

## Note

### Correlation between cervical thickness and histological severity of cervical intraepithelial neoplasia: A transvaginal ultrasound investigation

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Cervical cancer, with estimated incidences of >0.6 million worldwide, is considered as one among the top 10 cancers. As an affordable technique, ultrasonography is commonly used in gynecologic patient management. However, detection of cervical cancer at early stage, particularly cervical intraepithelial neoplasia (CIN) is difficult to be diagnosed directly on ultrasound. In this context, here, we looked on the possible correlation between the thickness of the cervix and the grade of cervical intraepithelial neoplasia (CIN) for diagnosis purpose. We measured the cervical thickness in 120 women with abnormal cervical cancer screening tests by transvaginal ultrasound examination (TVUS) in the mid-sagittal plane. All of the women had at least one biopsy. The cervical thickness calculated in each CIN grade and the receiver operating characteristic (ROC) curves were used to determine the best cut-off value of the cervical thickness to predicted CIN2 or higher (CIN2+, including CIN2 and CIN3). The ROC curve is produced by calculating and plotting the true positive rate against the false positive rate for a single classifier at a variety of thresholds. For example, in logistic regression, the threshold would be the predicted probability of an observation belonging to the positive class. Cervical thickness increased with histological severity, with a Spearman correlation coefficient of 0.549 ( $P < 0.001$ ). The mean cervical thicknesses were 21.5 mm for cervicitis ( $n=60$ ), 22.8 mm for CIN1 ( $n=20$ ), 24.9 mm for CIN2 ( $n=20$ ), 25.6 mm for CIN3 ( $n=20$ ). The area under the ROC curve was 0.827 for the detection of CIN2+. The best cut-off value for predicting CIN2+ was 23.6 mm (sensitivity=75.0%, specificity=81.2%). Cervical thickness was statistically significantly thicker in the CIN2+ grades than in cervicitis and CIN1 grade, possibly demonstrating the potential clinical use of ultrasound examination for evaluating women with abnormal cervical screening tests. Further studies are indicated.

**Keywords:** Adenocarcinoma, Adenosquamous carcinoma, Cervical cancer

Cervical cancer is a type of cancer that occurs in the cells of the cervix, which is the lower part of the uterus that connects to the vagina. The cervix plays a crucial role in the reproductive system, allowing the

passage of menstrual blood from the uterus into the vagina and serving as the channel for sperm to enter the uterus during sexual intercourse. There are two main types of cervical cancer, squamous cell carcinoma (SCC) which is most common accounting for about 70-90% of cases; and adenocarcinoma (AC) which develops in the glandular cells of the cervix that produce mucus and it accounts for 10-25% of cervical cancers. The SSC originates in the flat, thin cells (squamous cells) that line the outer surface of the cervix. In some cases, cervical cancers can be a mix of both squamous cell carcinoma and adenocarcinoma, known as adenosquamous carcinoma. Cervical cancer is the leading gynecologic cancer worldwide, with approximately 600,000 new cases and more than 340,000 deaths occurring annually<sup>1</sup>. However, most of these cases occur in low- and middle-income countries (LMICs), including China<sup>2</sup>. Nepal, Myanmar and Kyrgyzstan rank top in cervical cancer<sup>2</sup>.

Ultrasonography (US) or ultrasound is a non-invasive imaging technique that uses high-frequency sound waves to create images of the internal structures of the body. It plays a crucial role in the diagnosis and evaluation of cervical cancer, aiding in differentiation and characterization of abnormal findings. In the context of cervical cancer, ultrasonography is used to identify and locate tumor masses within the cervix or surrounding structures, and characterize the nature of the tumor, such as its size, shape, and consistency. It also helps in assessing the extent of tumor invasion into nearby structures, such as the parametrium (tissues adjacent to the cervix) and the bladder, and further evaluate the presence of enlarged or abnormal lymph nodes in the pelvic region. During procedures such as biopsies or drainage of fluid collections, ultrasound can be used to guide the placement of needles or catheters with precision. Ultrasonography is valuable for monitoring the response to treatment, such as radiation therapy or chemotherapy. While ultrasonography is a useful imaging tool, it is often complemented by other imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) for a more comprehensive assessment. The choice of imaging technique depends on factors such as the

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availability of resources, the specific clinical scenario, and the need for detailed anatomical information.

Ultrasonography is currently involved in nearly all steps of gynecologic patient management worldwide due to its low cost, and it is often the first method used to detect gynecologic neoplasms<sup>3,4</sup>. Research on cervical cancer mainly focuses on aspects such as disease detection, accurate assessment of tumor stage and volume, and early estimation of treatment planning and follow-up<sup>5-9</sup>. Detection of cervical cancer at early stage is difficult<sup>3</sup>, and cervical intraepithelial neoplasia (CIN) is almost impossible to be diagnosed directly on ultrasound if no measurable tumor can be found. However, we noticed that the cervical volume in some cervical cancer patients seems significantly larger than normal, and therefore hypothesized that the thickness of the cervix increases with the histological severity of CIN. Here, we studied the relationship between the histological grade at diagnosis of CIN and the thickness of the cervix on transvaginal ultrasound (TVUS) to see whether these parameters are correlated.

**Materials and Methods**

**Patient selection**

Cervical thickness measurements were obtained from 120 women between February 2018 and December 2021. All women participated in this study voluntarily and provided written informed consent. The inclusion criteria for the women were as follows: liquid-based cytology (i.e., ThinPrep cytologic test, TCT) screening abnormal and/or High-risk human papillomavirus (Hr-HPV) testing positive; compliance with colposcopy criteria after evaluation by

gynecologists; nonpostmenopausal; aged 20 years or older, not pregnant or breastfeeding; no history of treatment for CIN or hysterectomy; and no malignant disease. The exclusion criteria for the women were as follows: cervical myoma, cervical cyst (which may cause localized enlargement of the cervix) and adenomyosis (which may cause diffuse enlargement of the uterus, including the cervix).

**Ultrasound techniques**

In this study, all of the cervical thickness measurements were performed by a single ultrasonographer with ten years of experience in ultrasound. TVUS was performed with a 3-11 MHz frequency transducer using a Mindray Resona8S ultrasound machine, and all patients were examined in supine position with a full bladder. First, the sonographer performed a routine evaluation of the uterus, ovaries and adnexa. Second, the sonographer took measurements of the cervical thickness following a standardized protocol (Fig. 1) developed by two ultrasonographers with gentle compression. In the mid-sagittal plane view, when the external os and internal os were connected to the cervical axis, the ultrasound image was captured, and the measurement was performed with a caliper at the midpoint of the cervical length perpendicular to the cervical axis. The outcome of interest, cervical thickness, was defined as the distance between the two hyperechoic lines demarcating the cervix (i.e., the external border of the cervical stroma). A minimum of three measurements were performed for this variable, and the average was used to determine the cervical thickness. The data were stored for subsequent analysis.

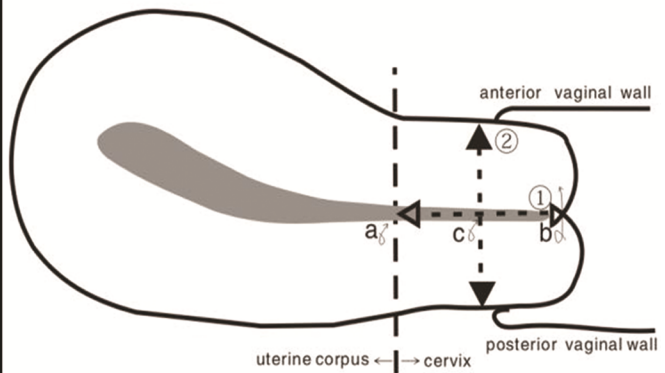
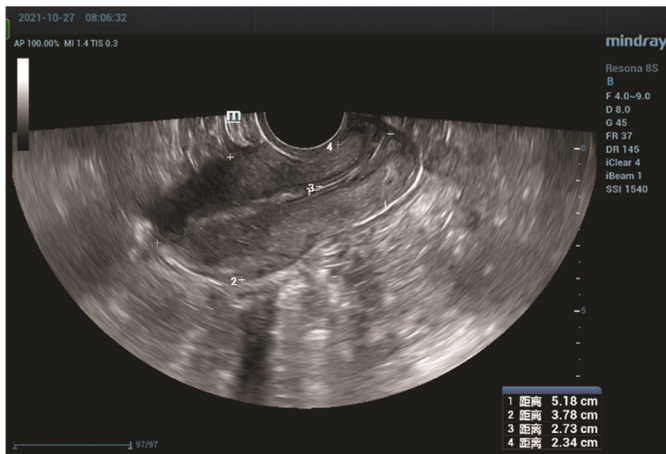


Fig. 1 — Measurement of cervical thickness on a transvaginal ultrasound image. Measurements obtained in the mid-sagittal plane along the axis of the cervix are shown. Point a: the internal os; point b: the external os; point c: the midpoint of the cervical canal; distance 1 (hallow arrow): the cervical length; distance 2 (solid arrow): the cervical thickness

### Colposcopy criteria

In our study, the cervical screening methods used include TCT and Hr-HPV testing. HPV testing detects 14 high-risk types, including types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (i.e., HPV16/18 and 12 other Hr-HPV types). The HPV results were reported independently of both the cytology and histopathology results. The TCT results were classified as negative for intraepithelial lesion or malignancy (NILM); atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesion (LSIL); high-grade squamous intraepithelial lesion (HSIL); atypical glandular cells (AGC) or ASCs that cannot exclude HSIL (ASC-H). The same cytologists who routinely interpret the histology tests from our hospital analyzed the TCT slides at the centre.

Diagnostic colposcopy was performed with standard procedures according to national guidelines. Women meeting any of the following criteria were referred for colposcopy: HPV16/18+ (i.e., positive for HPV16, HPV18 or both); positive for the other 12 Hr-HPV types with ASCUS or higher grade (i.e.,  $\geq$ ASCUS, including ASCUS, LSIL, HSIL, AGC and ASC-H); persistently positive for any of the other 12 Hr-HPV types (i.e., HPV testing remained positive after 6 months); and positive cytology for  $\geq$ ASCUS.

The same colposcopist examined all women referred for colposcopy and assessed the results of the screening tests. All suspicious areas were biopsied. Intraepithelial neoplasias were graded as cervicitis, CIN1, CIN2, CIN3 or cancer. Nearly all patients with histologically confirmed CIN2 or CIN3 lesions were treated by the loop electrosurgical excision procedure (LEEP), and patients with CIN1 lesions were followed up colposcopically. We considered the most severe diagnosis in our analysis, including those determined from punch biopsies and excisional biopsies.

The participants, clinicians, colposcopist and pathologists were blinded to the US results of the cervical thickness measurements but not to the cytology and HPV testing results.

### Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences software (SPSS version 19.0, IBM corp., New York, NY, USA). Correlations between the cervical thickness measurements and the histologically confirmed CIN grades were analyzed using the Spearman correlation

coefficient. Analysis of variance (ANOVA) was used for multigroup comparison of the mean cervical thickness, followed by the least significant difference (LSD) test for group-by-group comparisons. Then, we calculated the overall number of patients with CIN grade 2 or higher, and receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of the cervical thickness predicting CIN2 or higher. The optimal diagnostic cut-off value was identified according to the Youden index.

### Results and Discussion

A total of 120 women were ultimately eligible for analysis. The baseline characteristics are shown in Table 1. The mean age was 40.6 (range, 20-55) years, and the average time from ultrasound examination to biopsy in this study was 40.3 days. There were no significant difference in age, gestation, parturition, conventional ultrasound data such as Intrauterine device (IUD), normal proportion of uterine corpus in the different CIN grade groups. However, there were significant differences in the distribution of Hr-HPV results and TCT results among four different CIN grade groups. All of the patients had at least one punch biopsy. Of these, 19 patients with CIN2 and 18 patients with CIN3 were treated by LEEP; 2 patients with CIN3 underwent LEEP and hysterectomy.

The cervical thickness consistently increased from cervicitis to CIN3 lesions (Fig. 2). The mean cervical

Table 1 — Demographic characteristics of patients in different grades

|                         | Cervicitis<br>(n=60) | CIN1<br>(n=20) | CIN2<br>(n=20) | CIN3<br>(n=20) | p-<br>value |
|-------------------------|----------------------|----------------|----------------|----------------|-------------|
| Age                     | 39.4±8.6             | 42.2±9.8       | 40.4±6.8       | 43.0±7.3       | 0.306       |
| Gestation               | 2.3±1.3              | 2.6±1.4        | 2.5±1.1        | 2.6±1.1        | 0.871       |
| Parturition             | 1.2±0.5              | 1.3±0.6        | 1.2±0.4        | 1.4±0.5        | 0.676       |
| TCT                     |                      |                |                |                | 0.001       |
| NILM                    | 33 (55.0)            | 9 (45.0)       | 7 (35.0)       | 2 (10.0)       |             |
| $\geq$ ASCUS            | 13 (21.7)            | 10 (50.0)      | 10 (50.0)      | 11 (55.0)      |             |
| None                    | 14 (23.3)            | 1 (5.0)        | 3 (15.0)       | 7 (35.0)       |             |
| Hr-HPV                  |                      |                |                |                | 0.006       |
| HPV 16/18+              | 8 (13.3)             | 1 (5.0)        | 9 (45.0)       | 10 (50.0)      |             |
| 12 other HPV<br>types + | 24 (40.0)            | 9 (45.0)       | 7 (35.0)       | 3 (15.0)       |             |
| Negative                | 11 (18.3)            | 3 (15.0)       | 2 (10.0)       | 2 (10.0)       |             |
| None                    | 17 (28.3)            | 7 (35.0)       | 2 (10.0)       | 5 (25.0)       |             |
| IU device               |                      |                |                |                | 0.682       |
| Yes                     | 17 (28.3)            | 8 (40.0)       | 8 (40.0)       | 7 (35.0)       |             |
| None                    | 43 (71.7)            | 12 (60.0)      | 12 (60.0)      | 13 (65.0)      |             |
| Uterine corpus          |                      |                |                |                | 0.343       |
| Normal                  | 31 (51.7)            | 11 (55.0)      | 6 (30.0)       | 10 (50.0)      |             |
| Abnormal                | 29 (48.3)            | 9 (45.0)       | 14 (70.0)      | 10 (50.0)      |             |

[Results are presented as the mean (SD) or n (%).  $\geq$ ASCUS including ASCUS, LSIL, HSIL, AGC ASC-H]

thicknesses were 21.5 mm in 60 patients with cervicitis, 22.8 mm in 20 patients with CIN1, 24.9 mm in 20 patients with CIN2, 25.6 mm in 20 patients with CIN3. The Spearman correlation coefficient was 0.549 ( $P < 0.0001$ ). Additional cervical thickness comparisons based on disease grade were performed. The increased cervical thickness was statistically significant for CIN1 vs. CIN2 and CIN1 vs. CIN3 lesions ( $p=0.016$ ,  $0.001$ ). No differences in cervical thickness were found for cervicitis vs. CIN1 and CIN2 vs. CIN3 ( $p=0.053$ ,  $0.371$ ).

Figure 3 shows the diagnostic performance of the cervical thickness assessed using an ROC curve. The AUROC for the detection of CIN2+ lesions was 0.827 (95% confidence interval [CI]: 0.751-0.903). According to the Youden index, the best cut-off value for predicting

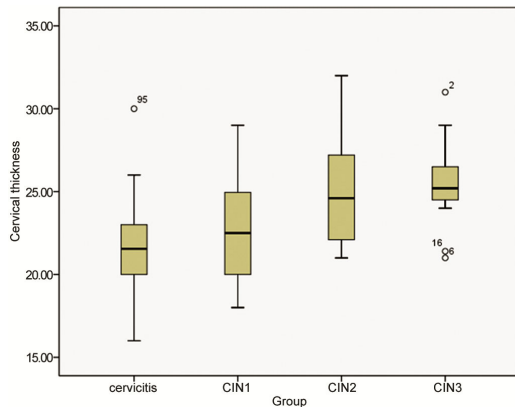


Fig. 2 — Box-and whisker plots of cervical thickness in patients with cervicitis, CIN1, CIN2 and CIN3. Group-by-group comparisons showed that  $p=0.053$  for cervicitis vs CIN1;  $p<0.001$  both for cervicitis vs CIN2 and for no CIN vs CIN3;  $p=0.016$  for CIN1 vs CIN2;  $p=0.001$  for CIN1 vs CIN3; and  $p=0.371$  for CIN2 vs CIN3

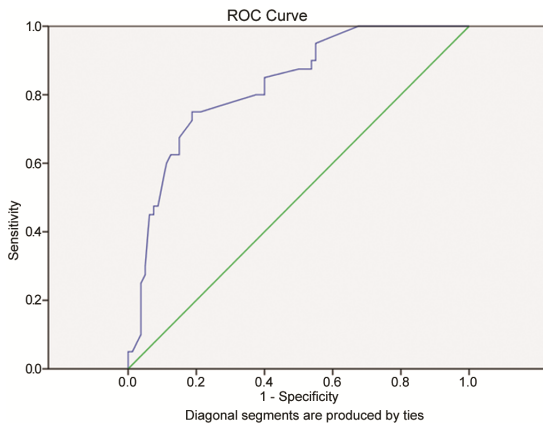


Fig. 3 — The diagnostic performance for predicting CIN2+ (i.e., CIN2 and CIN3) of the cervical thickness assessed using a receiver operating characteristic (ROC) curve. Area under the curve (AUC)= 0.827 (95% confidence interval [CI]: 0.751-0.903)

CIN2 or higher lesions was 23.6 mm (sensitivity 75%, specificity 81.2%, Youden index 0.562).

The key observation of our study was that the thickness of the cervix increased with increasing CIN grades on TVUS, which is the most common method of evaluating pelvic symptoms. To the best of our knowledge, our study is the first assessment of the correlation between cervical thickness and CIN grade. A thicker cervix was shown to be associated with progression to CIN2+ for patients with abnormal cervical screening tests, suggesting that cervical thickness may be a marker of progression.

We selected the middle cervical segment for thickness measurements for the following reasons. First and most importantly, this location is easy to visualize. Second, anatomy dictates that the cervix is roughly cylindrical, and the vaginal part of the cervix usually originates from the lower 1/3 to 1/2 of the cervix; thus, measurement is more difficult if the measured point is too low, which would interfere with identification of the cervix boundary.

HPV infection is recognized as an important cause of cervical cancer or precancerous lesions. HPV infection is very common in the population, but many HPV infections are transient and can spontaneously regress over 1~2 years<sup>10,11</sup>; persistent infection is the real cause of cervical lesions. However, because of a lack of pain and the anatomical location of the cervix, most people cannot feel the infection, regardless of whether it is transient or persistent.

Generally, ultrasound is considered unable to detect CIN directly, and literature reports on ultrasound and CIN were rare. In one study, three-dimensional power Doppler ultrasound (3D-PDU) was used to study cervical cancer and precancerous lesions and found that the vascularization index (VI), flow index (FI) and vascularization flow index (VFI) were significantly higher in women with precancerous lesions than in women with normal cervix and lower than in women with cervical cancer<sup>12</sup>. In another study<sup>13</sup>, contrasting 3D-PDU and immunohistochemistry (IHC) revealed that the vascularization index (VI) correlated with microvessel density. Furthermore, Belfort-Mattos *et al.*<sup>14</sup> showed that compared to CIN1, vascular endothelial growth factor (VEGF) immunoexpression levels were more diffuse in CIN2 and CIN3 lesions, which could promote vascular proliferation. In addition, Guillaud *et al.*<sup>15</sup> showed an increase in cell proliferation with progression through dysplastic

stages. We speculate that persistent infection with HPV, increased expression of VEGF, vascular proliferation and cell proliferation are the reasons why we can observe cervical thickening in CIN2+ grade. In this study, we noticed that the positive distribution of Hr-HPV subtypes at different CIN grades were inconsistent, which may also be one of the reasons for the difference of cervical thickness because the pathogenicity of different subtypes of Hr-HPV is not the same. Notably, the correlation assessed here was analyzed only in women with abnormal cervical screening tests and biopsy specimens and not in the general population.

The recommended screening methods are cytology and high-risk human papillomavirus (Hr-HPV) DNA testing<sup>16</sup>. However, cervical cytology has limited reproducibility and sensitivity; therefore, many repeated screenings are needed during a patient's lifetime to achieve programmatic sensitivity; Hr-HPV DNA testing is more sensitive and allows a long rescreening interval for women who test negative, but it lacks specificity and cannot discriminate between common transient infection and persistent infection<sup>17,18</sup>. Moreover, the cost of the basic tools is high, and the coverage of these two effective screening methods is low, as these methods are inaccessible by millions of women living in resource-poor areas. In China, screening for cervical cancer is still more opportunistic<sup>19</sup>.

In addition, HPV positivity is higher in women younger than 35 years<sup>20,21</sup>, which could lead to substantial over-diagnosis of CIN2 or higher lesions<sup>22</sup>, especially when Hr-HPV+ women within this age group are directly referred for colposcopy without further triage testing. Recently, multiple biomarkers with increased disease specificity for detecting high-grade CIN have been recognized; these biomarkers include Ki-67, p53, p16, and methylation markers which provide both high specificity and high sensitivity<sup>23-28</sup>. However, some molecular testing technology even requires sophisticated laboratory infrastructure.

Therefore, predicting outcomes for patients with abnormal screenings tests remains a complex challenge. In our study, we focused on the thickness of the cervix, adding one measurement step to the routine assessment (the thickness of the cervix is not measured on routine US), which is simple and easy to perform, does not increase patient discomfort, has no extra cost, and showed that cervical thickness

was statistically significantly thicker in the CIN2+ grades than in cervicitis and CIN1 grade, suggesting that ultrasound measurement of cervical thickness is likely to be clinically useful, while clinical examination has limitations in determining this parameter.

One limitation of our study is that the original histological classification of the cervical lesions was not reviewed. However, all classifications were performed by institutional pathology center with the same standard, and we observed that using the original diagnosis closely agrees with the treatment guidelines. A study by Kitchener *et al.*<sup>29</sup> suggested that rapid review is unlikely to be useful. In addition, we did not want to interfere with clinical management. Further, we considered only one variable without considering other parameters, such as the menstrual cycle. Moreover, the total sample size is also not large; therefore, further study in detail is required.

## Conclusion

The above results indicate that the cervical thickness may be a useful predictor of cervical precancerous lesions. Our findings suggest the possibility of ultrasound examination for Patients with abnormalities detected during cervical screening and expand the application of ultrasound in gynecology.

## Conflict of interest

Authors declare no competing interests.

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