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Original Article

Association of menopause, aging and treatment procedures with positive margins after therapeutic cervical conization for CIN 3: a retrospective study of 8,856 patients by the Japan Society of Obstetrics and Gynecology

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ABSTRACT

Objective: The Japan Society of Obstetrics and Gynecology conducted a retrospective multi-institutional survey of patients who underwent cervical conization in Japan. This study aimed to determine the predictive factors for positive surgical margins in cervical intraepithelial neoplasia grade 3 (CIN 3) patients after therapeutic cervical conization and those for positive margins in patients who did not experience recurrence and did not undergo additional treatment.
Methods: In 2009 and 2013, 14,832 patients underwent cervical conization at 205 institutions in Japan. Of these, 8856 patients who underwent therapeutic conization fulfilled the inclusion criteria. Their histologic findings and clinical outcomes were evaluated based on standard statistical procedures and clinical and demographic characteristics.
Results: Negative and positive margins were observed in 7,585 and 1,271 (14.4%) patients, respectively. The predictors of positive margins were menopausal status ($p<0.001$), loop electrosurgical excision procedure ($p<0.001$), and Shimodaira-Taniguchi (S-T) conization ($p<0.001$). Of 1,271 patients with positive margins, 1,060 underwent no additional treatment; among those 1,060 patients, 129 (12.2%) experienced recurrence. The predictors of positive margins in patients who did not undergo additional treatment and did not experience recurrence were age, parity, gravidity, S-T conization, and laser scalpel conization.
Conclusion: Menopausal status and treatment procedures were associated with positive margins after therapeutic conization of CIN 3. It is important to understand the characteristics of treatment procedures and select an appropriate procedure for each case. For elderly or menopausal patients with positive margins, immediate additional treatment is recommended.

Keywords: Cervical Intraepithelial Neoplasia Grade 3; Therapeutic Conization; Positive Surgical Margin; Menopause; Treatment Procedure; Aging

Presentation

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: I.M., M.M., E.T., K.Y., N.S., Y.M.,[2] K.H.; Data curation: I.M., M.M.; Formal analysis: I.M., M.M.; Investigation: I.M., M.M., Y.M.[1]; Methodology: I.M., M.M., E.T., K.Y., N.S., Y.M.,[2] K.H.; Project administration: M.M., K.H.; Resources: I.M., M.M.; Software: I.M., M.M.; Supervision: M.M., K.H.; Validation: I.M., M.M.; Visualization: I.M.; Writing - original draft: I.M.; Writing - review & editing: I.M., M.M., Y.M.,[1] E.T., K.Y., N.S., Y.M.,[2] K.H.

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INTRODUCTION

Therapeutic cervical conization is an effective method to treat patients with cervical intraepithelial neoplasia (CIN) grade 3 (CIN 3). Even if the CIN or a squamous intraepithelial lesion (SIL) extends to the surgical margin, the immune system can spontaneously resolve the disease postoperatively in the majority of cases [1]. However, a meta-analysis showed that after incomplete excision (excision with positive margins), the relative risk (RR) of posttreatment disease of any grade was 5.47, and the RR of CIN 2 or 3 or a high-grade SIL was 6.09 compared with the reference group with complete excision (excision with negative margins) [2]. Another meta-analysis reported that positive margins occur in 23.1% of cases and varied according to the treatment procedure (laser scalpel conization=17.8%; large loop excision of the transformation zone [TZ]=25.9%) [3]. The risk of residual or recurrent high-grade CIN or worse is also dependent on the anatomical localization of the margin (endocervical: hazard ratio [HR]=2.72; endocervical and ectocervical: HR= 4.98) [4]. Considering these reports, CIN 3 should be completely excised without inflicting iatrogenic harm in therapeutic conization because positive margins in cone specimens might indicate the probability of residual disease in the remaining cervical tissue and have been recognized as one of the most important predictors of CIN recurrence and cervical cancer development after therapeutic conization.

The 2017 Japan Society of Gynecologic Oncology guidelines for the treatment of uterine cervical cancer state that cervical conization is recommended as the final treatment for CIN 3 patients with negative margins, and that repeated cervical conization or total hysterectomy should be considered for CIN 3 patients with positive margins [5].

In this study, we aimed to determine the predictive factors for positive margins in CIN 3 patients after therapeutic cervical conization in Japan. We also aimed to determine the predictive factors for positive margins in patients who did not experience recurrence and did not undergo additional treatment in Japan.

MATERIALS AND METHODS

This retrospective (case-control) study was conducted by the subcommittee of the Gynecologic Oncology Committee of the Japan Society of Obstetrics and Gynecology (JSOG), responsible for the survey of cervical conization in Japan. The survey included the data of 205 participating Japanese facilities, including university hospitals, cancer centers, local core hospitals, private hospitals, and private clinics.

This study protocol was approved by the Tokai University Institutional Review Board (IRB approval No. 15R-095) and the review boards of all 205 participating centers. The requirement for informed consent was waived because of the retrospective nature of the study.

A total of 14,832 patients underwent cervical conization at 205 Japanese institutions in 2009 and 2013. We included patients who underwent cervical conization for therapeutic purposes and were diagnosed with CIN 3 (i.e., severe dysplasia and carcinoma in situ) after histopathological examination of the extracted cone specimens. Patients who were pregnant or who had given birth less than 1 year before this study, those who underwent cervical conization for diagnostic purposes, those with insufficient available data, and those diagnosed with CIN 1

or CIN 2, cervical cancer, adenocarcinoma in situ, or benign disease based on cone specimens were excluded. The surgical margins of the cone specimens were not graded; instead, they were categorized as positive if precancerous or cancerous lesions were present in the ectocervical and/or endocervical margins or as negative if the margins were without neoplasia. We defined histologically uncertain margins as positive. Of 11,737 patients who underwent therapeutic conization, 8,856 patients with CIN 3 fulfilled the inclusion criteria.

Their clinical records and pathological results were retrospectively reviewed. Patient data, including age, gravidity, parity, menopausal status, punch biopsy results (diagnosis before conization), pathological cone specimen results (diagnosis after conization), and type of treatment procedures (ultrasonic scalpel conization, electrical scalpel conization, laser scalpel conization, loop electrosurgical excision procedure [LEEP], Shimodaira-Taniguchi [S-T] conization, cold knife conization [CKC], and others), were collected. Furthermore, data regarding the status of surgical margins, additional treatment (if any), recurrence, post-conization complications, and postoperative follow-up period were investigated.

The study population was divided into 2 groups: patients with positive margins and patients with negative margins. We further divided the patients with positive margins who did not undergo any additional treatment into 2 groups, those who experienced recurrence and those who did not experience recurrence, for the subgroup analysis. Statistical analysis was performed using SPSS version 25.0 for Windows (SPSS Inc., Chicago, IL, USA) software. Discrete and categorical variables were expressed as median (range) and numerical (percentage) values, respectively. Predictive factors for positive margins in CIN 3 patients after therapeutic cervical conization, and those for positive margins in patients who did not experience recurrence despite not undergoing additional treatment were assessed using a multivariate logistic regression analysis. The multivariate logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) after simultaneously controlling for potential confounders. All p values were 2-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

A total of 14,832 patients who underwent cervical conization at 205 facilities in Japan participated in this survey. Of these, 6,162 (41.5%), 1,347 (9.1%), 7,138 (48.1%), 183 (1.2%), and 2 patients underwent surgery at university hospitals, cancer centers, local core hospitals, private hospitals, and private clinics, respectively. Finally, 8,856 patients who underwent cervical conization for therapeutic purposes and were histologically diagnosed with CIN 3 by a histopathological examination of the extracted cone specimens were included and reviewed in this study (**Fig. 1**).

The baseline clinicopathological characteristics of all patients are listed in **Table 1**. The median age of the study patients was 37 years (range, 18–88 years). The median values of gravidity and parity were 2 (range=0–13) and 1 (range=0–9), respectively. A total of 92.4% patients were premenopausal. Various treatment procedures, including ultrasonic scalpel conization (27.8%), electrical scalpel conization (24.3%), laser scalpel conization (17.2%), LEEP (15.0%), S-T conization (11.6%), and CKC or others (4.2%) were used for therapeutic conization. Positive surgical margins were found in 1,271 of 8,856 (14.4%) patients after therapeutic conization. Recurrence occurred in 395 of 8,856 (4.5%) patients.

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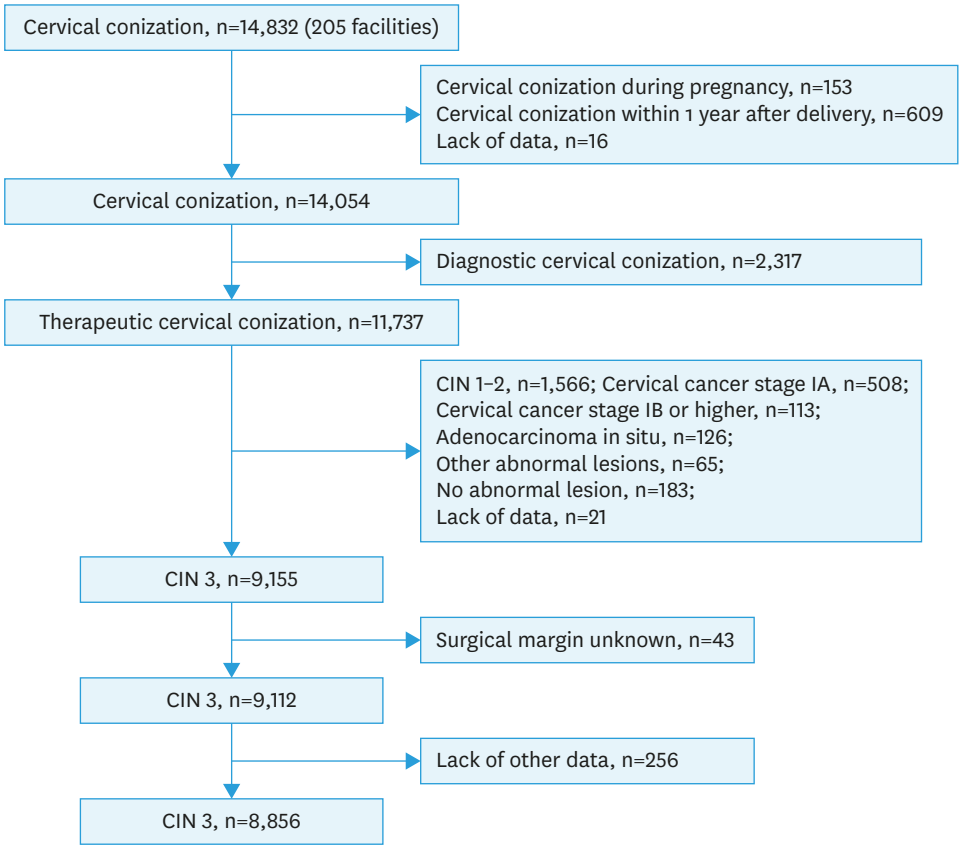

Fig. 1. Study patient selection flowchart.
CIN, cervical intraepithelial neoplasia.

We evaluated patient characteristics associated with positive margins. We used a multivariate logistic regression analysis to evaluate independent predictors of positive margins before therapeutic conization. Age, gravidity, parity, menopausal status, and type of treatment procedure (all of which were independent factors) were evaluated as potential predictors of positive margins (**Table 2**). We found that the menopausal status (OR=1.425; 95% CI=1.161–1.749; p<0.001) and 2 types of treatment procedures, LEEP (OR=1.786; 95% CI=1.533–2.081; p<0.001), and S-T conization (OR=1.524; 95% CI=1.279–1.817; p<0.001), were independent preoperative predictors of post-conization positive margins (**Table 3**).

Next, we evaluated 1,060 patients with positive margins postoperatively who did not undergo additional treatment. Of these patients, 129 (12.2%) experienced recurrence. We compared these patients with the remaining 931 (87.8%) patients who did not experience recurrence despite lack of additional treatment to determine independent predictors of recurrence in those diagnosed with positive margins. There were significant variations in age, menopausal status, parity, and treatment procedure types in both groups (**Table 4**). A subsequent multivariate logistic regression analysis showed that the independent predictors of recurrence were age (OR=1.036; 95% CI=1.007–1.066; p=0.014), parity (OR=1.576; 95% CI=1.148–2.164; p=0.005), gravidity (OR=0.719; 95% CI=0.557–0.929; p=0.012), S-T conization (OR=0.395; 95% CI=0.188–0.831; p=0.014), and laser scalpel conization (OR=0.421; 95% CI=0.209–0.847; p=0.015) (**Table 5**).

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Table 1. Baseline and follow-up characteristics of 8,856 patients involved in our population-based study

Characteristics	Parameters	Values
Age (yr)	Median	37 (18–88)
	25th–75th percentile	32–42
	<20	14 (0.2)
	20–29	1,373 (15.5)
	30–39	4,203 (47.5)
	40–49	2,485 (28.1)
	50–59	487 (5.5)
	60–69	210 (2.4)
	>70	84 (0.9)
Gravidity	Median	2 (0–13)
	25th–75th percentile	0–3
Parity	Median	1 (0–9)
	25th–75th percentile	0–2
Menopausal status	Premenopausal	8,182 (92.4)
	Postmenopausal	674 (7.6)
Punch biopsy (diagnosis before conization)	CIN 1 or CIN 2	536 (6.1)
	CIN 3	8,108 (91.6)
	Cervical cancer stage IA	158 (1.8)
	Cervical cancer stage IB or higher	9 (0.1)
	Adenocarcinoma in situ	16 (0.2)
	Others	29 (0.3)
Type of treatment procedure	Ultrasonic scalpel conization	2,463 (27.8)
	Electrical scalpel conization	2,151 (24.3)
	Laser scalpel conization	1,526 (17.2)
	LEEP	1,324 (15.0)
	S-T conization	1,024 (11.6)
	Cold knife and other methods	368 (4.2)
Surgical margin status	Positive	1,271 (14.4)
	Negative	7,585 (85.6)
Complications after conization	Yes	176 (2.0)
	No	8,680 (98.0)
Additional treatment after conization	Yes	294 (3.3)
	No	8,562 (96.7)
Recurrence	Yes	395 (4.5)
	No	8,461 (95.5)
Follow-up period	Median	28 (0–92)
	25th–75th percentile	15–39

Values are presented as median (interquartile range) or number (%).
CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure; S-T, Shimodaira-Taniguchi.

Table 2. Clinical and pathologic parameters of patients with positive and negative surgical margins

Variables	Negative margins (n=7,585)	Positive margins (n=1,271)
Age	37 (18–84)	37 (18–88)
Gravidity	2 (0–13)	2 (0–8)
Parity	1 (0–9)	1 (0–6)
Menopausal status		
Premenopausal	7,036 (92.8)	1,146 (90.2)
Postmenopausal	549 (7.2)	125 (9.8)
Type of treatment procedure		
Ultrasonic scalpel conization	2,176 (28.7)	287 (22.6)
Electrical scalpel conization	1,865 (24.6)	286 (22.5)
Laser scalpel conization	1,322 (17.4)	204 (16.0)
LEEP	1,055 (13.9)	269 (21.2)
S-T conization	840 (11.1)	184 (14.5)
CKC/other method	327 (4.3)	41 (3.2)

Values are presented as median (interquartile range) or number (%).
CKC, cold knife conization; LEEP, loop electrosurgical excision procedure; S-T, Shimodaira-Taniguchi.

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Table 3. Significant predictive factors for positive surgical margins

Predictive factors	Coefficient	SE	p-value	OR	95% CI	
					Lower	Upper
Menopausal status						
Premenopausal				Reference		
Postmenopausal	0.354	0.105	<0.001	1.425	1.161	1.749
Type of treatment procedure						
Ultrasonic scalpel conization				Reference		
LEEP	0.580	0.078	<0.001	1.786	1.533	2.081
S-T conization	0.421	0.090	<0.001	1.524	1.279	1.817

Multivariate logistic regression analysis to determine predictive factors of positive surgical margins. Initial predictive variables are as described in **Table 2**.
CI, confidence interval; LEEP, loop electrosurgical excision procedure; OR, odds ratio; SE, standard error; S-T, Shimodaira-Taniguchi.

Table 4. Clinical and pathologic parameters of patients with positive surgical margins with and without recurrence

Variables	No recurrence (n=931)	Recurrence (n=129)
Age	36 (18–88)	38 (19–73)
Gravidity	1 (0–8)	2 (0–7)
Parity	1 (0–6)	1 (0–5)
Menopausal status		
Premenopausal	876 (94.1)	110 (85.3)
Postmenopausal	55 (5.9)	19 (14.7)
Type of treatment procedure		
Ultrasonic scalpel conization	198 (21.3)	35 (27.1)
Electrical scalpel conization	211 (22.7)	36 (27.9)
Laser scalpel conization	158 (16.9)	12 (9.3)
LEEP	193 (20.7)	31 (24.0)
S-T conization	144 (15.5)	10 (7.8)
CKC or other method	27 (2.9)	5 (3.9)
Complications after conization		
Yes	21 (2.3)	6 (4.7)
No	910 (97.7)	123 (95.3)

Values are presented as median (interquartile range) or number (%).
CKC, cold knife conization; LEEP, loop electrosurgical excision procedure; S-T, Shimodaira-Taniguchi.

Table 5. Significant predictive factors for positive surgical margins in patients who did not undergo additional treatment and did not experience recurrence

Predictive factors	Coefficient	SE	p-value	OR	95% CI	
					Lower	Upper
Age	0.035	0.014	0.014	1.036	1.007	1.066
Gravidity	−0.329	0.130	0.012	0.719	0.557	0.929
Parity	0.455	0.162	0.005	1.576	1.148	2.164
Menopausal status						
Premenopausal				Reference		
Postmenopausal	0.029	0.450	0.949	1.029	0.426	2.484
Type of treatment						
Ultrasonic scalpel conization				Reference		
Laser scalpel conization	−0.866	0.357	0.015	0.421	0.209	0.847
ST conization	−0.929	0.380	0.014	0.395	0.188	0.831
Electrical scalpel conization	−0.002	0.262	0.993	0.998	0.597	1.668
LEEP	−0.067	0.272	0.805	0.935	0.548	1.595
CKC or other method	0.070	0.547	0.898	1.073	0.367	3.136
Complications after conization						
No				Reference		
Yes	0.340	0.507	0.503	1.405	0.520	3.798

Multivariate logistic regression analysis to determine predictive factors associated with positive margins in patients who did not experience recurrence despite lack of additional treatment. Initial predictive variables are described in **Table 4**.
CI, confidence interval; CKC, cold knife conization; LEEP, loop electrosurgical excision procedure; OR, odds ratio; SE, standard error; S-T, Shimodaira-Taniguchi.

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DISCUSSION

This was the first survey to assess cervical conization in Japan by the Gynecologic Oncology Committee of the JSOG. Our findings demonstrated that the menopausal status and 2 types of treatment procedures, LEEP and S-T conization, were associated with positive margins in CIN 3 patients who had undergone therapeutic conization. Furthermore, we found that the factors associated with positive margins in patients who did not experience recurrence despite lack of additional treatment were age, gravidity, parity, and 2 types of treatment procedures, S-T conization and laser scalpel conization. Although increasing age and high parity were found to be independent risk factors for recurrence, low gravidity, S-T conization, and laser scalpel conization were suggested to exert preventive effects.

In this study, menopausal status was strongly associated with positive margins. Similar reports were found by other studies. Xiang et al. [6] evaluated the incidence of positive margins in patients with CIN and microinvasive carcinoma after using electrosurgical knife conization and reported that there were 3 factors associated with positive margins: age 50 years or older (OR=3.0), postmenopausal status (OR=3.1), and the presence of microinvasive carcinoma (OR=2.7). Bilibio et al. [7] also reported that menopausal status was associated with residual disease; in particular, menopausal women with disease involvement in endocervical margins had a >80% risk of persistent lesions.

The reason why menopausal status is associated with an increased risk of positive margins was explained by the position of the squamocolumnar junction (SCJ). Although the SCJ is exocervical in women of childbearing age, it is often shifted deeper to an endocervical position during the postmenopausal period. The upper limits of CIN entering the deep cervical canal cannot be often visually confirmed by colposcopy, resulting in positive margins of such lesions. In the event of a discrepancy between the punch biopsy results and cytologic smear findings, or if the surgical excision margins could not be confirmed by colposcopy, the indications for therapeutic conization should be carefully determined because it will increase surgical difficulties and lead to positive margins.

The depth of therapeutic conization is also an important factor that could influence margin involvement. Performing appropriately deep cone excision without exerting iatrogenic harm is dependent on age, menopausal status, parity, location of the SCJ, TZ, and the shape of the cervix [8]. Bae et al. [8] reported that the OR for a group of women who were 40 to 59 years and a group of women 60 years or older with endocervical positive margins were 1.67 and 3.90, respectively, compared to a group of women 40 years or younger. Patients who underwent conization to a depth >20 mm were at lower risk for endocervical margin involvement than those who underwent conization to a depth of <20 mm (OR=0.29) [8]. Therefore, deep excision involving the upper limit of the lesion and extending to the upper cervical canal should be performed in therapeutic conization in menopausal patients to reduce the risk of positive margins.

However, extensive excision may cause postoperative complications such as cervical stenosis and obstruction, and the complications will make it impossible to perform cytological tests and biopsy for follow-up of positive margins and screening for endometrial cancer. According to the literature, the incidence of severe cervical stenosis and complete obstruction requiring surgical intervention was <1% [6]. Other studies showed that increasing age (46 years or older) was a risk factor for cervical stenosis (OR=4.27) [9]. A significant positive correlation

between the occurrence of postoperative cervical stenosis and postmenopausal status has been reported [10]. Although therapeutic conization is less invasive than hysterectomy, the individual risk-to-benefit ratio should be considered when planning conization for postmenopausal patients.

Another factor that could be related to positive margins is the treatment procedure. Each conization method has different advantages and disadvantages. Despite comprehensive studies on this topic, there is no obvious superior treatment procedure for CIN that prevents treatment failure [11]. In this study, ultrasonic scalpel conization, electrical scalpel conization, laser scalpel conization, LEEP, S-T conization, and CKC were used for treatment purposes, and 2 of these, LEEP and S-T conization, were found to be predictive of positive margins. S-T conization with a high-frequency current uses a triangular probe as the excision electrode and a small flat disk as the coagulation electrode. The triangular probe is inserted in the cervical canal to excise the diseased tissue; then, the small flat disk is applied to the cut surface of the cervix for coagulation (**Fig. S1**) [12].

It was interesting that LEEP with a loop-shaped probe and S-T conization with a triangular probe, both of which require the selection of an appropriate premade probe depending on the extent of the lesion, were associated with positive margins. Conization using premade inflexible probes might lead to positive margins in patients with widespread dysplasia, lesions deep in the cervical canal, or an atrophic cervix. Shaco-Levy et al. [13] reported that factors associated with surgical margin involvement include widespread dysplasia in the cone specimens (≥4 sections), older age (older than 35 years), and involvement of the endocervical glands.

A meta-analysis showed that cone specimens obtained using LEEP were shallower and had overall less volume and weight than those obtained using CKC (weighted mean differences: 5.1 mm, 2.6 mm, and 2.6 g, respectively) [14]. Shin et al. [15] reported that patients older than 45 years in the CKC group had a significantly lower incidence of positive margins than those in the LEEP group (14.3% vs. 52.6%). The volume and depth of conization samples obtained using LEEP are smaller than those obtained using scalpel conization and CKC with flexibility. The premade loop-shaped excision device might make complete removal of endocervical lesions difficult. The same could also be said about S-T conization, which uses a cutting probe with a triangular end and a slanted edge as an electrode. The cone size with the triangular probe in S-T conization is fixed based on the size of the TZ. Matsumura et al. [12] reported that one or both excision margins were positive in 178 of 455 (39.1%) patients who underwent S-T conization for CIN, carcinoma in situ, adenocarcinoma in situ, and microinvasive cervical carcinoma. The endocervical margin was positive in 51 (28.7%) cases, the ectocervical margin was positive in 84 (47.2%) cases, and both margins were positive in 43 (24.1%) cases. A total of 142 (79.8%) patients with positive margins underwent additional treatment [12]. These results indicate that unless the lesions are adequately evaluated and/or an appropriate premade probe is selected for therapeutic conization, the conization will result in positive margins and lead to treatment failure. Although therapeutic conization using any scalpel can be tailored to match the extent of the lesions, using a premade probe might make it difficult to modify the width and depth of excision in some cases. We suggest that the eligibility of patients for complete excision using LEEP and S-T conization should be carefully determined.

Surprisingly, we also found an association between S-T conization and the absence of recurrence in patients with positive margins who did not undergo additional treatment. When the upper limits of CIN are satisfactorily confirmed by colposcopy and an appropriate

premade probe is selected, any lesions extending to the upper cervical canal can be completely excised by inserting the triangular probe deeper into the cervix. In contrast, it is difficult to insert the loop-shaped probe deeply, leading to positive margins of endocervical lesions. This may be why despite the inflexibility of premade probes used for both LEEP and S-T conization, LEEP was associated only with positive margins and S-T conization was correlated with the occurrence of positive margins and a lack of recurrence among patients who did not undergo additional treatment. Additionally, in S-T conization, a small flat electrode is applied to the entire cervical stump after incision with the slanted edge of the triangular probe to coagulate and necrotize any remaining part of the lesion. This step may also contribute to the prevention of recurrence in patients with positive margins.

In our study, the recurrence rate was lower when laser scalpel conization was performed. After any therapeutic conizations, cauterization is usually added surgical margins of cervix. Laser conization has an advantage that surgical margins of cervix can be additionally vaporized after cone excision although ultrasonic vibration or high-frequency current do not have the ability of vaporization. The residual diseased tissue is necrotized during the coagulation and hemostasis procedure due to laser vaporization. The effects of laser vaporization on the cut surface of cervix after removal of the cone tissue can destroy and disappear residual lesions, consequently reducing the recurrence rate [16,17]. Laser conization, which can add vaporization to cauterization might be more effective than other conizations with only cauterization. This could explain why our study patients with positive margins after therapeutic conization using laser scalpel had decreased recurrence rates despite the lack of additional treatment. Ueda et al. [18] reported that although incomplete excision using laser scalpel conization (cone specimen margins positive for CIN) occurred in 230 of 1,874 (12.3%) patients in their study, the treatment failure rate was only 1.2%.

Increasing age was found to be a risk factor for recurrence in patients with positive margins who did not undergo additional treatment in our study. With aging, the body's immune system experiences change in lymphocyte subsets, cytokine levels, and immunological tolerance. Most studies have suggested that, in addition to age, changes in the immune system of postmenopausal women are attributed to estrogen deprivation [19]. Aging and/or menopause lead to increased pro-inflammatory cytokine levels, decreased $CD4^+$ T and B lymphocytes, and decreased cytotoxic activity of natural killer cells. IL-2 and interferon-γ, which are related to the activation and proliferation of T lymphocytes, are also decreased, thus contributing to a higher occurrence of neoplastic diseases [19-24]. Moreover, inflammatory processes induce oxidative stress and reduce cellular antioxidant capacity, resulting in increasing levels of free radicals that can lead to deoxyribonucleic acid mutations or other severe changes at the cellular level [25]. This phenomenon, which is known as immunosenescence, can explain why aging could be a risk factor for recurrence in patients with positive margins who do not undergo additional treatment.

A cohort study involving Swedish women indicated that those previously treated for CIN 3 were at a substantially increased risk for cervical cancer when they reached the age of 60 years. This risk accelerated with further aging. The data also showed that this risk is additionally increased in women who undergo treatment for CIN 3 later in life [26]. Although the optimal management of elderly and postmenopausal patients with positive margins remains controversial, we strongly recommend immediate additional treatment including hysterectomy because spontaneous resolution of positive margins by the patient's own immune response is unlikely for this age group. If the gynecologist is confident of the

diagnosis of CIN 3, immediate hysterectomy may be offered as the first treatment alternative for these patients.

In our study, in addition to age, high parity was a risk factor, but low gravidity was a preventive factor for recurrence in patients with positive margins who did not undergo additional treatment. Results observed by the International Collaboration of Epidemiological Studies of Cervical Cancer indicated a nonsignificant trend for CIN 3 and an increasing number of childbirths; however, the risk of CIN 3 only increased with the number of full-term pregnancies (RR for ≥7 births vs. nulliparous women after adjustment for the lifetime number of sexual partners and age at first sexual intercourse, 1.60). The overall RR with one full-term pregnancy increased by 1.07 [27]. High concentrations of estrogen and progesterone during pregnancy and delivery-related cervical trauma cause eversion of columnar epithelium onto the ectocervix, which favors exposure of the SCJ to human papillomavirus (HPV) infection. Because the perinatal death rate in Japan is extremely low, the number of full-term pregnancies can be regarded as practically equal to the number of births. High parity is considered to increase the risk of cervical cancer through the maintenance of the TZ on the ectocervix over the course of many years. Because aging and high parity independently increase the risk of recurrence for patients with positive margins, additional treatment is recommended for elderly and grand multipara patients with positive margins after therapeutic conization.

There were some limitations to the present study. First, the study had a retrospective design; therefore, pretreatment and posttreatment variables such as the lesion extent, colposcopy findings, cone depth, any grade of positive margins, and skill, and the level of the obstetricians and gynecologists performing therapeutic conization were not analyzed. Second, testing to detect high-risk HPV was not performed before therapeutic conization for all patients.

In conclusion, although therapeutic conization is a standard treatment for patients of any age diagnosed with CIN 3, therapeutic conization for menopausal and/or elderly patients should be carefully considered. We recommend immediate additional treatment including hysterectomy for elderly and/or menopausal patients and grand multipara women with positive margins. It is important to understand the characteristics of the treatment procedures and to select the appropriate treatment procedure for each case. Our study findings are of great relevance to clinical practice and should help all obstetricians and gynecologists when making decisions regarding the indication of therapeutic conization and additional treatment for patients with positive margins.

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SUPPLEMENTARY MATERIAL

Fig. 1

Simodaira-Taniguchi conization. Excision electrode (A), coagulation electrode (B). The probe is inserted into the cervical canal. A cone-shaped biopsy specimen is obtained by using the triangular probe with its linear excision electrode, and a coagulation electrode is applied to the cut surface of the cervix.

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