Is Cervical Punch Biopsy Enough for the Management of Low-Grade Cervical Intraepithelial Neoplasia?

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■ **Abstract**

Objective. This study aimed to analyze the correlation between the histopathologic results of excisional procedure and cervical punch biopsy and to investigate the accuracy rates of colposcopic punch biopsy and cervical cytology to detect cervical intraepithelial neoplasia (CIN) grade 2 and/or more severe lesions (CIN 2+).

Materials and Methods. Two hundred six patients who underwent excisional procedure in the gynecologic oncology clinic of the Zeynep Kamil Women and Children Diseases Education and Research Hospital between 2004 and 2011 were enrolled in a retrospective study.

Results. The correlation between the pathologic findings gained by excisional procedure and punch biopsy was weak ($p = .0001$, $\kappa = 0.03$). The overall concordance rate between the pathologic findings of cervical biopsy and excisional procedure was 57.29%. The rates of detecting more severe lesions by excisional procedure when compared to biopsies (biopsy underestimation) were 71.42%, 22.91%, 37.03%, and 12.72% for biopsy results with negative, CIN 1, CIN 2, and CIN 3/adenocarcinoma in situ lesions, respectively. Similarly, the rates of less severe lesions diagnosed by excisional procedure when compared to biopsies (biopsy overestimation) were 29.16%, 40.74%, and 15.45% for biopsy results with CIN 1, CIN 2, and CIN 3/adenocarcinoma in situ lesions, respectively. The rate of CIN 2+ lesions after excisional procedure in cases with previous biopsy results with either negative or CIN 1 was 27.27%.

Conclusions. Our results suggested that colposcopy-directed biopsy was neither a good diagnostic nor a reliable management method. We think that the indications of conization should be enlarged to avoid overlooking high-grade lesions. ■

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Cervical cancer can often be prevented through a program of screening and treatment of its precursor lesions. However, no screening or treatment modality is perfect, and unfortunately, invasive cervical cancer can develop even in women who participate in such programs [1]. Smear-based screening seems to have very serious adverse effects. The efficacy of the Pap test is hampered by high interobserver variability and high false-negative and false-positive rates that range between 20% to 30% and 5% to 70%, respectively [2,3].

Management of patients with cervical intraepithelial neoplasia (CIN) lesions is defined according to guidelines. Excisional methods such as cold-knife conization and loop electrosurgical excision procedure (LEEP) were used to provide a tissue specimen for pathologic examination and to treat CIN lesions by removing the affected tissue. However, there is a fact that the histopathologic results of either biopsy or excisional methods can be discordant to each other. There are "downgrading" and "upgrading" differences between those 2 histology results. Recent large-scale trials have questioned the accuracy of colposcopic biopsy [4–6]. Conization has been accepted as the best diagnostic and therapeutic procedure [7]. The management of the premalignant lesions of the uterine cervix can be affected in such cases, i.e., some of the patients can be overtreated while some others can be lost without treatment.

In this retrospective study, we aimed to analyze the correlation between the histopathologic results of excisional procedure, cervical punch biopsy, and cervical cytology. The accuracy rates of cervical cytology and

colposcopic punch biopsy in CIN grade 2 and/or more severe (CIN 2+) lesions confirmed by excisional procedure were also aimed to be investigated.

MATERIALS AND METHODS

A total of 244 patients underwent excisional procedure by cold knife conization or LEEP in the gynecologic oncology clinic of the Zeynep Kamil Women and Children Diseases Education and Research Hospital between the years of 2004 and 2011. Patients whose colposcopic biopsies had been performed in another hospital were not included in the study. Only patients (n = 206) with known results of Pap smear and who underwent colposcopic biopsies and excisional procedures in our hospital were enrolled in the present retrospective study. Loop electrosurgical excision procedure without previous biopsy was preferred to perform an approach consisting of both evaluation and treatment in the same sitting for 14 patients. Therefore, the correlation between the histopathologic results of excisional procedure and cervical punch biopsy could only be evaluated in 192 women. Cytologic findings were compared with the most severe histopathologic end results of both cervical punch and excisional procedures for the evaluation of the correlation between the cervical smear and pathologic findings. Patients' data were discussed retroactively from conization to cytology instead of from cytology to conization.

Loop electrosurgical excision procedure was preferred according to patients' characteristics such as age, parity, desire for childbearing, previous cytology results, and treatment histories. All histopathologic examinations of punch biopsies and postoperative excisional materials were analyzed by the gynecopathologist at our hospital. Cytology results were either reported by the pathology department of our hospital or came from external centers. The patients' data were collected by chart review. The study was reviewed by the local ethics committee.

The 2001 Bethesda System terminology was used for cytologic classification [8]. All biopsies were taken with a cervical punch biopsy tool. Cervical biopsies were taken either from colposcopically abnormal areas (181 patients) or randomly from 4 cervical quadrants if there was no obvious abnormality as well as in the presence of inadequate colposcopic results (11 patients). Routine endocervical curettage was performed to all patients. There was no pregnant woman in the study group.

The histologic diagnosis was deemed normal (absence of atypia), CIN grade 1 (CIN 1), CIN grade 2 (CIN 2), CIN grade 3 (CIN 3), adenocarcinoma in situ (AIS), squamous cell carcinoma, and adenocarcinoma. When more than 1 different cytologic or pathologic diagnosis had been reported, the most severe one was considered as the main diagnosis. The terms low- and high-grade lesions were used for CIN 1 and CIN 2+ lesions, respectively.

The indications of excisional procedures after cervical punch biopsy in the study were as follows; CIN 2+ lesions in biopsy (137 patients), discordance between cytology and biopsy results, i.e., high-grade smear/low-grade biopsy (17 patients), and either patient's preference due to fear of cancer and unwillingness to be followed up without treatment or physician's clinical suspect (38 patients).

Statistical analysis was performed with SPSS version 11.0 (SPSS, Chicago, IL) by using descriptive statistical methods. The correlation between histopathologic findings of punch biopsy and excisional procedures was assessed by kappa statistics (κ). In addition, accuracy was used to measure how correct a cervical biopsy with CIN 2+ lesion had identified and excluded a CIN 2+ lesion at excisional procedures and how correct a high-grade smear had identified and excluded a CIN 2+ histopathology.

RESULTS

The mean (SD) age of the patients in the study group was 38.62 (7.42) years (range = 20–58 y). The mean (SD) ages of the patients were 40.03 (6.21), 39.11 (7.4), 36.86 (7.3), 37.72 (6.23), and 42.5 (8.54) years for patients who had normal, CIN 1, CIN 2, CIN 3, and cervical cancer diagnosis according to pathology results of excisional procedures, respectively. The correlation between the pathologic findings gained by excisional procedure and punch biopsy was weak (p = 0.0001, κ = 0.03). The overall one-to-one concordance between the pathologic findings of biopsy and excisional procedure was 57.29%. The rates of detecting a more severe lesion by excisional procedure than gained by biopsies (biopsy underestimation) were 71.42%, 22.91%, 37.03%, and 12.72% for biopsy results with normal, CIN 1, CIN 2, and CIN 3/AIS lesions, respectively. Similarly, the rates of a less severe lesion detected by excisional procedure than gained by biopsies (biopsy overestimation) were 29.16%, 40.74%, and 15.45% for biopsy results with CIN 1, CIN 2, and CIN 3/AIS lesions, respectively. The rate of detecting a CIN 2+ lesion after excisional procedure in cases with biopsy results with either normal or CIN 1 was 27.27% (15/55). The rate of detecting a CIN 2+ lesion after excisional procedure in cases with biopsy results with CIN 2+ lesion was 83.21% (114/137). The

Table 1. Histopathologic Comparisons of the Cervical Punch Biopsy and Excisional Procedure

		Excisional procedure						
		Normal	CIN 1	CIN 2	CIN 3	AIS	SCC	Total
Biopsy	Normal, *n* (%)	2 (28.5)	1 (14.2)	2 (28.5)	2 (28.5)	—	—	7
	CIN 1, *n* (%)	14 (29.1)	23 (47.9)	1 (2.1)	10 (20.8)	—	—	48
	CIN 2, *n* (%)	5 (18.5)	6 (22.2)	6 (22.2)	10 (37.0)	—	—	27
	CIN 3/AIS, *n* (%)	4 (3.6)	8 (7.2)	5 (4.5)	78 (70.9)	1 (0.9)	14 (12.7)	110
	Absence, *n* (%)	6 (42.8)	4 (28.5)	1 (7.1)	3 (21.4)	—	—	14

CIN 1 indicates cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3; AIS, adenocarcinoma in situ; SCC, squamous cell carcinoma.

accuracy rate of a cervical biopsy with CIN 2+ lesion to identify and exclude a CIN 2+ lesion at excisional procedures was 80.20%. The histopathologic comparisons of the cervical punch biopsy and excisional procedure have been listed in Table 1.

When the smear results of all patients in the study group were evaluated, low-grade or normal smear results were detected in 41.26% (85/206) of the patients who had undergone excisional procedure. The rate of detecting a CIN 2+ lesion either by biopsy or excisional procedures after high-grade cytopathology was 87.50% (105/120). The accuracy rate of a high-grade cytopathology to detect a real CIN 2+ lesion was 68.29%. Of 133 patients with high-grade lesions in excisional procedure, 41 (30.82%) had low-grade or normal cytologic results. Of 14 patients with cervical cancer diagnosed at excisional procedure, 2 (14.28%) had low-grade smear results. The smear results of patients who had undergone excisional procedure have been listed in Table 2.

The distribution of rates of indications for excisional procedures was 66.50%, 19.79%, 8.25%, and 6.79% for CIN 2+ lesions at biopsy, patients' or physician's preference despite low-grade biopsy results, discordance between cytology and biopsy results, and direct excision without biopsy, respectively. Of the 137 patients with CIN 2+ lesions according to biopsy results, 94 (68.61%) had high-grade and 42 (30.65%) had low-grade smear results. Excisional procedure was carried out in 38 patients despite low-grade smear and biopsy results due to patients' or physician's preference, which resulted in the detection of CIN 2+ lesions in 6 patients (5 CIN 3 and 1 CIN 2). None of these 6 patients had previous CIN history. Both biopsy and smear interventions could not detect the existing high-grade lesions in 15.78% (6/38) of the patients. The comparison of biopsy and smear results has been listed in Table 3.

DISCUSSION

The incidence and mortality of cervical cancer has dropped by a large extent [9,10]. There seems to be little overdiagnosis in cervical cancer screening [11]. The most important problem in the management of abnormal cytology is the management of low-grade smear abnormality. If all patients with low-grade smears are referred for colposcopy and biopsies, it may be possible

Table 2. Correlation Between Histopathologic Results of Excisional Procedure and Cytopathology

		Excisional procedure				
		Normal, *n* (%)	CIN 1, *n* (%)	CIN 2, *n* (%)	CIN 3/AIS, *n* (%)	SCC, *n* (%)
Pap smear	Normal	—	4 (9.52)	1 (6.66)	2 (1.92)	—
	ASC-US	11 (35.48)	7 (16.66)	2 (13.33)	12 (11.53)	1 (7.14)
	ASC-H	1 (3.22)	5 (11.90)	1 (6.66)	13 (12.5)	3 (21.42)
	LSIL	8 (25.80)	14 (33.33)	6 (40)	16 (15.38)	1 (7.14)
	HSIL	11 (35.48)	11 (26.19)	5 (33.33)	56 (53.84)	9 (64.28)
	AIS	—	—	—	1 (0.96)	—
	AGC	—	1 (2.38)	—	2 (1.92)	—
	SCC	—	—	—	1 (0.96)	—
	Inadequate	—	—	—	1 (0.96)	—
	Total	31	42	15	104	14

CIN 1 indicates cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells cannot exclude HSIL; AGC, atypical glandular cell; SCC, squamous cell carcinoma.

Table 3. Comparison of Cervical Punch Biopsy and Pap Smear Results of the Patients

		Biopsy					
		Normal, *n* (%)	CIN 1, *n* (%)	CIN 2, *n* (%)	CIN 3/AIS, *n* (%)	SCC, *n* (%)	Absence
Pap smear	Normal	1 (14.28)	3 (6.25)	1 (3.70)	2 (1.81)	—	—
	ASCUS	1 (14.28)	15 (31.25)	4 (14.81)	12 (10.90)	—	1
	ASC-H	—	4 (8.33)	4 (14.81)	15 (13.63)	—	—
	LSIL	1 (14.28)	17 (35.41)	10 (37.03)	13 (11.81)	—	4
	HSIL	4 (57.14)	9 (18.75)	8 (29.62)	62 (56.36)	—	9
	AIS	—	—	—	1 (0.90)	—	—
	AGC	—	—	—	3 (2.72)	—	—
	SCC	—	—	—	1 (0.90)	—	—
	Inadequate	—	—	—	1 (0.90)	—	—
	Total	7	48	27	110	—	14

CIN 1 indicates cervical intraepithelial neoplasia grade 1; CIN 2, cervical intraepithelial neoplasia grade 2; CIN 3, cervical intraepithelial neoplasia grade 3; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ASC-H, atypical squamous cells cannot exclude HSIL; AGC, atypical glandular cell; SCC, squamous cell carcinoma.

to overrun the colposcopy clinics, and many patients will be overtreated or experience undue stress as if they might develop cervical cancer [12]. The diagnosis is usually provided by colposcopically directed biopsy. Different factors can be taken into account to plan a reasonable treatment. These include the patient's age, parity and further desire for fertility, menstrual status, general health, immune status, and availability for follow-up and return visit.

Traditionally after colposcopy, punch biopsies were taken from the cervix, and the patients were sent home to return in the future for their treatment. This may result in a loss of up to 25% of the patients [13]. That is why "one step see and treat" method was preferred in some patients.

The overall concordance was 57.29% between the histologic results of colposcopic biopsy and excisional procedure. The rate was low but similar to other studies [14,15]. High concordance rate, with 85.8% of overall concordance rate, was given in the study of Duesing et al. [5], and a possible explanation for the high accuracy rate was attributed to the monocentric design corresponding with highly educated colposcopists and the number of biopsies taken per patient. In the present study, however, colposcopy and biopsy had been carried out both by highly qualified and by inexperienced staff since our hospital is a teaching one. Although this might be the cause of the low concordance rate in the present study, it was a good indicator of the routine practice carried out in nonspecialized centers, too. In addition, studies have also shown that a higher level of experience did not improve colposcopic performance [16].

The rates of biopsy underestimation were 22.91% for CIN 1, 37.03% for CIN 2, and 12.72% for CIN 3/AIS lesions diagnosed by biopsies. Similar to our study, the rates of overall underestimation of CIN 3/AIS and CIN 2–3/AIS were 66% and 57% , respectively, in the analysis gained from the placebo arm of the Gardasil clinical trials [14]. The estimated sensitivity of colposcopy for the detection of CIN 3 has ranged from 54% to 85% as documented in a meta-analysis of studies from 1960 to 1996 [17]. All these results showed us that biopsy solely was neither a good diagnostic nor a reliable management method.

In our study, the accuracy rate of detecting CIN 2+ lesion with excisional procedure after biopsy result with CIN 2+ lesion was 80.20%. Either normal or CIN 1 biopsy results were detected in 11.27% (15/133) of patients with CIN 2+ lesions according to excisional procedure. The rate of CIN 2+ lesions according to conization despite normal and CIN 1 lesions in biopsy was 27.27% (15/55), which demonstrated that 27.27% of the patients with low-grade biopsy could have been skipped if only biopsy results would have been taken into account. The rate of patients with no high-grade pathology in both smear and biopsy results despite CIN 2+ lesion detected in excisional procedure was 15.78% (6/38). Therefore, we can speculate to enlarge the indication of excisional procedure in a selected group of patients who had no desire for future fertility to decrease those failure rates. Because high-grade lesions detected by excisional procedures are mostly concordant to high-grade biopsy results, there is no debate in the management of patients with high-grade lesions detected by biopsy. The real problem is the probability of missing a really high-grade lesion in a patient with a low-grade lesion according to biopsy. Accuracy of the biopsy results was better for high-grade rather than for low-grade

lesions as also reported by Boonlikit et al. [15] and Duesing et al. [5] previously.

In our study, the rate of detecting a CIN 2+ lesion either by biopsy or by excisional procedures after high-grade cytopathology was 87.50% (105/120). The accuracy rate of detecting CIN 2+ lesion by high-grade cytopathology was 68.29%. Of 133 patients with high-grade lesions according to excisional procedure, 41 (30.82%) had low-grade or normal cytologic results previously. Of the 14 patients in whom cervical squamous cell cancer was diagnosed, 2 (14.28%) had smear results with low-grade cytology. In the light of these findings, high-grade smear is a good tool for guidance. Direct conization may be a treatment modality (see and treat) in appropriate patients. However, low-grade smear is disputable and doubtful to rely on. Of 155 patients with CIN 2+ lesions diagnosed either by biopsy or by excisional procedure, 17 (10.96%) had atypical squamous cells of undetermined significance (ASC-US) cytopathology. Direct colposcopic biopsy or human papillomavirus (HPV) subgroup typing rather than triage can be used in the management of ASC-US smear results. In populations in which routine smear screening programs cannot be carried out, the smear repeat 4 to 6 months after the previous ASC-US cytopathology for the triage, which is 1 arm of the triage, has been weakened. The American Society of Colposcopy and Cervical Pathology consensus guidelines to triage women with ASC-US cervical Pap result with reflex high-risk HPV testing for further colposcopy and HPV triage have significantly reduced the number of women undergoing colposcopy from this category of lesion [18]. The reflex high-risk HPV testing has been an expensive method in our country. There is no widespread smear screening program in our country, yet. Besides, most of the patients in our study consisted of those who had applied to the outpatient gynecology clinic with reasons other than screening. We prefer colposcopic biopsy for all patients with an abnormal smear, including ASC-US, for the possibility of being lost to follow-up. However, colposcopic biopsy alone is not a highly reliable diagnostic method as demonstrated in the present and in other studies. Moreover, the rate of detecting a CIN 2+ lesion with an excisional procedure despite a previous diagnosis as CIN 1 according to biopsy was 22.91%, and the mean age of that group was 39.63 years (range = 32–56 y). Therefore, indications of excisional procedures for CIN 1 lesion should be enlarged to avoid overlooking high-grade lesions, or biopsy might be followed by a reflex high-risk HPV test. Absence of HPV subgroup typing was one of the deficient points of the present study.

The overall sensitivity of conventional cytology is from 50% to 75% for low-grade lesions and from 55% to 90% for high-grade lesions, while specificity varies from 80% for low-grade lesions to 96% for high-grade lesions [19,20]. High-risk HPV status evaluations and increasing the number of biopsy or molecular markers can improve the limitations of cervical cancer screening [14,17,21] but can increase the cost of screening and diagnosis. Therefore, we must individualize the patients when evaluating them for CIN lesions so as not to underestimate the high-grade lesions.

In conclusion, our results suggested that colposcopy-directed biopsy and cytology had limitations as a diagnostic tool. Both results must be evaluated in collaboration with clinical features of every patient individually. Data presented here were concordant with those of other studies in the literature. However, the real problem is the potential for underestimating really high-grade lesions. The American Society of Colposcopy and Cervical Pathology guideline recommends follow-up without treatment and cotesting at 1 year for the management of patients with CIN 1 or no lesion preceded by lesser abnormalities [22]. Since the compatibility of biopsies and excisional procedures is not 100% even in centers in which only 1 experienced colposcopist works, we think that the indications for excisional procedures should be enlarged, or a reflex high-risk HPV test can be proposed following a CIN 1 biopsy result, especially in patients who are older than 30 years to avoid overlooking high-grade lesions for the management of patients with CIN 1 biopsy results following low-grade cytology, instead of following up without treatment.

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