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Risk factors for residual disease after cervical conization in patients with cervical intraepithelial neoplasia grades 2 and 3 and positive surgical margins



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ABSTRACT

Objective: To evaluate risk factors for the persistence of cervical intraepithelial neoplasia (CIN) grade ≥ 2 following repeat surgical procedures in patients with CIN grades 2 and 3 and positive surgical margins. **Study design:** This study included patients with CIN grades 2 and 3 and positive surgical margins following loop electrosurgical excision procedures (LEEP), who had undergone additional surgery between 2007 and 2014. Factors associated with CIN grade ≥ 2 on biopsy results after the second operation were assessed by multiple logistic regression analysis. Factors considered included patient age, parity, menopausal status, smoking, referral cytology, initial LEEP pathology, time interval between LEEP and surgical procedures, presence of disease on endocervical sampling, endocervical surgical margins, glands, disease surrounding $\geq 50\%$ of the cervical circumference and requirement for multiple sweeps on initial LEEP to excise a lesion. The forward likelihood ratio method was used and significance was set at $p < 0.05$.

Results: Repeat surgical procedures were performed in 104 patients, 75 with CIN 2 and 29 with CIN 3, with 43 (41.3%) reported as normal or CIN 1. However, 57 (54.8%) patients had CIN ≥ 2 lesions and four (3.8%) had previously undiagnosed cervical cancer. Factors associated with CIN ≥ 2 lesions included requirement for multiple sweeps (vs. a single sweep; odds ratio [OR] 5.967; 95% confidence interval [CI] 2.183–16.311, $p < 0.001$) and involvement of $\geq 50\%$ of the cervical circumference (vs. $< 50\%$; OR 5.073; 95% CI 1.501–17.146, $p = 0.009$).

Conclusion: As lesions requiring multiple sweeps for excision and/or surrounding $\geq 50\%$ of the cervical circumference during initial conization are associated with recurrent CIN ≥ 2 lesions, attention should be paid during resection to prevent margin positivity. If surgical margins are positive, however, repeat surgical procedures should be considered in patients with CIN 2 and CIN 3 lesions and these risk factors.

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Introduction

Guidelines of the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the National Health Service Cervical Screening Programme (NHSCSP) recommend treatment of patients with cervical intraepithelial neoplasia (CIN) grade ≥ 2 [1,2]. Conization, however, may not completely excise these lesions, resulting in positive surgical margins. A study of 35,109

women with any grade CIN or invasive cancer found that 23% had positive surgical margins [3]. Positive surgical margin is the most important predictor of recurrence [4]. The risk of CIN grades 2 and 3 is higher in women with incomplete than complete excision of CIN (18% vs. 3%) [3].

Although American and European guidelines recommend repeat surgery for positive surgical margins following the excision of microinvasive cervical cancer [5–7], no consensus has yet been reached on further management of patients with positive surgical margins following removal of CIN 2 and CIN 3 lesions [1,2]. Management options for these patients range from follow up cytology and colposcopy to immediate conization and hysterectomy [1]. The NHSCSP recommends repeat excision only for patients aged > 50 years or if there is evidence of a glandular abnormality or invasive disease [2]. Periodic follow-up may increase recurrence

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rate and patient anxiety, as well as missing more severe underlying disease. Conversely, repeat surgery may result in complications and surgical morbidity. For example, repeat conization may reduce cervical stroma [8], leading to adverse obstetric outcomes in subsequent pregnancies, including pregnancy loss, preterm birth [8,9] and premature rupture of membranes [9,10].

To date, few studies have investigated predictors of residual disease in patients with positive surgical margins. The design of this study was methodologically different from that of other studies, as management options are clear for microinvasive cancer [5–7] and surgical treatment is not recommended for CIN 1 [1,11,12]. This study was therefore designed to assess factors associated with recurrence of CIN ≥ 2 lesions following repeat surgical procedures in CIN 2 and CIN 3 patients with positive surgical margins.

Materials and methods

Patients

The pathology records of patients who underwent loop electrosurgical excision procedures (LEEP) during the years 2007–2015 were retrospectively evaluated. The records of patients who underwent repeat procedures were reviewed, as were their initial LEEP reports. Pathology reports recording normal, CIN 1 and cervical cancer results were excluded. The involvement of surgical margins among pathology records reporting CIN 2 and CIN 3 lesions was carefully evaluated. Patients were included in the study if they had undergone a repeat operation for surgical margin positivity. Cytology and colposcopy were performed by expert colposcopists in our center; alternatively, patients with a known pathologic diagnosis were referred from other centers. The study protocol was approved by our institutional review board (IRB approval number: KA 15/307), which waived the requirement for informed consent due to the retrospective nature of the study.

Initial LEEP

All LEEPs were performed under colposcopic guidance by a single senior gynecologic oncologist with 40 years of experience. A 15–20 mm round loop electrode (Utah Medical Finesse II Electrosurgical Generator, Utah Medical Products, Inc, Midland, UT, USA) was used. The goal was to excise the complete transformation zone, including the visible cervical lesion and 10 mm \times 10 mm tissue located deeper in the endocervical canal, in a single sweep, followed by suturing of the sample at the 12 o'clock position. If the lesion was too large and/or involved both the anterior and posterior lips of the cervix, multiple sweeps were performed. The orientation of each sample was determined and reported to the pathologists. Before the procedure, 4 ml local anesthetic was injected into the cervix. During the procedure the electrosurgical unit was usually set at 60 W for cutting and 30 W for coagulation. Hemostasis was achieved by cauterization of the cone bed using a ball electrode at a setting of 60 W. After the excision procedure, endocervical curettage (ECC) was performed with a uterine curette (Size 0).

Further surgical procedures for patients with positive margins

The type of surgical procedure for patients with positive margins was based on each individual patient's clinical and pathological features and the suitability of repeat LEEP. Other surgical procedures included simple hysterectomy and trachelectomy with pelvic lymph node dissection. Surgery was performed as soon as possible to diminish patient anxiety.

Pathological examination

Positive surgical margins were defined as the presence of CIN 2 or CIN 3 at the ectocervix. Lesion severity, grade of CIN, largest lesion diameter, CIN 2 or CIN 3 involvement of endocervical surgical margins or glands, and the presence or absence of CIN 2 and CIN 3 in ECC sampling were recorded. The site of each CIN lesion and CIN 2 and CIN 3 involvement of $\geq 50\%$ of the cervical circumference were determined. The largest diameter of each CIN 2 or CIN 3 lesion was measured using a micrometer and Nikon Eclipse E600 microscope. The exact number of sweeps during LEEP procedures was based on the number of specimens in pathology reports.

Clinical and pathological parameters

Clinical features and the results of cytology, colposcopy and pathology were collected from hospital records. Based on the pathology reports of repeat operations, patients were divided into two groups, those with CIN ≤ 1 and CIN ≥ 2 lesions. CIN ≤ 1 lesions included CIN 1 and normal biopsy results, whereas CIN ≥ 2 lesions included CIN 2, CIN 3 and microinvasive cervical cancer. The presence of CIN ≥ 2 lesions on biopsy specimens of subsequent surgical procedures was defined as a response variable for statistical analysis. Continuous variables tested for their association with CIN ≥ 2 lesions included age, parity, time interval between procedures and lesion diameter; whereas categorical variables included menopausal status, smoking habitus, referral cytology, single or multiple sweeps during LEEP, CIN 2 or CIN

Table 1

Baseline demographic and clinical characteristics of patients and pathologic details of initial LEEP.

Characteristic	Parameters	Values (%)
Age (years)	Median	37
	25th–75th percentiles	33–42
Parity	Median	1
	25th–75th percentiles	0–2
	Nullipar	31 (29.8)
Time interval (days) between initial LEEP and subsequent surgery	≥ 1	73 (70.2)
	Median	7
Largest diameter of lesion (mm)	25th–75th percentiles	6–8
	Median	7
Menopausal status	25th–75th percentiles	4–10
	Premenopausal	90 (86.5)
Smoking habitus	Postmenopausal	14 (13.5)
	Smoker	51 (49.0)
Referral cytology	Non-smoker	53 (51.0)
	ASC-US	24 (23.1)
	LSIL	18 (17.3)
	ASC-H	10 (9.6)
Colposcopic biopsy pathology	HSIL	52 (50.0)
	CIN 2	76 (73.1)
	CIN 3	28 (26.9)
Initial LEEP pathology	CIN 2	75 (72.1)
	CIN 3	29 (27.9)
ECC	–	96 (92.3)
	+	8 (7.7)
Endocervical involvement	–	12 (11.5)
	+	92 (88.5)
Involvement of cervical circumference	<50%	72 (69.2)
	$\geq 50\%$	32 (30.8)
Glandular involvement	–	46 (44.2)
	+	58 (55.8)
Number of sweeps	1	59 (56.7)
	>1	45 (43.3)

Abbreviations: LEEP, loop electrosurgical excision procedure; HR-HPV, high risk human papilloma virus; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; ASC-H, atypical squamous cells suspicious for HSIL; LSIL, low-grade squamous intraepithelial lesions; CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage.

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