Limited frequency of malignant change in lobular endocervical glandular hyperplasia

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HIGHLIGHTS
- Clinical diagnosis of lobular endocervical glandular hyperplasia was consistent with pathological diagnosis.
- The rate of malignant change of lobular endocervical glandular hyperplasia during follow-up was limited (1–2%).
- Worsening cytology and increasing lesion size may be important signs of malignant change of lobular endocervical glandular hyperplasia.

INTRODUCTION
Lobular endocervical glandular hyperplasia is morphologically characterized by multiple cysts of the uterine cervix, its potential as a precursor of minimal deviation adenocarcinoma has been reported. However, the natural history of the disease and the frequency of malignant change are not fully understood. We evaluated the frequency of malignant change of clinical lobular endocervical glandular hyperplasia and explored useful parameters indicating malignant change.

METHODS
The clinical courses of 175 patients with cervical multi-cystic lesions who visited Shinshu University Hospital between June 1995 and June 2019 were retrospectively analyzed. We examined the results of follow-up and outcomes of the patients diagnosed with lobular endocervical glandular hyperplasia and investigated the frequency of malignant transformation.

RESULTS
Of the 175 patients, 15, 84, and 76 were clinically diagnosed with suspected malignancy, suspected lobular endocervical glandular hyperplasia, and suspected nabothian cyst, respectively. Of these patients, 69 patients with suspected lobular endocervical glandular hyperplasia were followed, and 12 underwent hysterectomy after a mean follow-up of 57.1 (range: 3–154) months due to lesion enlargement (increase in tumor diameter of >20%) and/or worsening cytology. Of these 12 patients, two had lobular endocervical glandular hyperplasia with atypia and one had minimal deviation adenocarcinoma. Of 69 patients, the rate of malignant change was 1.4% (1/69). The growth rates of the lesions for these three patients during follow-up were significantly higher than those of nine patients who underwent surgery with lobular endocervical glandular hyperplasia without atypia and 48 follow-up cases of suspected lobular endocervical glandular hyperplasia. The cut-off value of the growth rate suggesting malignant transformation was 38.1% (84.6% sensitivity and 100% specificity). Tumor size and cytology did not change in the remaining 57 cases continuing follow-up.

Conclusion An increase in tumor size and worsening cytology are important parameters for detecting malignant transformation of lobular endocervical glandular hyperplasia during follow-up. However, the frequency of malignant change of this disease may be limited. These results suggest that conservative management may be an option for clinical lobular endocervical glandular hyperplasia.
ultrasonography, MRI, or computed tomography who visited Shinshu University Hospital between June 1995 and June 2019 were enrolled in the study. The study included 94 patients with a multicystic lesion, whose clinical courses were reported in our previous study.6 We retrospectively examined the results of follow-up and outcomes of the patients who were clinically diagnosed with lobular endocervical glandular hyperplasia and investigated the frequency of malignant transformation.

**Diagnosis, Treatment, and Follow-up**
In this study, ‘cervical multi-cystic lesion’ was tentatively defined by the presence of a cluster(s) of cysts in the cervix, and women having such findings were included in further analyses. In women with multiple cervical cysts, the primary clinical diagnosis and management were based on our protocol (Figure 1).5 6 In this protocol, the combination of three parameters (MRI, cervical pap cytology, and gastric-type mucin) was used for the clinical diagnosis, and we verified the usefulness of our protocol in a retrospective follow-up study.6 As we reported previously, T2 weighted MRI findings were classified as follows: (i) solid pattern (a solid component was noted, suggesting malignancy); (ii) invasion pattern (diffuse and solid high T2 weighted signal with an unclear margin in the cervical stroma, suggesting malignancy); (iii) cosmos pattern (diffuse or microcystic pattern surrounded by medium to large cysts, suggesting lobular endocervical glandular hyperplasia); (iv) microcystic pattern (aggregation of small cysts without peripheral large cysts, suggesting lobular endocervical glandular hyperplasia or malignancy); and (v) coarse cystic pattern (irregular aggregation of medium to large cysts without a solid or microcystic component, suggesting nabothian cysts).

A cytological diagnosis was made according to the Bethesda system. In particular, atypical glandular cells–not otherwise specified was regarded as suggesting lobular endocervical glandular hyperplasia without atypia, whereas atypical glandular cells–favor neoplastic suggested a lesion with atypia or carcinoma. Gastric-type mucin in the cervical mucus was examined using a latex agglutination assay (HIK1083 test, Kanto Kagaku, Tokyo, Japan) or by the detection of ‘yellow’ or ‘orange’ mucin in the cervical pap smear.7–9 Accordingly, the patient was clinically diagnosed with suspected malignancy when pelvic MRI revealed a predominant solid component or invasive lesion and/or atypical glandular cells–favor neoplastic in the pap cytology. Patients with this category underwent immediate biopsy and hysterectomy. A patient was clinically diagnosed with suspected lobular endocervical glandular hyperplasia when a cosmos pattern on MRI, normal or atypical glandular cells–not otherwise specified cytology, and gastric mucin were noted. Patients with this category underwent follow-up with (conization or hysterectomy) or follow-up every 3–6 months. A patient was clinically diagnosed with suspected nabothian cysts when MRI showed coarse, multiple cysts with a clear margin, with negative cytology, and gastric-type mucin. The patients were recommended to undergo follow-up every 3–12 months.5 6

In this study, lesion size was measured by MRI in three dimensions. The dimension that showed the largest change was subjected to measurement as a growth rate. The growth rate (%) was calculated according to the following formula; (current size−basal size)/basal size ×100. The current size indicated the diameter at the time of measurement during follow-up, and the basal size was the initial size or the minimum size during follow-up. Similar to the revised response evaluation criteria in solid tumors, an increase or decrease in lesion size was defined as >20% enlargement or 30% reduction in growth rate, respectively. A pathological diagnosis was made according to the classification of the World Health Organization for glandular tumors and precursors of the uterine cervix.9 In this study, we defined lobular endocervical glandular hyperplasia with atypia as...
as follows: with at least one of the following morphologic features, including nuclear enlargement, irregular nuclear contour, distinct nucleoli, and/or loss of cell polarity.

The Mann–Whitney U test was used for statistical analysis. In patients undergoing follow-up, when MRI findings suggested signs of malignancy, such as an increase in lesion size, new detection of a solid or invasive pattern, lesions with a high signal intensity on diffusion weighted imaging, or when cellular atypia was detected by pap smear, follow-up was discontinued and surgery was recommended.

RESULTS

A total of 175 patients were included in the analysis and mean age was 46.5 years (range 24–76). The numbers of patients with suspected malignancy, suspected lobular endocervical glandular hyperplasia, and suspected nabothian cysts were 15, 84, and 76, respectively. Mean ages (±standard deviation) of patients in each group were 45.8±7.6, 46.9±9.4, and 46.0±8.9; respectively. The proportions of patients complaining of watery discharge in each group were 26.7%, 52.4%, and 21.1%, respectively (Figure 2).

Patients who Underwent Immediate Hysterectomy

The clinicopathological data of 15 patients in this category are summarized in Table 1. All patients underwent hysterectomy immediately after the clinical diagnosis (radical hysterectomy, n=8; total abdominal or laparoscopic hysterectomy, n=7) (Table 1). Of these 15 patients, 10 patients had adenocarcinoma (gastric-type mucinous carcinoma in nine and other in one). Malignant lesions were detected in nine patients by cervical biopsy. Eight showed a solid pattern on MRI, and 10 had an abnormal cytology.

Patients with Suspected Lobular Endocervical Glandular Hyperplasia

Eighty-four patients were initially diagnosed with this category (Figure 2). Of these 84 patients, 13 underwent hysterectomy immediately after the diagnosis (Table 2). Five of these 13 patients underwent a hysterectomy due to atypical cells detected by conization, the accidental association of cervical intraepithelial neoplasia grade 3, adenocarcinoma in situ, atypical polyoid adenomyoma, and endometrial carcinoma. The remainder selected hysterectomy for alleviation of symptoms or prophylaxis. The final histological diagnosis was lobular endocervical glandular hyperplasia in 11 patients (including with atypia in two, with cervical intraepithelial neoplasia III in one, and with adenocarcinoma in situ in one). The other two patients had tunnel cluster and nabothian cysts. The diagnostic accuracy for suspected malignancy and suspected lobular endocervical glandular hyperplasia was 66.7% (10/15) and 84.6% (11/13), respectively.

Patients who Underwent Surveillance

Patients with Suspected Lobular Endocervical Glandular Hyperplasia

Of 71 patients who did not select immediate hysterectomy, 14 and 5 underwent punch biopsy and conization, respectively. Eventually, 69 patients were followed up for more than 6 months (Figure 2, online supplementary Table 1), except for one (Table 3) who underwent hysterectomy 3 months after the initial diagnosis because of increasing lesion size. The clinical findings of all patients were observed every 3–12 months and the mean follow-up period was
Of the 69 patients in this category, 24 showed no change in lesion size on MRI, 19 showed an increase, and 14 showed a decrease. Of the 14 patients with a decreased lesion, 8 (57.1%) had this size reduction after menopause. Of the 69 patients under surveillance, 12 eventually underwent hysterectomy after follow-up for the reasons listed in Table 3. The mean duration of follow-up was 57.1 (range 3–154) months.

Histologically, one had minimal deviation adenocarcinoma, two had lobular endocervical glandular hyperplasia with atypia, and the remainder had lobular endocervical glandular hyperplasia. It is noteworthy that the malignant change in one patient occurred after 5 years of follow-up. Accordingly, the rate of minimal deviation adenocarcinoma or lobular endocervical glandular hyperplasia with atypia was 4.3% (3/69), and the rate of malignant change was 1.4% (1/69). Regarding the reasons for hysterectomy, 10 had suspected malignancy due to enlargement or deteriorating cytology and two were due to other diseases (atypical endometrial hyperplasia and adenomyosis) (Table 3). All 12 patients who underwent hysterectomy showed a cosmos pattern on MRI. Four patients also showed new findings suggestive of malignancy during follow-up.

### Table 1

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>MRI findings</th>
<th>Cytology</th>
<th>‘Yellow/orange’ mucin</th>
<th>HIK1083 test</th>
<th>Cervical biopsy/ conization</th>
<th>Mode of surgery</th>
<th>Pathological diagnosis</th>
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<tbody>
<tr>
<td>1</td>
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<td>LRH, BSO, PLN</td>
<td>GAS</td>
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<td>+</td>
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<td>RH, BSO, PLN</td>
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<td>GAS, MDA</td>
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<td>MDA</td>
</tr>
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<td>RH, BSO, PLN</td>
<td>GAS, MDA, LEGH with atypia, LEGH</td>
</tr>
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<td>TAH, BSO</td>
<td>GAS, AIS, LEGH with atypia, LEGH</td>
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<td>RH, BSO, PLN</td>
<td>GAS, MDA, LEGH</td>
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<td>Adenocarcinoma/adenocarcinoma LEGH</td>
<td>TAH, BSO</td>
<td>GAS, LEGH</td>
</tr>
<tr>
<td>9</td>
<td>41</td>
<td>SP</td>
<td>AGC-FN</td>
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<td>+</td>
<td>Adenocarcinoma/NA</td>
<td>RH, BSO, PLN</td>
<td>GAS, UEA</td>
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<td>RH, BSO, PLN</td>
<td>Serous carcinoma, LEGH</td>
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<td>SP, IP</td>
<td>NILM</td>
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<td>–</td>
<td>Normal/NA</td>
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<td>AGC-FN</td>
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<td>TAH</td>
<td>LEGH with atypia</td>
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<td>IP</td>
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<td>+</td>
<td>LEGH with atypia/NA</td>
<td>TAH</td>
<td>LEGH with atypia</td>
</tr>
<tr>
<td>14</td>
<td>42</td>
<td>CP</td>
<td>AGC-FN</td>
<td>+</td>
<td>+</td>
<td>Normal/LEGH with atypia</td>
<td>TLH</td>
<td>LEGH with atypia</td>
</tr>
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<td>15</td>
<td>47</td>
<td>MP</td>
<td>NILM</td>
<td>–</td>
<td>NA</td>
<td>NA/NA</td>
<td>RH, BSO, PLN</td>
<td>LEGH</td>
</tr>
</tbody>
</table>

AGC-FN, atypical glandular cells-favor neoplastic; AGC-NOS, atypical glandular cells-not otherwise specified; AIS, adenocarcinoma in situ; BSO, bilateral salpingo-oophorectomy; CP, cosmos pattern; GAS, gastric-type mucinous carcinoma; IP, invasion pattern; LEGH, lobular endocervical glandular hyperplasia; LRH, laparoscopic radical hysterectomy; MDA, minimal deviation adenocarcinoma; MP, microcystic pattern; MRI, magnetic resonance imaging; NA, not available; NILM, negative for intraepithelial lesion or malignancy; PAN, para-aortic lymphadenectomy; PLN, pelvic lymphadenectomy; RH, radical hysterectomy; SP, solid pattern; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; UEA, usual-type endocervical adenocarcinoma.

64.6 (range 3–154) months. Of the 69 patients in this category, 24 showed no change in lesion size on MRI, 19 showed an increase, and 14 showed a decrease. Of the 14 patients with a decreased lesion, 8 (57.1%) had this size reduction after menopause.

Of the 69 patients under surveillance, 12 eventually underwent hysterectomy after follow-up for the reasons listed in Table 3. The mean duration of follow-up was 57.1 (range 3–154) months. Histologically, one had minimal deviation adenocarcinoma, two had lobular endocervical glandular hyperplasia with atypia, and the remainder had lobular endocervical glandular hyperplasia. It is noteworthy that the malignant change in one patient occurred after 5 years of follow-up. Accordingly, the rate of minimal deviation adenocarcinoma or lobular endocervical glandular hyperplasia with atypia was 4.3% (3/69), and the rate of malignant change was 1.4% (1/69). Regarding the reasons for hysterectomy, 10 had suspected malignancy due to enlargement or deteriorating cytology and two were due to other diseases (atypical endometrial hyperplasia and adenomyosis) (Table 3). All 12 patients who underwent hysterectomy showed a cosmos pattern on MRI. Four patients also showed new findings suggestive of malignancy during follow-up.
endocervical glandular hyperplasia in two. Gastric-minimal deviation adenocarcinoma in one (Table 3) and lobular neoplastic, and the histological diagnoses of three patients were change, and 17 showed an increase in size. MRI was not available patients showed a decrease in lesion size on MRI, 9 showed no period was 52.4 (range 7–151) months. Of the 66 patients, 8 showed an increased lesion size. The average lesion enlargement rate of these patients was 91.2%±44.9% (range+38.1 to +148%), (p=0.01). Receiver operating characteristic analysis was performed to test the specificity and sensitivity of the two groups. The cut-off value of the growth rate was 38.1% (84.6% sensitivity and 100% specificity) and the area under the curve was 0.923 (95% confidence interval 0.821).

The three patients who developed minimal deviation adenocarcinoma were positive in all follow-up patients. The three patients who developed minimal deviation adenocarcinoma or lobular endocervical glandular hyperplasia with atypia showed an increased lesion size. The average lesion enlargement rate of these patients was 91.2%±44.9% (range+38.1 to +148%), whereas of those pathologically (nine cases) or clinically (48 cases) diagnosed with lobular endocervical glandular hyperplasia was −1.8±41.0% (range −61.5 to +148%), (p=0.01). Receiver operating characteristic analysis was performed to test the specificity and sensitivity of the two groups. The cut-off value of the growth rate was 38.1% (84.6% sensitivity and 100% specificity) and the area under the curve was 0.923 (95% confidence interval 0.821).

Patients with Suspected Nabothian Cysts
Sixty-six patients with this category underwent regular follow-up (Figure 2, online supplementary Table 1). The mean follow-up period was 52.4 (range 7–151) months. Of the 66 patients, 8 patients showed a decrease in lesion size on MRI, 9 showed no change, and 17 showed an increase in size. MRI was not available in 32 patients. No cytologic change was noted in any of the patients in this category.

### DISCUSSION

Gastric-type mucinous carcinoma of the cervix shows gastric-type differentiation, and minimal deviation adenocarcinoma is defined as its well differentiated variant. These carcinomas were reported to be associated with aggressive behavior, chemotherapy resistance, and poor prognosis. However, clinical symptoms and morphological findings of these carcinomas were similar to those of lobular endocervical glandular hyperplasia. In those, the number of patients undergoing follow-up is also sharply increasing, especially in young women. Therefore, precise and early detection of its malignant change is extremely important. To address this issue, we focused on two clinical parameters indicative of its malignant change: lesion enlargement and worsening cytology. Accordingly, we detected three suspected lobular endocervical glandular hyperplasia with atypia cells in early stages.

The results of this study demonstrated that the rate of malignant change of clinical lobular endocervical glandular hyperplasia was 1.4%, which is lower than previously considered. To our knowledge, this is the first report on the frequency of its malignant change. We recently reported that there was no driver gene mutation in four cases of non-atypical lobular endocervical glandular hyperplasia, suggesting its metaplastic nature. This result of genetic analysis may be consistent with the present data. In comparison with our
Table 3  Summary of 12 patients with suspected lobular endocervical glandular hyperplasia who underwent hysterectomy after follow-up

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>Reason for operation</th>
<th>MRI findings</th>
<th>Growth rate (%)</th>
<th>Cytology</th>
<th>‘Yellow/orange’ mucin</th>
<th>HIK1083 test</th>
<th>Cervical biopsy / conization</th>
<th>Mode of surgery</th>
<th>Pathological diagnosis, stage</th>
<th>F/U period (months)</th>
<th>State at last F/U</th>
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<tbody>
<tr>
<td>29</td>
<td>50</td>
<td>s/o malig</td>
<td>Increased size, worsening cytology</td>
<td>CP</td>
<td>38.1</td>
<td>AGC-NOS → AGC-FN</td>
<td>+</td>
<td>+</td>
<td>s/o Adenocarcinoma/MDA</td>
<td>RH, BSO, PLN, OM</td>
<td>MDA, IIB</td>
<td>58</td>
</tr>
<tr>
<td>30</td>
<td>55</td>
<td>s/o malig</td>
<td>Increased size</td>
<td>CP</td>
<td>87.5</td>
<td>AGC-NOS</td>
<td>+</td>
<td>+</td>
<td>NA/NA</td>
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<td>LEGH with atypia</td>
<td>3</td>
</tr>
<tr>
<td>31</td>
<td>33</td>
<td>s/o malig</td>
<td>Increased size</td>
<td>CP</td>
<td>148</td>
<td>NILM → AGC-NOS</td>
<td>- → +</td>
<td>- → +</td>
<td>NA/LEGH with atypia</td>
<td>TAH, BSO</td>
<td>LEGH with atypia</td>
<td>154</td>
</tr>
<tr>
<td>32</td>
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<td>s/o malig</td>
<td>Increased size, DR</td>
<td>CP</td>
<td>29.1</td>
<td>AGC-NOS</td>
<td>+</td>
<td>+</td>
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<td>TAH, BSO</td>
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<td>AGC-NOS</td>
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<td>Increased size, DR, worsening cytology</td>
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<td>NA/NA</td>
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*Atypical endometrial hyperplasia.
†Adenomyosis.

AGC-FN, atypical glandular cells-favor neoplastic; AGC-NOS, atypical glandular cells-not otherwise specified; BSO, bilateral salpingo-oophorectomy; ca, carcinoma; CP, cosmos pattern; DR, diffusion restriction; F/U, follow-up; IP, invasion pattern; LEGH, lobular endocervical glandular hyperplasia; MDA, minimal deviation adenocarcinoma; MRI, magnetic resonance image; NA, not available; NED, no evidence of disease; NILM, negative for intraepithelial lesion or malignancy; No malig, no malignancy; OM, omentectomy; OvCa, ovarian cancer; PLN, pelvic lymphadenectomy; RH, radical hysterectiony; s/LEGH, suspected lobular endocervical glandular hyperplasia; s/o Adenocarcinoma, suspicious of adenocarcinoma; s/o malig, suspicious of malignancy; SP, solid pattern; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy.
previous articles, the diagnostic accuracy of the present series was similar. In addition, a strength of our study was the identification of the malignant transformation ratio of suspected lobular endocervical glandular hyperplasia during follow-up (1.4%, 1/69).

In this study, lobular endocervical glandular hyperplasia with atypia was detected in two patients with suspected disease during follow-up (Table 3). Lesion enlargement was observed in both patients, but worsening cytology was not detected. Interestingly, one patient in this category was found to have minimal deviation adenocarcinoma (Table 3) and showed both lesion enlargement and worsening cytology (from atypical glandular cells—not otherwise specified to atypical glandular cells-favor neoplastic). This is consistent with a previous report. The present study suggests the importance of cytologic change rather than size change. However, it should be noted that two lobular endocervical glandular hyperplasia cases also showed worsening cytology, and some may be associated with an increase in size and worsening cytology, suggesting that the detection of worsening cytology in association with increased lesion size does not necessarily indicate the presence of malignancy.

Of 13 patients with suspected lobular endocervical glandular hyperplasia who underwent an immediate hysterectomy, four were associated with malignant/premalignant lesions (Table 2). The rate of association with malignant/premalignant lesions was high in this series (30.1%, 4/13). However, the reason for immediate surgery in four patients was these malignant/premalignant lesions pathologically diagnosed before the operation instead of cervical multi-cystic lesions incidentally detected.

MRI is regarded as a useful tool in the diagnosis of multi-cystic lesions of the uterine cervix. In our study, we defined an increase in size >20% as a 'size increase'. Although the number of patients with cancer was limited, the receiver operating characteristic analysis revealed that an increased lesion size of 38.1% or more may be closely associated with the onset of malignant transformation. There was a significant difference in the growth rate between typical lobular endocervical glandular hyperplasia and atypia or minimal deviation adenocarcinoma. Interestingly, this study revealed that 57.1% (8/14) of patients with suspected lobular endocervical glandular hyperplasia showed a reduced lesion size after menopause. Lobular endocervical glandular hyperplasia has been reported to harbor estrogen receptor positive spindle cells in the stroma, thus decreased serum levels of estrogen may be involved in the size reduction. There were two patients (Table 3) with suspected malignancy due to diffusion restriction on MRI indicated by a high signal intensity on diffusion weighted imaging and decreased intensity on the apparent diffusion coefficient map. However, these patients were diagnosed with lobular endocervical glandular hyperplasia and not cancer. Previous studies reported that no diffusion restriction was observed in malignant tumors associated with lobular endocervical glandular hyperplasia, possibly due to the low cell density and low viscosity of intra-tumor mucins. In contrast, a study reported that diffusion restriction is important in the diagnosis of malignant tumors, and another reported that malignant tumors associated with lobular endocervical glandular hyperplasia exhibited diffusion restriction. In the present study, we could not deny the possibility of malignancy because of the presence of diffusion restriction. Further research is needed to evaluate the diagnostic potential of MRI in the detection of malignancy, especially those cases containing abundant mucin. It is not practical to follow women with suspected lobular endocervical glandular hyperplasia with periodic MRI. In addition, the positive predictive value of MRI alone for detecting malignancy is not high. Moreover, in the patient who later developed minimal deviation adenocarcinoma, cytology rather than MRI was effective in finding malignancy.

In conclusion, an increase in tumor size and worsening cytological findings are important parameters for detecting potentially malignant lobular endocervical glandular hyperplasia during follow-up. Furthermore, the frequency of malignant transformation of this lesion was small. Therefore, conservative management is an option for patients with this disease. Further research is needed to clarify the natural history, rate of malignant transformation, and useful clinical markers of malignant change.

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