The purpose of this study was to examine the reproducibility of both the diagnosis of endometrial hyperplasia (EH) or adenocarcinoma, and the histologic grading (HG) of endometrioid adenocarcinoma (EC). **Methods:** Ninety-three cases of EH or adenocarcinomas were reviewed independently by 21 pathologists of the Gynecologic Pathology Study Group. A consensus diagnosis was defined as agreement among more than two thirds of the 21 pathologists. **Results:** There was no agreement on the diagnosis in 13 cases (14.0%). According to the consensus review, six of the 11 EH cases (54.5%) were diagnosed as EH, 48 of the 57 EC cases (84.2%) were EC, and 5 of the 6 serous carcinomas (SC) (83.3%) were SC. There was no consensus for the 6 atypical EH (AEH) cases. On the HG of EC, there was no agreement in 2 cases (3.5%). According to the consensus review, 30 of the 33 G1 cases (90.9%) were G1, 11 of the 18 G2 cases (61.1%) were G2, and 4 of the 4 G3 cases (100.0%) were G3. **Conclusions:** The consensus study showed high agreement for both EC and SC, but there was no consensus for AEH. The reproducibility for the HG of G2 was poor. We suggest that simplification of the classification of EH and a two-tiered grading system for EC will be necessary.

**Key Words:** Endometrioid adenocarcinoma; Serous carcinoma; Endometrial hyperplasia
The majority of endometrioid carcinomas (EC) cover a spectrum of histologically distinguishable hyperplastic lesions that range from endometrial hyperplasia (EH) without cytologic atypia, to EH with atypia (AEH), to well differentiated EC.\textsuperscript{1,2} This continuum of EH has been accepted by the World Health Organization (WHO) and the International Society of Gynecologic Pathologists (ISGP).\textsuperscript{3} A variety of cardinal histologic features, such as cytologic atypia, architectural crowding or a stromal desmoplastic reaction, are important to differentiate EH without atypia from AEH, and to differentiate AEH from EC. Accurately diagnosing the precursors to EC, which may precede cancer by several years, presents a major challenge to pathologists.\textsuperscript{4}

The Endometrial Collaborative Group has proposed the new term "endometrial intraepithelial neoplasia" (EIN) to characterize early malignant lesions.\textsuperscript{2,4,5} However, the term EIN has not yet undergone rigorous prospective evaluation nor has the reproducibility of the results with using this term been determined. It should be considered whether all well differentiated EC and AEH would be diagnosed as EIN, as proposed by BERGERON et al.\textsuperscript{6}

Many studies have confirmed that the histological grade is a significant prognostic indicator for EC.\textsuperscript{7-10} The most widely used histologic grading system for EC is the three-tiered International Federation of Gynecology and Obstetrics (FIGO) system.\textsuperscript{9-11} Although FIGO grading has significant predictive value, some histologic features such as the recognition of small amounts of solid growth, distinguishing squamous from nonsquamous solid growth and assessing the degree of nuclear atypia are difficult to evaluate.\textsuperscript{12}

Uterine serous carcinoma (SC) is also a major histological subtype of endometrial carcinoma. Recent studies have identified the precursor lesions, which are classified as intraepithelial SC or endometrial intraepithelial carcinoma (EIC) and superficial SC, as representing the noninvasive and early invasive stages of uterine SC, respectively.\textsuperscript{13-15} Given the aggressive behavior of SC compared to EC and the differences in management, it is important to correctly differentiate SC from EC of a high nuclear grade, and especially owing to the overlapping histologic features such as the papillary architecture.\textsuperscript{16}

Consistency in the pathologic diagnoses of the precursor lesions or carcinomas of the endometrium is important for choosing the proper therapy. The objective of this study was to examine the consensus of both the diagnosis of EH without atypia, AEH, endometrioid and serous carcinomas, and the histologic grading of EC.

MATERIALS AND METHODS

Ninety-three cases of EH or adenocarcinoma from 13 institutions in Korea were used in this study (Table 1). The endometrial curettage specimens and/or the hysterectomy specimens were independently reviewed by 21 pathologists of the Gynecologic Pathology Study Group (GPSG) with using the standard ISGP/WHO criteria.\textsuperscript{3} Review of the hysterectomy specimens consisted of the slides representing the most severe pathology. The biopsy review diagnoses by the study panel were subdivided into the following four categories: EH without atypia, AEH, EC and SC. The “less than EH” category encompassed a spectrum of diagnoses that included secretory or proliferative endometrium, benign polyps and inactive endometrium. The cases placed in the “less than EH” category were excluded from this study. For the EC cases, the histologic grade based on the FIGO grading system was also reviewed.\textsuperscript{11}

The study panel diagnosis was defined as agreement among more than half of the 21 pathologists, and a consensus diagnosis was defined as agreement among more than two thirds of the 21 pathologists.

<table>
<thead>
<tr>
<th>Table 1. Number of endometrial curettage and hysterectomy specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
</tr>
<tr>
<td>Curettage</td>
</tr>
<tr>
<td>Hysterectomy</td>
</tr>
<tr>
<td>Curettage/hysterectomy</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Fig. 1. Comparison between the study panel diagnosis and the consensus diagnosis of the endometrial lesions.
RESULTS

The study panel review of the cases was interpreted as follows: eleven of the 93 cases (11.8%) were diagnosed as EH without atypia, six cases (6.5%) were diagnosed as AEH, 57 cases (61.3%) were diagnosed as EC and six cases (6.5%) were diagnosed as SC. For 13 cases (14.0%), there was no agreement on the diagnosis. According to the consensus diagnosis, six of the 11 EH without atypia cases (54.5%) were diagnosed as EH without atypia, 48 of the 57 EC cases (84.2%) were diagnosed as EC, and 5 of the 6 SC cases (83.3%) were diagnosed as SC. For 6 AEH cases, there was no consensus on the diagnosis (Fig. 1).

According to the study panel review, 33 of the 57 EC cases (57.9%) were G1, 18 cases (31.6%) were G2 and 4 cases (7.0%) were G3. In 2 cases (3.5%), there was no agreement on the histologic grade. According to the consensus review, 30 of the 33 G1 cases (90.9%) were G1, 11 of the 18 G2 cases (61.1%) were G2 and 4 of the 4 G3 cases (100.0%) were G3 (Fig. 2).

We reviewed the 34 cases that had no agreement on the diagnosis or no consensus (Table 2). In 20 cases (58.8%), the main cause of discrepancy was the presence of focal lesions. Seven cases exhibited focal crowding of architecturally abnormal, cribriform glands in the background of EH without atypia or AEH. Five cases had focal cytologic atypia in the background of EH (Fig. 3). For three cases, there was focal hyperplasia within an otherwise proliferative endometrium. Three cases showed patchy small foci of a desmoplastic stromal reaction (Fig. 4). One case showed a focal villoglandular carcinoma component in a back-

**Table 2. Pathologic findings of 34 cases of no agreement on the diagnosis or no consensus**

<table>
<thead>
<tr>
<th>Pathologic findings</th>
<th>No agreement on the diagnosis (N=21)</th>
<th>No consensus (N=34)</th>
<th>Total (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal crowding of cribriform glands</td>
<td>4</td>
<td>3</td>
<td>20 (58.8%)</td>
</tr>
<tr>
<td>Focal cytologic atypia</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal hyperplasia</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal desmoplastic stroma</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal villoglandular growth</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Focal squamous morules</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diffuse lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Architectural crowding with ambiguous cribriform pattern</td>
<td>3</td>
<td>9</td>
<td>14 (41.2%)</td>
</tr>
<tr>
<td>Extensive metaplasia</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tubuloglandular architecture with high grade nuclei</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2.** Comparison between the study panel grade and the consensus grade of endometrioid carcinoma.

**Fig. 3.** One case lacking agreement on the diagnosis shows focal cytologic atypia (arrow) in a background of endometrial hyperplasia (inlet).

**Fig. 4.** One case lacking agreement on the diagnosis shows patchy small foci of a desmoplastic stromal reaction (arrow).
background of AEH (Fig. 5). One EC case that lacked consensus was a focal lesion with extensive squamous morules in a background of stromal predecidualization with atrophic glands. Some of the pathologists diagnosed such cases as AEH, and others diagnosed them as EC.

In 14 cases (41.2%), there were diffuse lesions. Twelve cases that lacked agreement on the diagnosis or no consensus showed architectural crowding, and this was associated with early cribriform features (Fig. 6) and equivocal cytologic atypia, making it difficult to differentiate AEH from low grade EC. One case showed extensive papillary and eosinophilic metaplasia in architecturally complex or fragmented glands. One SC case that lacked consensus exhibited a tubuloglandular architecture with a high nuclear grade (Fig. 7). Two EC cases that lacked agreement on the histologic grade showed mixed patterns of low grade and

Fig. 5. One case lacking agreement on the diagnosis shows a focal villoglandular carcinoma component in a background of atypical endometrial hyperplasia (inlet).

Fig. 6. One case lacking agreement on the diagnosis shows focal crowding of architecturally abnormal glands with early cribriform features in a background of endometrial hyperplasia without atypia.

Fig. 7. One serous carcinoma case lacking consensus exhibits a tubuloglandular architecture with a high nuclear grade and psammoma bodies.

Fig. 8. One endometrioid carcinoma case lacking agreement on the histologic grade shows mixed patterns of low grade (inlet) and high grade carcinomas.

Fig. 9. One serous papillary carcinoma case is limited to a benign endometrial polyp. The high power view shows a high nuclear grade (inlet).
high grade carcinoma (Fig. 8).

**DISCUSSION**

The WHO 4-class EH classification is currently widely accepted, and it primarily divides hyperplasias into those with and those without cytologic atypia, while the degree of glandular crowding (simple vs complex) has secondary importance. Regarding the hyperplastic categories without atypia, differentiating between simple and complex hyperplasia is not reproducible. In addition, these two categories have essentially the same prognosis, and their differentiation is not helpful and it may even be confusing to the clinician.\(^6\) EH without atypia, whether simple or complex, is likely to respond to hormonal therapy.\(^17,18\) In this consensus study, the interobserver reproducibility for the classification of EH cases into simple or complex was very poor, so we did not classify EH as simple or complex.

According to the previous consensus studies, the reproducibility for the key assessment measure of the presence or absence of cytologic atypia is also poor.\(^19,20\) Several expert panels have emphasized the considerable interobserver and intraobserver variability using these systems, and this underlined the difficulty of making the diagnosis of premalignant changes of the endometrium on biopsy specimens.\(^6,21\) AEH has been reported to be a poorly reproducible diagnosis, with experts differing in significant proportions of cases not only for the referring pathologists but also with each other.\(^19,20,22\)

The factors that contribute to low reproducibility include: 1) multiple independent criteria to classify a lesion because each pathologist must assign a relative value or weight to each potentially conflicting criterion, 2) the fragmentary nature of the curettage specimens, 3) the presence of borderline lesions, 4) the uncertainty about the significance of focal hyperplasia, 5) the inadequacy of descriptions and the lack of understanding of the terms used to define the architectural or cytological atypia, and 6) the difficulty associated with the translation of verbal descriptions into light microscopic images and the associated interobserver reproducibility of the translations.\(^23\)

In this consensus study, six of the 11 EH cases without atypia (54.5%) were diagnosed as EH without atypia and 48 of the 57 EC cases (84.2%) were diagnosed as EC. For the 6 AEH cases, there was no consensus on the diagnosis. These results are comparable to those of Bergeron et al.\(^6\) For 34 cases of this study, there was no agreement on the diagnosis or no consensus. The main cause of discrepancy was the presence of focal lesions in 20 cases (58.8%). Seven cases exhibited focal crowding of architecturally abnormal, partly cribriform glands in the background of EH without atypia or AEH. In 14 cases (41.2%), there were diffuse lesions. Twelve cases that lacked agreement on the diagnosis or no consensus showed architectural crowding that was associated with early cribriform features and equivocal cytologic atypia, which made it difficult to differentiate AEH from low grade EC. Differentiation between AEH and EC was problematic, especially when the lesions were focal or patchy in distribution.

According to the GOG study on the diagnosis of AEH in 2006, a panel of 3 GOG pathologists concurred with the referring diagnosis for only 39% of the patients. The mean percentage of agreement was the lowest for complex hyperplasia and for AEH.\(^23\) There was a lack of agreement for the diagnoses of complex hyperplasia and AEH, and a lack of reproducibility for the recognition of the histologic feature of the stromal alterations and the cribriform pattern of growth that are used to differentiate AEH from well differentiated EC. Thus, the histologic classification needs to be simplified by inclusion of a combined category, called EH, for simple and complex hyperplasia, and also a combined category, called endometrioid neoplasia, for AEH and well differentiated EC. The diagnoses of EH and endometrioid neoplasia are highly reproducible between observers from different institutions.\(^5\)

EH includes “benign EH” caused by protracted estrogen exposure and an “EIN” category of monoclonal premalignant disease.\(^25\) EIN is a precursor to EC, and the former is characterized by monoclonal growth of the mutated cells, a distinctive histopathologic appearance by its altered cytology and crowded architecture. EIN has a 45-fold elevated cancer risk.\(^1\) EIN is a clonal proliferation of architecturally and cytologically altered premalignant endometrial glands that are prone to malignant transformation to EC. EIN lesions are noninvasive, genetically altered neoplasms that arise focally and they may convert to a malignant phenotype upon acquisition of additional genetic damage.\(^5\)

The diagnostic criteria of EIN include glandular crowding with an area of glands greater than the stroma. The cytology of the architecturally crowded area is different from the background and it is clearly abnormal. The area of an EIN lesion that meets the architectural and cytologic criteria for diagnosis must measure a minimum of 1 mm at the maximum dimension, and this is a scale that usually encompasses more than 5-10 glands.\(^6\) Although the foci of EC seem to have developed from the EIN, the distinction between EIN and EC is of clinical importance.
EIN lesions are composed of clusters of individually recognizable glands with a simple, but often pseudostratified lining epithelium, whereas EC may have one or more specific patterns not seen in EIN, such as solid, cribriform or complex interlacing mazelike growth. The EIN classification is much stronger than the WHO classification for predicting cancer outcomes during follow-up. Even though we did not apply the EIN criteria in this series, the discrepancy might have been reduced if the EIN classification was used.

Although the three-tiered FIGO grading has significant predictive value for EC, the reproducibility of the G2 FIGO grading is limited. A binary architectural grading system has been proposed based on the amount of solid growth, the pattern of myometrial invasion and the presence of necrosis. According to this system, a tumor is classified as high grade if at least two of the following three criteria were present: 1) more than 50% solid growth (without distinction of squamous from nonsquamous epithelium), 2) a diffusely infiltrative, rather than expansile, growth pattern, and 3) tumor cell necrosis. For tumors that were confined to the endometrium, only the percent of solid growth and necrosis were evaluated, and those tumors with both solid growth of more than 50% and necrosis were considered as high grade. The recently proposed simple architectural binary grading system that divides tumors into low-grade lesions and high-grade lesions based on the proportion of solid growth (< or =50% or >50%) has been shown to have superior prognostic power and greater reproducibility. According to the consensus review in this study, 30 of the 33 G1 cases (90.9%) were G1, 11 of the 18 G2 cases (61.1%) were G2 and 4 of the 4 G3 cases (100.0%) were G3. In this series, the consensus for the G2 cases was poor.

Uterine SC can exhibit an architecturally, well-differentiated tubuloglandular morphology with or without an accompanying papillary growth pattern. These features make it difficult to distinguish SC from EC. Because of the aggressiveness of SC, it is important to correctly classify endometrial carcinomas that exhibit tubuloglandular architecture with a high nuclear grade. In this study, 5 of the 6 SC cases (83.3%) were SC according to the consensus diagnosis. One case that had no consensus exhibited tubuloglandular architecture with a high nuclear grade. Immunohistochemical staining facilitates the distinction of SC from EC. The combination of no p53 expression, a positive PR expression and the loss of PTEN best distinguishes between EC and SC. Point mutations in the p53 suppressor gene might partly explain the rapid growth of this malignant tumor and its unfavorable outcome. The association of an endometrial polyp with SC was first reported in a study by Silva and Jenkin in which 16 patients with superficial SC involving an endometrial polyp were described. In this current study, the three serous papillary carcinomas were limited to the benign endometrial polyps (Fig. 9). The carcinoma was exclusively composed of a serous papillary subtype in 2 cases and was admixed with an endometrioid type in one case. Microscopically, the tumors were architecturally characterized by complex broad or thin papillae with epithelial stratification, and they were cytologically characterized by pleomorphic, hyperchromatic nuclei and prominent nucleoli with occasional macronucleoli. The nuclei were bizarre, and some cells had a hobnail appearance.

Although our observations were based on a small number of cases, this study suggests that simplification of the EH classification system is sorely needed. Other studies of a two-tiered grading system compared with the current 3 level grading system for EC will be useful. Future studies based on the results from this study will include a biomarker analysis in an effort to characterize those endometrial lesions that are predictive of carcinoma.

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