitative cell and tissue analysis is routinely applied in endometrial (pre)malignancies. Reasons for this are higher accuracy, reproducibility and objectivity when compared to subjective assessment of type and grade, the possibility of detecting changes and differences, and better compatibility with clinical requests (two-class instead of three- or four-class system). Furthermore, prognostication is at least as good or better than with the usual subjective methods. Clinical prospective intervention trials are currently being set up. © 1995 Wiley-Liss, Inc.

Key words: Carcinoma, cytometry, endometrium, hyperplasia, morphometry, prognosis

In gynecological tumors, such as those of the breast, endometrium, ovary, cervix and vulva, histological typing and grading are correlated with both the prognosis and certain biochemical characteristics of the tumor. However, the difficulty in practice is that assessing histological type and grade is subjective and not always perfectly reproducible. Computerized quantitative microscopic analysis of cell and tissue features can thus be helpful; it not only provides objective and measurable criteria, but may also help detect changes which may escape subjective assessment by the pathologist [1–3].

Apart from the conceptual background of quantitation in cancer pathology, this article will discuss some applications to endometrial (pre)-malignancies as examples. Nearly all parts of the gynecological tract have been subjected to quantitative cell and tissue analysis and a complete discussion would greatly exceed the available space here. Detailed descriptions of these other quantitative gynecopathological cancer applications can be found elsewhere [4].

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CONCEPTUAL BACKGROUND

Limitations of Histological Type

In spite of the evidence that microscopic features of primary gynecologic tumors have important prognostic value, the use of histological data in clinical decision making is restricted. At times, gynecological oncologists do not always find the results of microscopic studies relevant or sufficiently reliable. Lack of agreement between pathologists can be one reason, so the causes of disagreement require our attention. Two histological characteristics have been correlated with the prognosis of gynecologic tumor patients—type and grade. Indeed, in individual patients, the prognostic impact of certain rare subtypes is considerable and unambiguous. In FIGO I endometrial carcinomas, papillary, adenosquamous, clear cell, and glassy cell cancers are associated with a poor prognosis (5-year survival rates are typically around 35% versus 80–95% in the other types). However, most cases are of the usual endometrioid type. For the same reasons, the prognostic value of typing cancers of other sites is limited. Consequently, grading is probably more important for predicting the outcome in an "average" individual patient, but grade assignment carries an implicit difficulty.

Difficulties in Grading

As early as 1926, Broders [5] proposed four cancer grades depending on the percentage of "undifferentiated" cells present in the tumor sections. They are: grade 1: 1–25%; grade 2: 26–50%; grade 3: 51–75%; and grade 4: 76–100%. Allen and Hertig [6] proposed three grades (well, moderately well, and poorly differentiated) based on the total histological appearance of the tumor. If accurately performed, the prognostic value of grading is evident from a number of studies. However, in diagnostic practice very few pathologists will actually perform a differential count of atypical nuclei. Consequently, the prognostic value of nuclear grade can vanish.

In addition to this practical aspect of grading which diminishes the prognostic value, a significant implicit error source is found due to the continuous nature of (pre)malignant lesions [7]. For a detailed comment on error sources in the classification of continuous lesions, reference is made to the original publications [7]. It is well documented that in continuous lesions the lack of reproducibility of assessments of the same slide by different pathologists can be embarrassingly high [8]. Grade is a typical example of a continuous deviation, ranging from benign to extremely malignant with a number of classes in between (Fig. 1). The "decision borders" between these classes are not always uniquely defined, but even if they were, a distinction cannot always be made with 100% consistency. Reproducibility between different observers may not be very high at all [9]. Thus, considerable prognostic variability can be expected within the same grade when assessed by different pathologists. Indeed, in a multicenter evaluation of the same Stage I endometrial cancers, the prognostic value of grades assessed by three pathologists varied considerably [10]. The same phenomenon was found in a multicenter evaluation of ovarian tumors [11]. Nevertheless, a clear overall prognostic trend is usually evident. The microscopic image of a primary tumor has important prognostic value, but reproducible methods should be applied to extract and make use of this.

Thirdly, it is not always fully realized that a certain grade bears a certain *prognostic probability*. A patient with a poorly differentiated cancer is not condemned to death, but has a higher probability (for example, 70%) of having aggressive metastases. On the other hand, a patient with a well-differentiated tumor is not "safe"; she still has a certain (albeit low) chance of dying from metastatic disease.

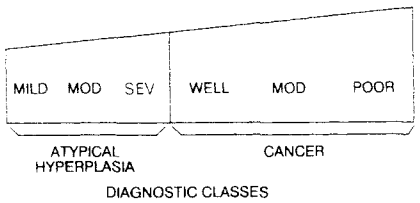

Fig. 1. Tumor grades form a continuous spectrum.

A final difficulty of grading connected with this prognostic probability is that three or four classes are usually discerned; for example, simple, complex, atypical, and complex atypical hyperplasia in premalignant lesions, and poorly, moderately, and well-differentiated malignant cancer. Such a three- or four-grade classification scheme does not adequately correspond with clinical practice, which usually requires black-and-white decisions: Hysterectomy or not? Radiotherapy or not? Rather than asking "Is it well, moderately, or poorly differentiated," we should ask: "What is the chance of aggressive locoregional disease or metastases in this particular case?" Thus, instead of a three- or four-class system, we should seek to develop a two-class system (Fig. 2). Quantitative pathological applications for gynecological tumors are not yet ideal, but seem to approach this goal better than conventional grade and type. In the following discussion, the applications so far developed for endometrial (pre)malignancies will be described.

ENDOMETRIAL HYPERPLASIAS

Endometrial hyperplasia (EH) is usually considered a precancerous lesion, although the number of publications with actual proof of this is fairly limited. In older studies, 10–20% of EH patients developed endometrial carcinoma [12]. In the 170 patients of Kurman *et al.* [13], 13/170 (8%) progressed to cancer; and in our study [14] of 42 patients, there were 8 cases (19%) with subsequent carcinoma. These two studies taken together found that 21 out of 212 EHs (9.9%) had cancer in the follow-up.

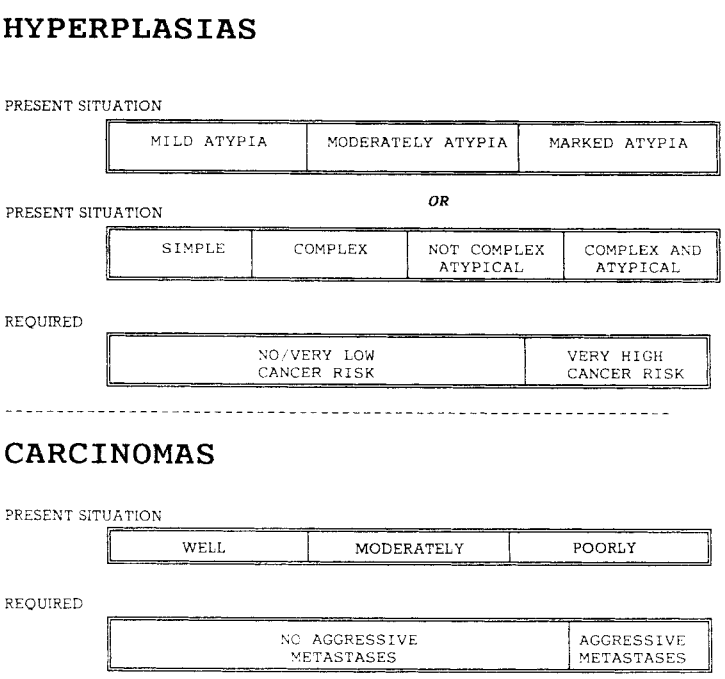

Fig. 2. The usual 3- or 4-class grading systems versus the 2-class system.

Although the percentage of patients with EH that progresses to cancer is small, until recently there were no adequate criteria to predict the outcome of an individual case. Therefore, when EH was diagnosed, hysterectomy was the treatment of choice. In addition, pathologists disagree in differentiating between certain cases of hyperplasia and well-differentiated carcinoma. Recently, attempts have been made to better define different "grades" of hyperplasia, as well as to predict which patients with hyperplasia will have cancer in the follow-up.

Currently, the preferred method is subjective grading of cytologic atypia and glandular complexity as described by Kurman *et al.* [13]. For a detailed description, reference is made to the original publication. Briefly, cytologic atypia is characterized by nuclear enlargement, rounding, pleomorphism, prominent nucleoli, irregularly dispersed, clumped chromatin, loss of polarity, and stratification. Glandular complexity is characterized by glands with irregular outlines demonstrating marked structural complexity with (complexity present) or without (complexity absent) back-to-back positioning. In this way four different subdivision are obtained: (1) simple hyperplasia (SH) is a proliferative lesion displaying mild glandular complexity, but not cytologic atypia; (2) complex hyperplasia (CH) is defined as hyperplasia displaying glandular complexity; (3) simple atypical hyperplasia (SAH) is an endometrial proliferation showing cytologic atypia without glandular complexity; and (4) complex atypical hyperplasia (CAH) is defined as hyperplasia with cytologic atypia accompanied by glandular complexity. The likelihood of cancer increases from less than 1% in SH to 29% in both glandular complexity and cytologic atypia (CAH). If one of the two features was positive, intermediate risk values were found [13].

We have re-investigated the predictive value of the Kurman classification [15]. Table I shows the results of the percentages of cases with later-occurring cancer in our study and others. In SHs, cancer risk is low. If cytologic atypicality is present but glandular complexity is absent, or if glandular complexity is present in the absence of cytologic atypicality, the cancer rate figures are 7% and 17% respectively. Compared with the 3% of cancers in patients with glandular complexity

TABLE I. Cancer Rates in Different Types of Endometrial Hyperplasia

Type	Kurman *et al.* [13] Total with cancer			Baak *et al.* [15] Total with cancer		
	n^a	n^b	%	n^a	n^b	%
a. Simple hyperplasia (SH): proliferative lesion, no glandular complexity	93	1	1%	8	0	0%
b. Complex hyperplasia (CH): no atypicality, glandular complexity	29	1	3%	6	1	17%
c. Simple atypical hyperplasia (SAH): cytologic atypicality, no glandular complexity	13	1	8%	14	1	7%
d. Complex atypical hyperplasia (CAH): cytologic atypicality, glandular complexity	35	10	29%	11	5	45%
TOTAL	170	13	8%	39	7	18%

a = total number; b = cases with cancer in follow-up.

only in the Kurman study [13], the 17% cancer rate in the present study is not significantly different ($p > 0.10$). If both features are "positive" (which is the case in 11 of the 39 cases, or 28%), cancer risk is high (45%) in our material. Thus, although the results in Kurman's and our study are not exactly the same, they are comparable. Yet the Kurman classification has certain disadvantages. First, reproducibility may not always be perfect. Secondly, four instead of two grades are discerned. Finally, the sensitivity and specificity are not very high.

Application of morphometry to cases of endometrial hyperplasia and carcinoma has shown that these diagnoses can be distinguished accurately with this technique [16–19]. The morphometric 4-class rule discerns two groups of endometrial hyperplasia—morphometric mild and severe hyperplasia (EH-1 and EH-2), and two carcinoma groups—well and moderately differentiated to poorly/undifferentiated carcinoma (ECA-1 and ECA-2/3). Each individual case is classified in each of these four morphometric "grades" with a certain numerical classification probability. In approximately 5% of cases, classification probability between morphometric severe hyperplasia (EH-2) and well-differentiated carcinoma (ECA-1) is ambiguous (*i.e.*, numerical classification probability in any of the classes: $0.30 < p < 0.70$, *e.g.*, SH = 0.65, ECA-1 = 0.35). In such cases, the more simple morphometric 2-class rule is applied, which classifies a case as either hyperplasia or carcinoma. In the large majority, ambiguous cases can be unambiguously assigned to either EH or carcinoma ($p > 0.70$). Routine application of these diagnostic morphometric 4-class and 2-class rules over a longer period gave a considerable improvement over subjective routine evaluation [20].

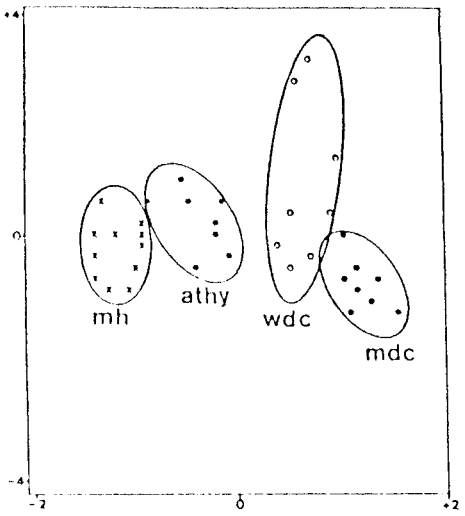

Fig. 3. The morphometric 4-class rule distinguishes four "grades": mild hyperplasia (MH), severe hyperplasia (AT), well (WDC) and moderately/poorly/undifferentiated carcinoma (MPDC), also called EH-1, EH-2, ECA-1, and ECA-2, respectively [19].

Colgan *et al.* [21] described a morphometric classification rule for predicting the outcome of EH. Using stepwise regression and discriminant analyses, they found that two quantitative nuclear features, the mean and standard deviation of the longest nuclear axis, were especially useful in predicting whether or not EH will progress to cancer. Thus, larger and more anisokaryotic nuclei are correlated with a higher risk of progression. With their predictive F-rule, 83% of their 24 cases were correctly predicted. In another study [22], the predictive F-rule was tested in 42 cases of EH obtained from a total of 2,662 curettage specimens diagnosed as hyperplasia or carcinoma. Among these 42 cases, 8 (19%) progressed to cancer. Of the eight cases with progression, seven scored above zero (unfavorable) and one just below that value (*i.e.*, F ≈ 0.3). Of the 34 cases without progression, a fairly high number had false positive, unfavorable F-values.

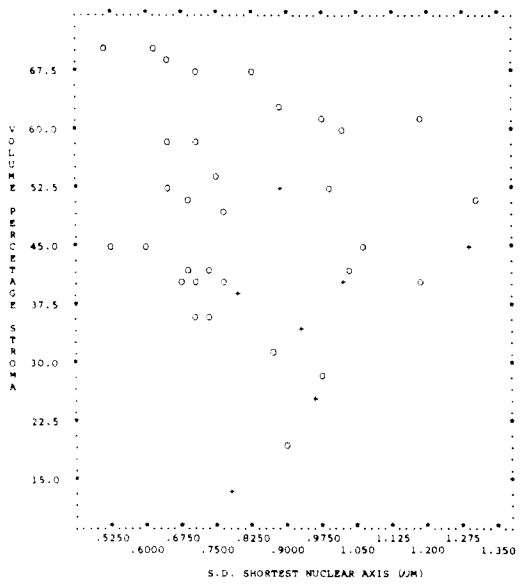

Fig. 4. Bivariate plot of the volume percentage stroma and the standard deviation of the shortest nuclear axis. Open circles = cases without progression to cancer. Black crosses = cases with progression [22].

As it was unlikely that nuclear morphometrical features are the only morphological factors reflecting outcome of disease, other quantitative histologic parameters describing gland architecture have also been studied with stereology for their potential value in selecting patients who will progress to cancer. Using linear stepwise-regression and discriminant analyses, the volume percentage stroma and the standard deviation of the shortest nuclear axis were the best discriminators, although the outer surface density of the glands also adds to the discriminating power. With the resulting linear function of three variables, a D-score for each patient was computed as shown in Figure 5.

In total, using these combined architectural and nuclear morphometrical features, 20 (62.5%) of the 32 cases without progression were separated from those who subsequently progressed. In the other 19 cases with low D-score values, 7

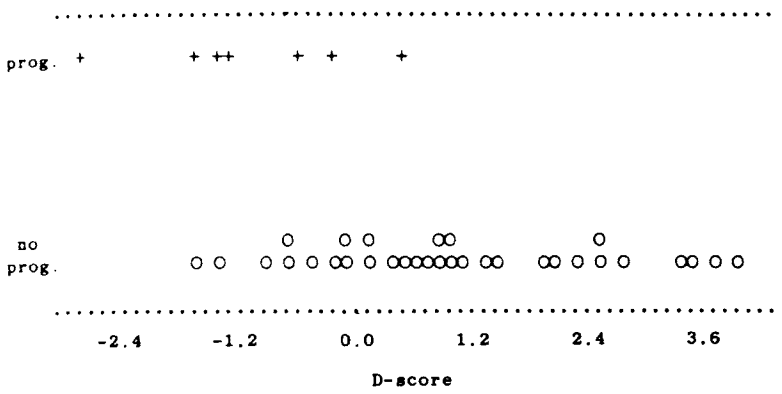

Fig. 5. D-scores of the endometrial hyperplasia patients with and without progression to cancer [22].

D-score = 0.6229 + 0.0439 (volume % stroma) – 3.9934 (SD of shortest nuclear axis) – 0.1592 (outer surface density glands).

progressed (37%) (Fig. 5). This is a considerable improvement over nuclear morphometric features alone. Compared with the qualitative feature classification rule described by Kurman *et al.* [13], there is a major advantage in the two-group over the four-group classification system. Nuclear arrangement (stratification) and proliferation-associated features improve these results slightly, but the assessment takes much more time. Further analysis showed that DNA ploidy by flow cytometry has no prognostic value at all [23].

SPECIFICITY, SENSITIVITY AND PREDICTIVE VALUE OF PROGNOSTIC TESTS IN ENDOMETRIAL HYPERPLASIA

It is important to compare the sensitivity and specificity of Kurman's criteria in predicting the outcome for patients with endometrial hyperplasia (with cancer-or-not in the follow-up as the decision criterium) with that of the morphometric rules. Sensitivity is defined here as the percentage of cases with cancer detected later in the follow-up, as correctly predicted by one of the two methods; likewise, specificity is the percentage correctly predicted in the absence of cancer in the follow-up. A low sensitivity means many false negatives (which would result in undertreatment); a low specificity would result in overtreatment. Thus, the morphology of the endometrium (*i.e.*, the presence or absence of cancer) in the hysterectomy specimen, or no clinical evidence of cancer in long-term follow-up patients (> 5 years) was considered the endpoint. Other reasons for hysterectomy, such as age or intractable metrorrhagia, are beyond the scope of the present study and not considered here.

From the clinical point of view of endometrial hyperplasias, sensitivity (as defined above) is generally required to be (close to) 100% (no undertreatment); a low specificity (overtreatment) is apparently regarded as less important. Because of this, different thresholds of the qualitative feature categories were analyzed: SH versus the others, SH + CH versus SAH + CAH, and so on. For the D-score, different threshold values and the resulting sensitivities and specificities were evaluated and the original cut-off value of 0.6 was chosen.

Table II shows the sensitivity and specificity of the prognostic values of the different approaches. The sensitivity of the morphometric classification rule is 100% and the specificity is 59%. Other approaches with different decision thresholds, using sensitivity as the judgement criterion, show that the next best approach is the presence or absence of both nuclear atypicality and glandular complexity. This approach gives a higher specificity than the morphometric method, but at the expense of the sensitivity (Table II). This means that using the Kurman criteria, some of the cases with later-occurring cancer would actually be false negatives, and hence be missed. One hundred percent sensitivity (*i.e.*, all progressive cases correctly classified) can be

TABLE II. Sensitivity and Specificity of the Prognostic Value of Different Techniques in Predicting the Outcome of Endometrial Hyperplasias

Technique	Sensitivity (%)	Specificity (%)
Qualitative Features		
Complexity positive, or not	86	66
Atypicality moderate/marked, or not	86	41
One of both or both features positive, or not	100	25
Both complexity positive and atypicality moderate/marked, or not	71	81
Morphometric Features		
Morphometric rule, $D < 0.6$ high risk; $D \geq 0.6$ low risk threshold	100	59

obtained with qualitative analysis by classing each patient with positive cytologic atypicality or glandular complexity or both as a "positive". However, this would mean that only 8 of the 39 cases (20%) would be classified as "true negative" and the specificity would be very low (25%), making such an approach less valuable. Thus, the D-score gives the best overall result.

CARCINOMAS

The incidence of endometrial carcinoma has increased in recent years, and in some countries, has become the second most frequent gynecologic tumor. Although a favorable evolution may be expected in approximately 75% of cases, a proportion of women with Stage I endometrial carcinomas will die as a result of their neoplasm within a few years of initial treatment. There are currently no accurate means of identifying those tumors likely to pursue a fatal course. Moreover, the death rate has not decreased and more precise predictors of outcome would be of considerable value in individualizing therapy, which is essential for improving the prognosis of patients. In general, stage, degree of myometrial invasion, and nuclear and histologic grade and type have some predictive value as to the aggressiveness of the disease, but none of these factors is very accurate. Moreover, for the reasons mentioned above, determination of the histologic type is of limited value, and grade of endometrial carcinoma is not always perfectly reproducible.

It also has been reported that the incidence of steroid hormone receptors has prognostic value [24], but not all authors affirm this. Chromosomal instability leading to structural or numerical aberrations is recognized as an early feature of malignant transformation. Extensive cytogenetic studies have been carried out in a variety of tumors, but the procedure is laborious and not always available.

In the prospective study of van der Putten *et al.* [10] using patients' status at the 5-year follow-up as the decision threshold, the smallest and yet strongest set of independent parameters which best discriminated between survivors and non-survivors in Stage I carcinomas was found with multivariate stepwise linear regression analysis. The combination of these three prognostic features resulted in an endometrial carcinoma Stage I prognostic index (ECPI-1), formulated as shown in Figure 6, which is dependent on mean shortest nuclear axis expressed in μm with one decimal, ploidy, and depth of myometrial invasion. The result is a classification rule ECPI-1 < 0.87 = survivor, and ECPI-1 ≥ 0.87 = non-survivor. The prognostic rule consisting of these features overshadowed the value of all other features investigated. In an independent test set of other patients, all non-survivors and 93% of the survivors were correctly classified, thus confirming the ac-

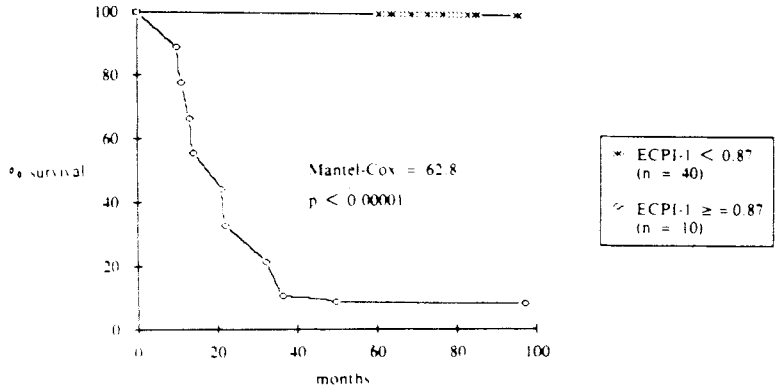

Fig. 6. Endometrial carcinoma Stage I: Kaplan-Meier survival curve of patients according to the ECPI-1 score low (< 0.87) and high (≥ 0.87) values. The former have a favorable outcome [24].

ECPI-1 = 0.694 (mean shortest nuclear axis, μm) + 0.6939 (code DNA) + 0.2398 (myometrial invasion) − 5.7283.

Code DNA: 1 = diploid, 2 = peritetraploid, 3 = aneuploid. Myometrial invasion: 1 = ≤ one-third, 2 > one-third EPCI-1 < 0.87 = survivor; EPCI-1 ≥ 0.87 = non-survivor.

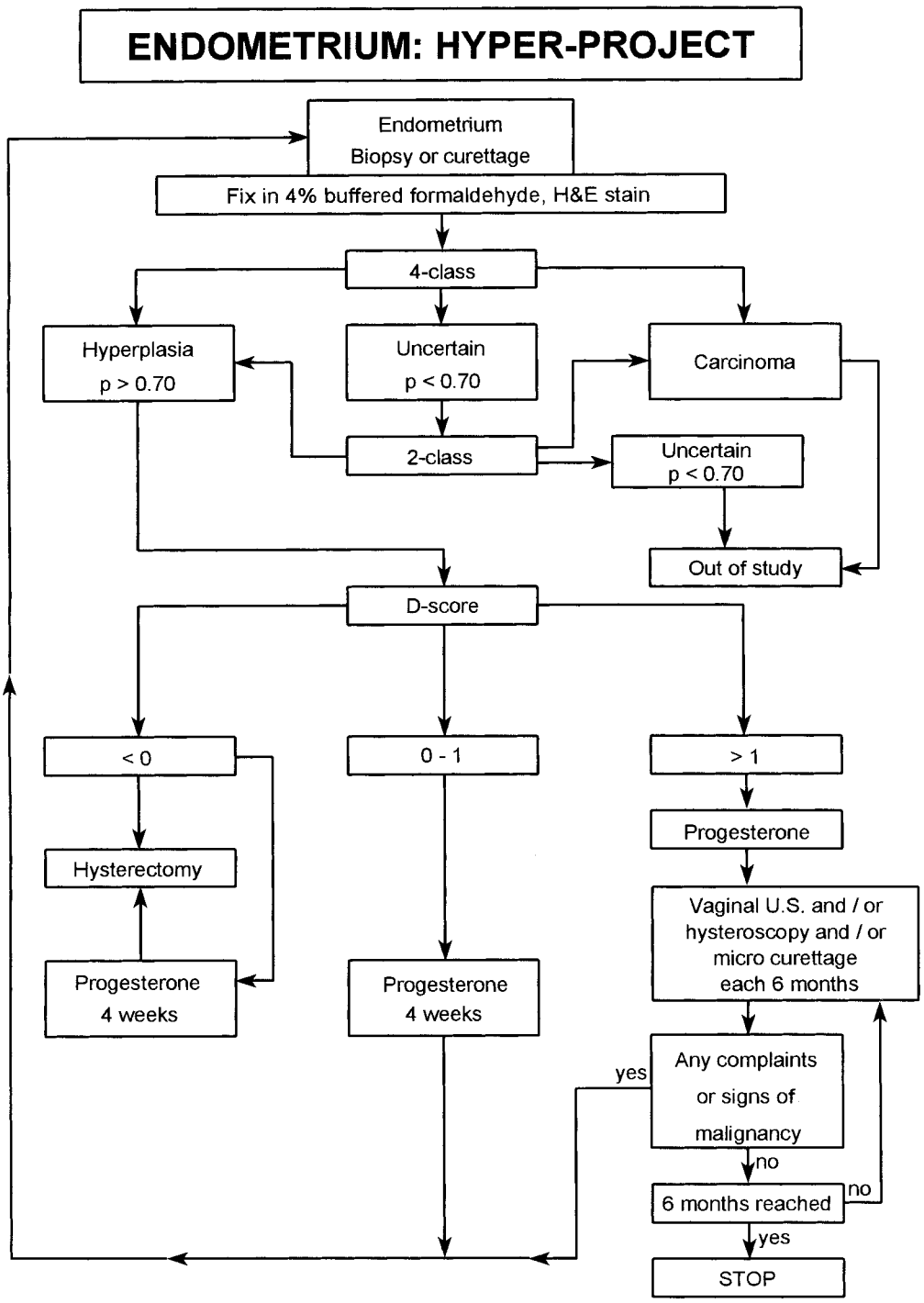

Fig. 7. Schematic diagram of the endometrial hyperplasia HYPER-project.

curacy and reliability of the developed rule to predict the outcome of future patients with Stage I endometrial adenocarcinoma. Further evaluation of these promising results on a third set of 77 patients with long-term follow-up again confirmed these results [25]. In a Good Laboratory Practice (GLP) Phase IV prospective multicenter study in The Netherlands begun in 1986, the overriding value of the ECPI-1 score was confirmed in our 1994 interim evaluation of 471 FIGO 1 patients (unpublished results).

CLINICAL QUALITATIVE PATHOLOGY IN ENDOMETRIAL HYPERPLASIAS AND CARCINOMAS: THE HYPER-PROJECT

Based on the promising findings described above, we used the following protocol in our hospital in cases of endometrial curettage or hysterectomy specimens suspected to be hyperplasia or carcinoma. (1) Perform morphometry and stereology on the endometrial curettage; (2) apply the 4-class rule. Classify the case as EH-1, EH-2, CA-1 or CA-2/3; (3) if the numerical classification probability is below 0.70 in any of the four morphometric classes or after duplicate assessments (which occurs in approximately 5% of all cases), the result is regarded as ambiguous. In that case, the 2-class rule is then applied. This is a simplified test that "grades" an individual case as hyperplasia or carcinoma only. The 2-class rule results in unambiguous classification (*i.e.*, $p > 0.70$) in approximately 90% of all cases that are ambiguous with the 4-class rule; (4) if the case is morphometrically hyperplasia, apply the D-score for prediction of the risk of cancer; (5) if the case is carcinoma, apply the ECPI-1 rule. DNA ploidy is only used on hysterectomy specimens, and not on curettage specimens (which are of little prognostic value [unpublished results]).

The 4-class and 2-class rules have been used routinely since 1981, and are a warning signal for the pathologist to take a close look to his qualitative, subjective diagnosis. Indeed, it has resulted in consultation with other pathologists and regular correction of the original histologic grade.

The D-score was introduced as a routine test in 1985, but contrary to the 4-class and 2-class rules (that have long since been used as diagnostic classifiers), it has not been used so far as a validated methodology for therapeutic decision making. The reason is obvious: according to GLP criteria, therapeutic decision making requires a GLP Phase V trial (prospective therapeutic intervention study). Such a trial, called the HYPER-project, is currently being organized in The Netherlands. Figure 7 shows the design of the HYPER-project. With respect to the ECPI-1 score, it is obvious that FIGO 1 endometrial cancers with a high ECPI-1 score behave as badly as FIGO 3 and 4 cancers. The difference with these "really" advanced cancers is that cases with an unfavorable ECPI-1 score probably have a small metastatic tumor load. Thus, of all advanced endometrial cancers, they may be the most suitable for adjuvant systemic therapy. However, a prospective randomized trial in these women with heavy cytotoxic drugs may be somewhat difficult as many of them are fairly advanced in age. Thus, it seems that non-toxic substances are very suitable and will be well accepted in a prospective randomized intervention study of FIGO 1 endometrial cancers with a high ECPI-1.

ACKNOWLEDGEMENTS

Supported in part by grant #28/1203 of the Praeventiefonds and grant #95/103 of the SBDM.

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