Comparison of cervical cytology with histopathology

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Abstract

Aim: Cervical cancer is still a health problem in countries where cervical cancer screening is not routinely performed. A significant decrease in the rate of mortality from cervical cancer has been observed since the Pap test was introduced. Within the last decade liquid-based cytology (LBC) has replaced the Pap test. Our aim is to compare cervical smears prepared with the liquid-based cytology method with histopathological findings. Material and Method: Cervical smears and corresponding cervical biopsy reports of 300 patients diagnosed with epithelial cell abnormality between 2014-2016 were reevaluated retrospectively. Smears were prepared with the LBC test SurePath. Biopsy materials were stained with hematoxylin eosin. Slides were reported according to Bethesda 2014 classification. Biopsy materials were classified into 4 categories according to the WHO 2014 classification. Results: Cytology results of 273 patients (91%) were abnormal. Biopsy results showed lesions such as low grade cervical intraepithelial lesion, high grade cervical intraepithelial lesion, and squamous cell carcinoma in 178 patients (59.3%). The calculated sensitivity and specificity for LBC were 89.89% and 7.38% respectively, indicating low accuracy of specificity for LBC. Discussion: The management of treatment in diagnosis of epithelial cell abnormality in cervical cytology should be according to the sets of specified protocols. Because we may encounter high grade squamous intraepithelial lesions in biopsy with the diagnosis of atypical squamous cells of undetermined significance (ASCUS) in cytology, the necessity of colposcopy can be disputed for the management of this group of lesions.

Keywords
2014 Bethesda System; Cervical Cancer; Liquid-Based Cytology
Introduc
Cervical cancer is still a health problem in countries where cervi-
cal cancer scanning is not routinely performed; despite this, cervi-
cal cancer is one of the human malignancies that can be
successfully reduced by medical intervention [1,2]. Premalig-
nant lesions are characterized by abnormal cellular or epithelial
architecture in the areas surrounding the junction between the
squamous and columnar epithelium [3]. The American Society
for Colposcopy and Cervical Pathology (ASCCP) recommends
initial cervical sampling for women 21 years old, Pap test every
three years for women 21-29 years old; it prefers co-testing
(Pap test and HPV testing) every five years for women over 30
years old. In 1940 the Pap test was developed by George Papat-
ial [4]. An important decrease in the rate of mortality from
cervical cancer has been observed following introduction of the
Pap test [4]. In the Pap test technique, because of the coverage
of abnormal cells with blood, mucus, or inflammation, there can
be increase in the false negative rates [5,6,7]. The liquid-based
cytology (LBC) test was developed in 1960s and 1970s to de-
crease the rates of false negatives [8]. The 2001 Bethesda
system, the most widely accepted classification to report cervi-
cal cancer, was updated in 2014 with no significant changes. In
the Bethesda system, squamous epithelial cell abnormality is
divided into five categories: Atypical squamous cells of undeter-
mined significance (ASCUS), atypical squamous cells cannot ex-
clude HSIL (ASC-H), low grade squamous intraepithelial lesion
(LSIL), high grade squamous intraepithelial lesion (HSIL), and
squamous cell carcinoma (SCC). According to the WHO classi-
fication 2014, squamous cell tumors and precursor lesions are
divided into 3 categories: Low grade squamous intraepithelial
lesion, high grade squamous intraepithelial lesion, and squa-
mous cell carcinoma, NOS [9]. In this study we compared our
cytology results of ‘squamous epithelial cell abnormality’ with
histopathologic results and aimed to evaluate the accuracy of
cytology in detecting precancerous lesions and squamous cell
carcinoma.

Material and Method
The Pap test reports of 300 patients who had both cervical
tests and cervical biopsies diagnosed with epithelial cell
abnormality between 2014-2016 were reevaluated retrospec-
tively. Cervical cytology materials were taken by a “broom-like”
device with detachable head and this head was placed in etha-
nol-based preservative fluid. The LBC test SurePath was used.
Slides that contained more than 5000 epithelial cells were
evaluated according to the Bethesda 2001 classification. Biop-
sy materials were routinely stained with the hematoxylin eosi
method. After histopathological examination we classified the
results into 4 categories according to the WHO classification
2014. For statistical analyses SPSS statistics 24 (IBM SPSS,
Turkey) was used. We determined the sensitivity, specificity, and
positive and negative predictive values of each method—Sure-
Path LBC and histopathology.

Results
All Pap test reports between 2014-2016 were documented with
a retrospective database search. 20452 cervical cytology re-
ports were analyzed; ASCUS, ASC-H, LSIL, HSIL, and SCC rates
were 3.93%, 0.1%, 1.11%, 0.51%, and 0.01% respectively. The
mean age of the patients was 40.08 (range: 16-85 years). Cytol-
ogy results of 273 patients (91%) were abnormal, while 27 pa-
tients (9%) had normal results. Of the 273 patients, 140 (46.7%)
were ASCUS, 25 (8.3%) were ASC-H, 78 (26 %) were LSIL, 28
(9.3 %) were HSIL, and 2 (0.7 %) were SCC (Table 1). Among
the 300 patients, 122 patients (40.7%) had normal biopsy re-
results, 114 patients (38%) were LSIL, 61 patients (20.3%) were
HSIL, and 3 patients (1.0%) were SCC (Table 2). Comparison of
LBC with histopathology showed that of the 273 patients with
abnormal cytology, 160 (58.6%) had abnormal biopsy results.
18 patients had abnormal biopsy results while cytology was
normal and 9 patients had normal biopsy results while cytology
was abnormal (Table 3). The calculated sensitivity and speci-
cificity for LBC were 89.89% and 7.38%, indicating low accuracy.
The sensitivity, specificity, and positive-negative predictive val-
dles of cervical cytology for ASCUS, ASC-H, LSIL, HSIL, and SCC
diagnoses are given in Table 5.

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27</td>
<td>9.0</td>
</tr>
<tr>
<td>ASCUS</td>
<td>140</td>
<td>46.7</td>
</tr>
<tr>
<td>ASC-H</td>
<td>25</td>
<td>8.3</td>
</tr>
<tr>
<td>LSIL</td>
<td>78</td>
<td>26</td>
</tr>
<tr>
<td>HSIL</td>
<td>28</td>
<td>9.3</td>
</tr>
<tr>
<td>SCC</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1. Liquid-based cytology results of all patients

<table>
<thead>
<tr>
<th>Biopsy results of patients</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>122</td>
<td>40.7</td>
</tr>
<tr>
<td>LSIL</td>
<td>114</td>
<td>38</td>
</tr>
<tr>
<td>HSIL</td>
<td>61</td>
<td>20.3</td>
</tr>
<tr>
<td>SCC</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Biopsy results of all patients

<table>
<thead>
<tr>
<th>LBC</th>
<th>Biopsy</th>
<th>Abnormal</th>
<th>Normal</th>
<th>Kappa</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>160 (58.6%)</td>
<td>113 (41.4%)</td>
<td>0.10</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18 (66.6%)</td>
<td>9 (33.3%)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Correlation of cytology and biopsy results

<table>
<thead>
<tr>
<th>Cytology / Biopsy</th>
<th>Normal</th>
<th>LSIL</th>
<th>HSIL</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>9</td>
<td>12</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>ASCUS</td>
<td>80</td>
<td>47</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>ASC-H</td>
<td>12</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>LSIL</td>
<td>19</td>
<td>45</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>HSIL</td>
<td>2</td>
<td>3</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>SCC</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4. Detailed correlation of cytology and biopsy results

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>34%</td>
<td>34%</td>
<td>45%</td>
<td>26%</td>
</tr>
<tr>
<td>ASC-H</td>
<td>7%</td>
<td>90%</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>LSIL</td>
<td>33%</td>
<td>84%</td>
<td>76%</td>
<td>46%</td>
</tr>
<tr>
<td>HSIL</td>
<td>15%</td>
<td>98%</td>
<td>93%</td>
<td>44%</td>
</tr>
</tbody>
</table>
Discussion
Cervical cancer is a preventable disease if we are successful in early diagnosis. Since the introduction of cytology into clinical practice by Papanicolaou and Traut in 1944, we have been able to detect preinvasive stages, thereby reducing the morbidity and mortality of this disease. By 2001, revised Bethesda system terminology had created the need for a standard approach to manage abnormal cervical cytology cases for managing minor cervical cytological abnormalities [10]. In 2014 the Bethesda system was updated with no significant changes. Then, the American Society for Colposcopy and Cervical Pathology (ASCCP) initiated a process for developing evidence-based consensus guidelines to aid clinicians in managing abnormal cytology results [11,12]. Over the years, knowledge has advanced and standard scanning programs have changed. In 2012, national organizations published guidelines such as the Lower Anogenital Squamous Terminology (LATS) and the American Society for Colposcopy and Cervical Pathology (ASCCP) consensus, which recommend longer scanning intervals and a later age to start scanning [13,14]. The 5-year risk of CIN 3 is only 8/10,000 in women aged 30-64 years with negative co-test [15]. Today, co-testing with cytology and HPV testing at 5-year intervals is preferred for women aged 30-64 years for cervical cancer scanning [16,17]. In our study, the squamous cell abnormalities were present in 91% of the cytology materials. ASCUS was present in 46.7%, ASC-H in 8.3%, LSIL in 26%, HSIL in 9.3%, and SCC in 0.7% of the cases. In the ASCUS diagnosed group, 57.1% had healthy cervical biopsy, 33.6% were LSIL, and 9.3% were HSIL. ASCUS is the most common cytological abnormality. It carries the lowest risk of HSIL and one-third to two-thirds are not human papilloma virus (HPV) associated [13]. LATS and ASCCP guidelines are recommended to manage ASCUS cases with HPV-negative co-testing results with routine follow-up at 3 years. For women with HPV positive ASCUS, colposcopy is recommended. If we can’t identify cervical intraepithelial lesion in HPV positive AS­CUS by colposcopy, co-testing at 12 months is recommended. For women with ASCUS cytology and no HPV result, repeating cytology at 1 year is acceptable [13]. Overtreatment should be avoided as the routine use of diagnostic excisional procedures such as loop electrosurgical excision for women with an initial ASCUS in the absence of HSIL is not appropriate [13]. Biopsy of LSIL patients with cytology showed LSIL in 57.7% and HSIL in 17.9%. LSIL is highly associated with HPV infection. According to ASCCP consensus guidelines, colposcopy is recommended for women with LSIL cytology and no HPV test or positive HPV test. For LSIL cases with negative HPV test, repeating co-testing at 1 year is preferred; colposcopy is also acceptable. According to analysis of the Kaiser Permanente Northern California Medical Care plan (KPNC), women with LSIL at ages of 21-24 years carry a lower risk of HSIL than older women [14]. Following up these women with cytology at 12 months is recommended [13]. In the KPNC database, risk of HSIL in HPV-negative LSIL cases is low, similar to ASCUS alone [14]. Fallani et al. compared biopsy results of patients with ASCUS and SIL cytological diagnosis; biopsy of ASCUS patients showed LSIL in 36.3% and HSIL in 15.7% [15]. The researchers found LSIL in 67.7% and HSIL in 20.8% of the SIL patients [16]. In our outcomes, abnormal biopsy findings were 42.9% in the ASCUS group, 52% in the ASC-H group, 75.6% in the LSIL group, 92.8% in the HSIL group and 100% in the SCC group. Atlagan et al. reported biopsy positivity 56% in the ASCUS group, 50% in the ASC-H group, 66% in the LSIL, and 100% in the HSIL group [19]. The ASCUS/SIL ratio is useful for assessment of intra­laboratory and interlaboratory comparison. The prevalence rates for both ASCUS and SIL depend on the risk factors of the patient population and ASCUS / SIL ratio provides some degree of correction [20]. In a study by Geisinger et al., the ASCUS / SIL ratio changed from 0.58 to 1.02 [21]. The Turkish Cervical Cancer and Cervical Cytology Research Group indicated a value of 2.0 for ASCUS /Sil ratio [22]. Our ASCUS / Sil ratio is nearly 1.4. The management of treatment in diagnosis of epithelial cell abnormality in cervical cytology should be according to the sets of specified protocols. Our study suggests that we may encounter HSIL with the diagnosis of ASCUS. Clinicians should keep in mind that results of microscopic evaluation depend on factors such as appropriate sampling, adequacy of the material, preparation of the slide, and the attention and experience of the pathologist. Our proposal for clinicians is to evaluate cyto­logical diagnosis with other diagnostic methods and select the best treatment method for patients according to the guidelines.

Scientific Responsibility Statement
The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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