EJGO European Journal of Gynaecological Oncology

Original Research

The effect of different cervical transformation zone types on the colposcopic diagnosis of cervical intraepithelial neoplasia

Aiping Fan[1], Chen Wang[1], Liqin Zhang[1], Ye Yan[1], Yingmei Wang[1], Cha Han[1], Fengxia Xue[1]

[1]*Department of Gynecology and Obstetrics, Tianjin Medical University General Hospital, Tianjin (China)*

Summary

Purpose: To analyze the effects of cervical transformation zone (TZ) on the colposcopic diagnosis of cervical intraepithelial neoplasia (CIN). *Materials and Methods:* The authors retrospectively evaluated 482 patients who underwent conizaion between September 2012 and September 2016. The cytology, colposcopic impressions and histological diagnoses from biopsy and cone specimens were compared. *Results:* An agreement of 88.1% was observed between high-grade cytology and final histological diagnoses among the three TZ types. Significant differences between the colposcopic impressions and final histological diagnoses were observed for TZ types 1 and 2 *vs.* type 3. The overall agreement was 89.1% regarding the histology findings on colposcopically directed biopsy (CDB) and cone specimens, which correlated significantly with TZ ($p = 0.004$) and the number of cervical biopsies ($p = 0.032$). The agreement between histology results on endocervical curettage (ECC) and the final histology results was 28.24% in the patients with TZ type 3. *Conclusions:* Cervical TZ types variably influence colposcopically diagnostic accuracy for CIN, and TZ type 3 was associated with the lowest accuracy.

Key words: Cervical intraepithelial neoplasia; Colposcopically directed biopsy; Colposcopy; Squamous intraepithelial lesions of the cervix; Transformation zone.

Introduction

World Health Organization reported that cervical cancer is the fourth most frequent cancer in women, with an estimated 530,000 new cases in 2012 representing 7.9% of all female cancers. Given the widespread implementation of cervical cancer screening, colposcopy has become a complementary method for identifying cervical intraepithelial neoplasia (CIN) and early cervical cancer. As a colposcopic diagnosis can directly affect the implementation of subsequent treatment for CIN, colposcopists must carefully ensure the accuracy of a colposcopic diagnosis of CIN. However, the subjective nature of colposcopic image interpretation makes it very important to identify the cervical transformation zone (TZ) type during colposcopy.

In addition, the 2011 version of the International Federation for Cervical Pathology and Colposcopy terminology confirmed the obligatory nature of the cervical TZ classification terminology [1]. In this context, TZ type 1 is located entirely on the ectocervix, TZ type 2 involves the endocervical canal, whereas the squamocolumnar junction (SCJ) remains visible, and TZ type 3 indicates endocervical involvement without a fully visible SCJ. The lesion appearances vary according to cervical TZ type, which might directly affect the accuracy of a colposcopic diagnosis of CIN. The present study evaluated data from patients who underwent cervical TZ excision because of CIN or microinvasive carcinoma (MIC) at the present center between September 2012 and September 2016. The effects of the different cervical TZ types on the colposcopic diagnosis of CIN were evaluated.

Materials and Methods

This retrospective cohort review included 506 patients from the present center who underwent cervical TZ excision after a cervical biopsy revealed low-grade squamous intraepithelial lesion (LSIL) or higher-grade disease between September 2012 and September 2016. The exclusion criteria were previous cervical treatment (cryosurgery, microwave, laser, or conization treatment), pregnancy, or clinical suspected cervical cancer that was visible to the naked eye. After excluding 24 cases, the authors retrospectively collected data for 482 cases from the hospital's archived database. This study did not influence the patients' diagnoses or treatments. The need for informed consent was waived by the ethics review board of the General Hospital of Tianjin Medical University. This study was approved by the institutional review board at this hospital (Ethical. NO. IRB2017-YX-007).

At this center, all colposcopies were performed by two colposcopists who had worked in this field for more than five years, and had received American Society for Colposcopy and Cervical Pathology (ASCCP) colposcopic training. They were experienced examiners. They did detailed colposcopic description. All visible lesions were classified according to the 2011 International Federation for Cervical Pathology and Colposcopy terminology. During colposcopy, the examiner performed colposcopically directed biopsies (CDBs) in the most serious lesions using cervical biopsy forceps with 5- to 6-mm jaws, yielding 3- to 4-mm biopsies. Conizations were performed using either cold knife conization or the loop electrosurgical excision procedure. All biopsy specimens

Revised manuscript accepted for publication August 8, 2017

were formalin fixed, paraffin embedded, and cut into four 4-µm-thick serial sections. Cone specimens were formalin fixed, paraffin embedded, and processed sagittally in 2-mm-thick sections. Slides with a thickness of 4 mm were cut at intervals of 250 µm and stained using haematoxylin and eosin. After examining all specimens, an experienced pathologist made a histopathological diagnosis according to the 2012 Lower Anogenital Squamous Terminology. In uncertain cases immunohistochemical stains were performed with labeling index for Ki67 to evaluate the proliferative activity, and for p16 protein expression to determine the different degrees of CIN. A pathology slide review was not performed for the present study.

Because the biopsy may had already completely removed the higher grade dysplasia, cone histology results would thus have been lower than biopsy results. All results in which the biopsy histology result was the same grade as or higher than that of the cone specimen were interpreted as being consistent. On the contrary, all results in which the biopsy histology result was lower than that of the cone specimen were interpreted as being inconsistent.

Regarding cervical cytology, cervical assessment was done by liquid-based Pap test. A positive result was defined as the presence of atypical squamous cells of uncertain significance (ASCUS), atypical squamous cells but cannot exclude a high-grade squamous intraepithelial lesion, LSIL, high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells, and invasive cervical cancer.

All data were analyzed using SPSS software (version 20.0). Statistical analyses were performed using the χ^2 test, Fisher's exact probability test, or a one-way analysis of variance as appropriate. Differences with p-values of < 0.05 were considered statistically significant.

Results

The present study included 482 patients who underwent conization. The median age was 42.7 (range, 18–73) years. Detailed patient characteristics and relevant clinical findings are shown in Table 1.

In this study, 36 cases with normal cytology received further colposcopy and cervical biopsy because of positive HPV 16/18 infection. Nine cases with no dysplasia and/or LSIL on CDB received diagnostic conization because of pathology discrepancies (persistent HSIL cytology and normal and/ or LSIL on CDB). Ten cases with LSIL on CDB were treated mainly because of persistent postcoital bleeding and repeated abnormal cytology such as ASCUS and/or LSIL cytology.

Little difference was found in the distribution of TZ type classification between examiners ($\chi^2 = 0.552$, $p = 0.759$). In women younger than 30 years, 16 cases were classified as type 1 TZ, 12 cases as type 2 TZ, and three cases as type 3 TZ. In those aged 30~50 years, 94 cases were classified as type 1 TZ, 205 cases as type 2 TZ, and 44 cases as type 3 TZ. In those aged 50 years or older, 14 cases were classified as type 1 TZ, 53 cases as type 2 TZ, and 41 cases as type 3 TZ. The distribution of TZ types in each age group was also similar between examiners (in women younger than 30 years, $\chi^2 = 0.195$, $p = 0.907$; in those aged 30~50 years, $\chi^2 = 2.017$, $p = 0.365$; in those aged 50 years or older, $\chi^2 = 3.808$, $p = 0.149$).

Table 1. — *Patient characteristics and relevant clinical findings.*

Characteristics and clinical findings	n.	%
Age (years)	482	
< 30	31	6.4
30–49	343	71.2
≥50	108	22.4
Menopausal status	482	
Premenopausal	397	84.4
Postmenopausal	85	15.6
Transformation zone types		
1 type	124	25.7
2 type	270	47.6
3 type	88	18.3
Cytology	450	
Normal	36	8.0
ASCUS	82	18.2
LSIL	121	26.9
ASC-H	22	4.9
HSIL	185	41.1
AGC	4	0.9
Histology (biopsy)	479	
No dysplasia	2	0.4
LSIL	17	3.5
HSIL	445	92.9
MIC/ invasive carcinoma	15	3.1
Histology (ECC)	116	
No dysplasia	70	60.3
LSIL	2	1.7
HSIL	36	31.0
MIC/carcinoma	3	2.6
Specimens can not be evaluated	5	4.3
Histology (conization)	482	
No dysplasia	19	3.9
LSIL	66	13.7
HSIL	374	77.6
MIC/carcinoma	23	4.8

TZ: transformation zone; ASCUS: atypical squamous cells of uncertain significance; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; MIC: micro-invasive cervical cancer.

The 124 patients with TZ type 1 had an average age of 37.7 years, the 270 patients with TZ type 2 had an average age of 42.8 years, and the 88 patients with TZ type 3 had an average age of 47.9 years. There was a statistically significant difference in ages according to TZ type (F = 30.416, p <0.001); 5.6% of patients with TZ type 1 was postmenopausal, 14.8% of patients with TZ type 2 was postmenopausal, and 43.2% of patients with TZ type 3 was postmenopausal ($p < 0.001$).

Colposcopic findings were divided into HSIL or LSIL/normal changes during the colposcopy. The group with high-grade colposcopic changes included 84 patients with TZ type 1, 189 patients with TZ type 2, and 54 patients with TZ type 3. The group with low-grade/normal colposcopic changes included 40 patients with TZ type 1, 81 patients with TZ type 2, and 34 patients with TZ type 3.

The overall agreement between the colposcopic impres-

Table 2. — *Agreement between the colposcopy impressions and final histological results from the three cervical TZ types.*

Type of TZ	Colposcopy impression	Final histological results				Agreement rate (%)
		Total	HSIL	LSIL/ normal	MIC/invasive cancer	
T1	HSIL	84	78	0	6	67.7%
	LSIL/normal	40	33	6	1	
T2	HSIL	189	179	0	10	68.5%
	LSIL/normal	81	75	6	0	
T3	HSIL	54	40	1	13	50.0%
	LSIL/normal	34	31	3	0	

T1 vs. T2: χ^2 = 0.277, p = 0.599; T1 vs. T3: χ^2 = 7.637, p = 0.006; T2 vs. T3: χ^2 = 11.086, p = 0.001. LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; MIC: micro-invasive cervical cancer; TZ: transformation zone.

Table 3. — *Agreement between the histological results of the biopsy and the results after conization.*

Indicators	n	Concordant	Discordant	Accuracy	χ^2	*p*
≤ 2 biopsies	131	110	21	84.0%	4.989	0.032
≥ 3 biopsies	348	317	31	91.1%		
Type of TZ						
1	124	118	6	95.2%	11.214	0.004
2	270	241	29	89.3%		
3	88	71	17	80.7%		
Examiner						
1	246	223	23	90.7%	1.081	0.308
2	236	207	29	87.7%		

TZ: transformation zone.

sions and the final histological diagnoses differed by TZ type. The concordance rates were 67.7% (84/124) among patients with TZ type 1, 68.5% (185/270) among patients with TZ type 2, and 48.9% (43/88) among patients with TZ type 3 (χ^2 = 13.924, p = 0.001). No significant difference was detected when we compared types 1 *vs.* 2 (χ^2 = 0.277, p = 0.599). However, significant differences were detected when the authors compared types 1 *vs.* 3 (χ^2 = 7.637, p = 0.006) and types 2 *vs.* 3 (χ^2 = 11.086, p = 0.001) (Table 2).

CDB was carried out in a total of 479 patients, and three patients were only examined with endocervical curettage (ECC). The authors observed an agreement of 89.1% (427/479) regarding the CIN findings when we compared the CDB and cone specimens although the disease severity was underestimated in 4.6% of the cases (22/479) (Table 3). The final histological diagnoses included HSIL for 438 patients and MIC for 30 patients.

The agreement between the final results and the biopsy results correlated significantly with the TZ (p = 0.004) (Table 3). The highest correlation of 95.2% was found in the patients with TZ type 1; the lowest correlation was in the patients with TZ type 3, only reaching 80.7%. The patients with TZ type 3 had an average age of 47.9 years and were most likely to be postmenopausal (p < 0.001).

The correlation between histology results and the number of biopsies taken was also compared. Two or less biopsies were taken in 131 cases; three or more biopsies were taken in 348 cases. The accuracy was higher when three or more biopsies were obtained compared to the results for two or less biopsies (91.1% and 84.0%; p = 0.032) (Table 3).

The study also looked at the impact of the experience of the examiners who carried out the colposcopy and found no significant difference in accuracy of CDB between examiners(p = 0.05) (Table 3).

ECC was carried out in all the patients with TZ type 3. For three patients, the specimens obtained could not be evaluated. In the patients with TZ 3 type, the agreement between histology results on ECC and the final histology results was 28.2%. Although only three patients were examined with ECC, the histology results on ECC were consistent with the final histology results.

A total of 450 patients underwent cervical cytological examinations. The results revealed 185 cases of HSIL. The cases with HSIL cytology included 45 cases with TZ type 1, 99 cases with TZ type 2, and 41 cases with TZ type 3. The overall agreement between HSIL cytology and the final histological diagnosis was 88.1% (163/185). There was non-significant overall agreement between the high-grade cytology findings and final histological diagnoses for the three cervical TZ types (χ^2 = 5.088, p = 0.079).

Discussion

The special anatomical characteristics of the cervix allow clinicians to perform direct clinical examinations and CDB. Although CDB is widely used, concerns regarding the accuracy of colposcopy-directed punch biopsies for HSIL diagnosis are increasing. For example, previous reports [2] have revealed unexpectedly low sensitivities of colposcopy and CDB, thus raising considerable concerns regarding the possibility of missing a CIN2+. In addition, a Norwegian study [3] of 520 women with negative CDB results revealed that 78 women (23.8%) were found to have CIN2+ during the six-month follow-up period after their biopsy.

The present study revealed several differences between the histological results from the CDB and corresponding cone specimen. In this context, a previous study [4] revealed an agreement rate of only 51.6% between the maximum CIN grades from guided cervical biopsies and the corresponding cone specimens. Furthermore, underestimation occurred in 46.7% of the cases, whereas overestimation occurred in only 1.6%. However, other studies [5, 6] reported a high agreement (85.8% and 89.6%) between biopsy and conization results. The present study also revealed a high agreement rate (89.1%) between the histological results from the CDB and corresponding cone specimen. However, among the 19 cases with LSIL/normal findings based on the CDB, 26.3% had HSIL based on cone specimens. Moreover, among the 445 cases with HSIL findings based on the CDB, 3.37% (15/445) had MIC.

These findings highlight the risk related to false-negative biopsies by colposcopy.

Identifying the TZ is an essential step in colposcopy. The present study revealed varied agreement between the colposcopic impressions and the final histological diagnoses according to the three TZ types. Although the difference was not statistically significant when the authors compared types 1 *vs.* 2, they observed significant differences when they compared types 1 and 2 *vs.* 3. These findings indicate that the accuracy of colposcopic diagnosis varies according to the cervical TZ type, and that this accuracy was significantly lower for TZ type 3 (*vs.* types 1 and 2). This result is likely associated with the incomplete visualization of the lesions in cases with TZ type 3. Furthermore, the present study also revealed that the agreement between the final results and the biopsy results correlated significantly with the TZ, and the lowest correlation was in the patients with TZ type 3, only reaching 80.7%. The patients with TZ type 3 had an average age of 47.9 years and were most likely to be postmenopausal. This finding further suggests that the accuracy of a CDB-based histological diagnosis is highest for women with TZ types 1 and 2. Moreover, CIN lesions in TZ type 3 extend deeper into the endocervical canal, and the inability to clearly visualize these lesions might increase the difficulty of colposcopy and decrease the accuracy of a cervical biopsy. These factors likely contributed to the higher numbers of missed diagnoses based on CDB among the TZ type 3 cases, suggesting that CDB is more valuable for evaluating cases with TZ types 1 and 2.

Furtado *et al.* [7] reported that colposcopy has a low sensitivity for the diagnosis of cervical MIC (23%), and suspected microinvasion was observed in 14.5% of cases with unsatisfactory colposcopy and 8.6% of cases with satisfactory colposcopy. A recent Chinese study [8] also revealed that CDB has a sensitivity of 4.4% (6/135) for diagnosing MIC, and was therefore inadequate for diagnosing this condition when used alone. In the present study, 30 cases were finally histologically diagnosed as MIC, although 15 cases had been originally diagnosed with HSIL based on the CDB specimens. Thus, the sensitivity of CDB for diagnosing cervical MIC was 50.0% (15/30), and underestimation of MIC occurred in 50.0% (15/30). Among the 15 underestimated cases, 13 cases had TZ type 2 or 3, suggesting that the CIN lesions extended relatively deep into the endocervical canal and thus might have influenced the missed diagnoses.

The relative inexperience of colposcopists appears to also have a negative effect on the accuracy of CDB. The present study revealed that little difference was found in the distribution of TZ type classification between examiners and the agreement between biopsy findings and conization results does not appear to depend on the examiner's experience ($p = 0.308$). Vallikad E *et al.* [9] reported that the inter-observer agreement for the TZ type classification was moderate (Kappa = 0.53 to 0.66). However, another study [10] reported that examiners with less experience (one to two years) had similar rates of correlation between histological findings to those of examiners with moderate (three to five years) or examiners with extensive experience (more than five years).

Although all CDBs in the present study were performed by experienced colposcopists, biopsy specimens were only collected from the most severe suspicious lesions. Other studies [11, 12] revealed that increasing the number of biopsies could increase the sensitivity of colposcopic diagnosis and detection of histologic HSIL, regardless of the operator's skill or patient characteristic. The present study revealed that taking three or more biopsies was found to result in a significantly better correlation compared to two or less biopsies. In addition, Nakamura *et al.* [13] proposed that ECC be performed for special populations, such as women referred after the detection of low-grade cytology, those with an invisible SCJ (TZ type 3), or those older than 40 years. The present study also revealed statistically significant differences between age and TZ type distributions, with TZ type 3 being more common among older women (average age: 47.9 years). Similar findings were revealed in a prospective multicenter study by Luyten *et al.* [14] who reported that TZ type 3 was most commonly reported among women older than 50 years (70%). These results suggest that the SCJ may be invisible in perimenopausal women (approximately 50-years-old), and that CIN lesions may extend into the endocervical canal. Therefore, ECC may be useful in this subset of patients.

As an ancillary diagnostic technique to colposcopically directed biopsy, ECC is of questionable value on the diagnosis of CIN. Müller *et al.* [10] revealed that an agreement (49.1%) between ECC (results for ECC are the same or higher) and the final histology results. In the present study, ECC was carried out in all the patients with TZ type 3. However, an agreement between histology results on ECC and final histology was only 28.2%. In contrast to CDB, ECC has only a limited role in the routine diagnosis of CIN. However, Solomon *et al.* [15] reported, in women aged 40 and older, the sensitivity of colposcopic biopsy decreased and the sensitivity of ECC increased. Thus, ECC may be useful in older women undergoing colposcopy for equivocal or mildly abnormal cytology. In the present study, although only three patients with TZ 3 type were examined with ECC independently of biopsy, the histology results on ECC were consistent with the final histology results.

The present study also revealed that the overall agreement between HSIL cytology and the final histological diagnosis was good (88.1%). As colposcopy appears to be inadequate for patients with TZ type 3, cytology should be combined with ECC to ensure correct final diagnoses, especially in patients with HSIL cytology.

However, the missed diagnoses might also be related to the invisibility of early-stage cervical cancer during col-

poscopy, the presence of multifocal lesions, the inability to target abnormal areas using biopsy forceps, the inability of punch to provide comprehensive lesion specimens, the small size, and superficial nature of biopsy specimens. Furthermore, the 2016 Colposcopy and Programme Management guidelines from the National Health Service Cervical Screening Publications [16] indicate that care must be taken to not overlook invasive disease. An excisional form of biopsy is recommended to remove the entire endocervical lesion in most cases meeting the following criteria: (1) when most of the ectocervix is replaced with a high-grade abnormality, (2) when a low-grade colposcopic change is associated with high-grade dyskaryosis (severe) or worse disease, and (3) when the lesion extends into the endocervical canal. Punch biopsies are not considered reliable in those circumstances, and it is possible that the colposcopy procedures in the present study missed the MIC/carcinoma lesions, thus highlighting the importance of cervical TZ in the colposcopic diagnosis of CIN.

The present study had several limitations. Firstly, the design was retrospective, and enrolment bias may have occurred; however, this study defined histological references using conization results. Secondly, biopsy specimens were only taken from suspicious lesions, and normal control biopsy specimens were lacking.

Many factors might affect the accuracy of CDB for CIN diagnosis. During colposcopy, in addition to considering patient age, cytology, and HPV results, it is important to carefully observe the cervical TZ type, combined with abnormal colposcopic findings to determine the scope of cervical biopsy. Furthermore, especially in cases with TZ type 3, CIN lesions may extend into the endocervical canal; if indicated, here ECC or even an diagnostic excisional form of biopsy may be recommended to avoid misdiagnosis. However, few studies have evaluated the relevance of cervical TZ types, and further prospective studies are needed.

Acknowledgements

The authors thank Dr. Tao Shi of Department of Pathology for Tianjin Medical University General Hospital for his help in the data collection.

This study was supported by the National Natural Science Foundation of China (No. 81471419).

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Corresponding Author:
CHA HAN, M.D., PHD.
Department of Gynecology and Obstetrics
Tianjin Medical University General Hospital
No. 154, Anshan Road, He Ping District
Tianjin 300052 (China)
e-mail: 2608750667@qq.com