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Research article

Analysis of pathological and clinical characteristics of cervical conization according to age group in Japan

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ABSTRACT

Objective: With increased screening, more patients with precancerous or early cervical cancer are now being identified. Age at pregnancy, and thus number of patients requiring fertility preservation, have also increased, resulting in more diagnostic and therapeutic cervical conization (conization) procedures. We here investigated the pathological and clinical characteristics of patients undergoing conization, with a focus on age. The objectives of our study were to identify the risk factors potentially involved in cervical intraepithelial neoplasia (CIN) recurrence or persistence, additional treatment after conization, the effects of conization on pregnancy, and the actual status of conization in Japan.

Study design: A "Subcommittee for Investigation of Cervical Conization" within the Gynecologic Oncology Committee in the Japan Society of Obstetrics and Gynecology investigated pathological and clinical characteristics of conization at 205 institutions in Japan. We analyzed pathological and clinical characteristics according to age $\leq$50 and >50 years.

Results: Patients aged 20–40 years accounted for 12904 (87%) of the 14,832 study patients (median: 37 years, range: 16–88 years). However, 1838 (12.4%) were aged >50 years. The commonest post-operative diagnosis was CIN grade 3 in all age groups. Rates of invasive cancer, post-operative detection of more advanced lesions, positive surgical margins, additional treatment, and recurrence were significantly higher in patients aged $\geq$50 years than those aged <50 years (all $p < 0.01$), whereas rates of post-operative complications did not differ significantly between age groups. The relationship between cerclage and the incidence of amniorrhexis or premature birth did not differ significantly in any age group.

Conclusion: Post-conization management of patients aged $\geq$50 years requires considering the high rates of detection of more advanced lesions post-operatively, positive surgical margins, and recurrence. Cerclage should not be performed post-conization without careful consideration.

1. Introduction

Given that cervical cancer is typically preceded by precancerous lesions known as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL) [1], cervical cancer is now readily preventable and treatable provided it is managed correctly while in its precancerous state. Unfortunately, morbidity from cervical cancer is increasing in Japan. It was reportedly diagnosed in 10908 women in 2012, as compared with 7000–8000 women in the 1990s [1]. This increase in incidence may be related to the fact that Japan had the lowest Pap test

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rate (23.7%) of the 22 countries surveyed in the Organization for Economic Co-operation and Development Health Working Papers in 2007 [2]. However, according to statistics compiled from a Comprehensive Survey of Living Conditions by the Ministry of Health, Labor and Welfare, the Pap test rate has been increasing, reportedly being 37.7% in 2007 and 42.3% in 2016. One consequence of this increase has been augmentation of the ratio of CIN3 and cancer from 1.06 in 2008 to 1.85 in 2014, meaning that the role of cervical conization (conization) has expanded considerably. The safety and effectiveness of conization as a treatment and diagnostic option at any age is clearly evident, not only because of its fertility-sparing effect, but also because conization can be performed under regional anesthesia, resulting in short hospital admissions, which is advantageous in our aging society. This trend is becoming more evident the Japan Society of Obstetrics and Gynecology (JSOG) reported that approximately 80% of patients with CIN3/high squamous intraepithelial lesion (HSIL) were treated with conization in 2014 [3], whereas conization was performed in only 19.6% of patients with stage 0 disease in 1990 [2].

When CIN is detected during the fertile age range, conservative treatment such as a loop electrosurgical excision procedure (LEEP) or conization is mandatory for eradicating the lesion while preserving reproductive function [4]. However, the optimal management of the same lesions diagnosed after menopause is still contentious, mainly because the physiological characteristics of post-menopausal women differ considerably from those of pre-menopausal women. Physiological changes in the region of the squamocolumnar junction (SCJ) after menopause require particular consideration when performing conization. Internalization of the SCJ in the endocervix in these women is associated with post-operative complications and failure of conservative treatment according to several studies [5, 6].

Current screening programs in Japan include women ≥20 years of age. Consequently, a high proportion of screened women are post-menopausal, meaning that these patients are not infrequently diagnosed as having CIN [2]. Moreover, with increasing late childbearing in Japan, the incidence of women undergoing conization before pregnancy is increasing. Generally, women with a history of conization have a shorter cervical length in pregnancy than those who have not undergone conization, significantly increasing their risk of preterm birth, perinatal morbidity, and mortality [7, 8, 9, 10, 11, 12, 13]. Consequently, the effectiveness, indications, and risk factors for conization in both post-menopausal women and those in the fertile age range need to be investigated.

The consequences of conization have not been confirmed in large scale settings in Japan. In this retrospective study, we conducted a nationwide survey to elucidate the patient characteristics and clinical outcomes of 14832 women who had undergone cervical conization in 2009 and 2013. We used the findings of this survey to investigate how age affects clinical outcomes after conization. First, we point out that this is the first large study of conization in Japan. Therefore, the objectives of our study were to identify the risk factors potentially involved in CIN recurrence or persistence, additional treatment after conization, the effects of conization on pregnancy, and the actual status of conization in Japan. Moreover, we determined the indications for conization and developed a guideline for CIN and invasive cervical cancer by analyzing data according to age, focusing especially on young women who want to preserve the ability to bear children and post-menopausal women in Japan.

2. Materials and methods

We first established a “Subcommittee for Investigation of Cervical Conization” within the Committee on Gynecologic Oncology in the Japan Society of Obstetrics. This subcommittee conducted a retrospective cohort study of 14832 consecutive women who had undergone conization in 2009 and 2013 in 205 institutions in Japan. All patients had been followed-up for at least 2 years. The median follow-up was 36 months and ranged from 24 to 224 months. We examined the patients’ clinical records and pre- and post-operative histologic findings and evaluated clinical outcomes using standard statistical procedures.

The pretreatment investigative protocols for recommending conization involved cytology (low squamous intraepithelial lesion (LSIL) or HSIL), colposcopy, target biopsy, and reporting of CIN or invasive cancer histologically [14, 15]. Conization was used for ‘therapeutic’ and/or ‘diagnostic’ purposes. The ‘therapeutic’ use of conization defined the successful treatment by excision of lesions for which the pathological indicators in cytology, colposcopy and histology findings all showed the same successful results. In contrast, ‘diagnostic’ defined the use of conization to identify severe lesions for which the prior results of cytology, colposcopy and histology disagreed, and suspicious invasive cases required a correction in diagnosis for staging and treatment. The indications for performing conization were as follows: histological diagnosis of CIN2+ lesions in biopsy specimens; discordance between cytology and biopsy results and suspected micro-invasive squamous or glandular disease in the absence of endometrial pathology. We based a pre-operative diagnosis of CIN on biopsy findings and used histologically-diagnosed CIN categories or the 2018 International Federation Of Gynecology and Obstetrics (FIGO) staging of cervical carcinomas rather than cytological findings when assessing pre- and post-treatment of cervical cancers. FIGO stages of cervical carcinomas comprised stages IA, IA1, IA2, IB, IB1, and IB2 [16]. Adenocarcinoma in situ was reported as ‘AIS’, whereas sarcoma and polyps were reported as ‘other’. Surgical margins were considered positive if the cervical lesion was close to (≤1 mm) or involved the resection margin, including the ectocervical margin, endocervical margin, or both. Additional management for those with positive surgical margins included hysterectomy, repeat conization, ablative treatment, trachelectomy, radiation therapy, or follow-up alone. The criteria for recurrence were based on positive histological findings in colposcopy-directed biopsies. Recurrence was considered to have occurred if a diagnosis of CIN2 or -3 was observed in histological specimens.

Statistical analysis was performed with SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were compared with the Mann–Whitney *U*-test or Student's *t*-test, as appropriate. Categorical variables are expressed as numbers and frequencies and were compared using the χ^2 test. Differences with p-values of <0.05 were considered significant. This study was approved by the ethics committee of Tokai University (Institutional Review Board [IRB] registration number, 15R-095).

3. Results

The clinical features and pathological details determined by pathological examination of conization specimens from the 14832 women are shown in Table 1. The median patient age was 37 years (16–88 years); at inclusion, 1436 (9.7%) women were post-menopausal. The most common preoperative histological diagnosis was CIN3 in 11691 (78.8%) women. In all 14832 women who had been treated by conization for therapeutic or diagnostic reasons, the surgically removed tissue was examined histologically to make a diagnosis. As with the preoperative histological diagnoses, the most common post-operative histological diagnosis was CIN3 in all age groups (Figure 1). Table 2 shows the relevant post-operative pathological variables according to age. Therapeutic conization was performed more frequently than diagnostic conization in all age groups. However, the rate of diagnostic conization was greater in older patients, with more than 40% of conizations in >60-year-old women having been performed for diagnostic purposes. The rates of positive surgical margin, post-operative detection of more advanced lesions, recurrence, and additional treatment were higher in older than in younger patients. However, the rate of post-operative complications was similar in all age groups.

Next, pathological and clinical characteristics were analyzed according to age group (≤50 years vs. >50 years) (Figure 2). Of the 14832

Table 1. Preoperative clinical and demographic characteristics of 14832 patients.

Characteristic		
Age (years)		
	Median	37
	<20	23 (0.1)
	20–29	2138 (14.4)
	30–39	6597 (44.4)
	40–49	4236 (28.5)
	50–59	1103 (7.4)
	60–69	518 (3.5)
	70–79	196 (1.3)
	80≤	21 (0.1)
Gravida		
	0	4001 (27.0)
	1	2858 (19.3)
	2 or more	7973 (53.7)
Para		
	0	5525 (37.2)
	1	3049 (20.6)
	2 or more	6258 (42.2)
Menopausal status		
	Premenopausal	13396 (90.3)
	Postmenopausal	1436 (9.7)
Preoperative histological diagnosis		
	CIN1–2	1536 (10.4)
	CIN3	11691 (78.8)
	IA1 or IA2	750 (5.0)
	IB1 or more	203 (1.4)
	AIS	260 (1.8)
	Others	392 (2.6)

Values are presented as number (%).
CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ.

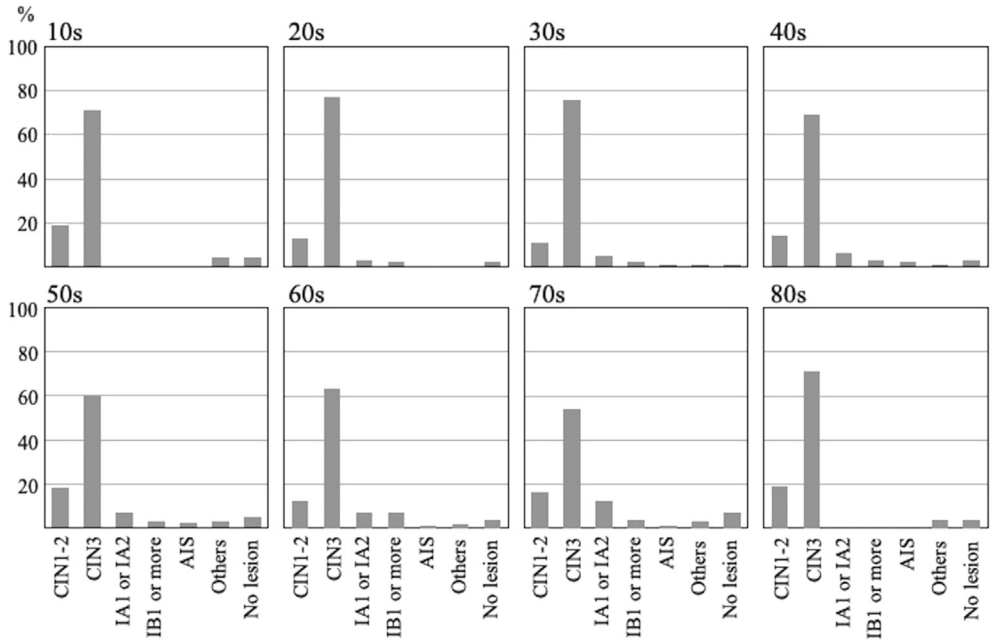

Figure 1. Diagnoses were made by histological examination of surgical specimens. The commonest post-operative histological diagnosis was CIN3 in all age groups (70% of women in their 10s, 78% in their 20s, 77% in their 30s, 69% in their 40s, 60% in their 50s, 63% in their 60s, 54% in their 70s, and 71% in their 80s).

patients, 12994 (87.6%) were aged ≤50 years, and 1838 (12.4%) were aged >50 years. The rate of post-operative complications did not differ significantly between the age groups (Figure 2A). In contrast, the rates of positive surgical margins, post-operative detection of more advanced lesions, recurrence, invasive cancer, and additional treatment were significantly higher in patients aged ≥50 years than in those aged <50 years ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.01$, $p < 0.001$, respectively) (Figure 2B, C, D, E, F).

Table 2. Postoperative pathological parameters according to age.

Characteristic		<20	21–30	31–40	41–50	51–60	61–70	71–80	>80	Total
Aim of conization										
	Therapeutic	100	91	88	81	68	59	57	71	64.4
	Diagnostic	0	9	12	19	32	41	43	29	35.6
Surgical margin	–	100	97	85	83	83	76	71	76	83.9
	+	0	3	15	17	17	24	29	24	16.1
Postoperative detection of more advanced lesions	–	96	92	90	90	89	86	88	85	10.5
	+	4	8	10	10	11	14	12	15	89.5
Recurrence	–	96	96	96	96	93	92	90	90	93.9
	+	4	4	4	4	7	8	10	10	6.1
Additional treatment	–	100	96	93	86	78	69	70	90	85.3
	+	0	4	7	14	22	31	30	10	14.7
Postoperative complications	–	96	96	97	97	95	92	96	100	96.1
	+	4	4	3	3	5	8	4	0	8.9
Preterm birth		–	17	14	16	–	–	–	–	15

Values are presented as %.

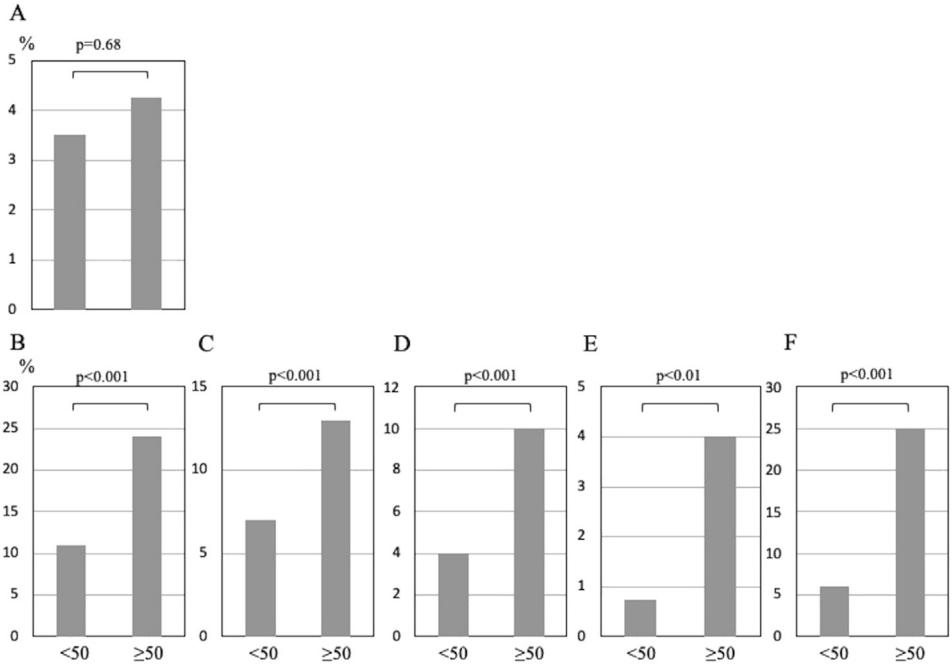

Figure 2. The rates of post-operative complications (A) did not differ significantly between age groups. However, the rates of positive surgical margins (B), post-operative detection of more advanced lesions (C), recurrence (D), invasive cancer (E), and additional treatment (F) were significantly higher in patients aged ≥50 years than in those aged <50 years (all $p < 0.01$).

Table 3. Relationship between positive surgical margin and recurrence in each age-group.

	Recurrence +		Recurrence –		P value
	Margin +	Margin –	Margin +	Margin –	
10s	0	1	0	22	0.21
20s	25	69	300	1744	0.003
30s	93	180	900	5424	0.0001
40s	59	104	640	3433	0.0001
50s	16	43	176	868	0.04
60s	19	23	110	366	0.004
70s	8	11	49	128	0.19
80s	1	1	4	15	0.42

Values are presented as number.

Table 4. Pregnancy outcome depends on cerclage.

	Gestation at birth (%)			Preterm PROM (%)		
20s	<37 weeks	≥37 weeks	*P*-value			*P*-value
with cerclage (n = 59)	14 (24)	45 (76)	0.6	10 (17)	49 (83)	0.55
without cerclage (n = 359)	75 (21)	284 (79)		53 (15)	306 (85)	
30s						
with cerclage (n = 111)	29 (26)	82 (74)	0.16	12 (11)	99 (89)	0.87
without cerclage (n = 640)	127 (20)	513 (80)		78 (12)	562 (88)	
40s						
with cerclage (n = 3)	1 (33)	2 (67)	0.36	0 (0)	3 (100)	0.75
without cerclage (n = 34)	4 (12)	30 (88)		3 (9)	31 (91)	

Values are presented as number (%).

Of the 14832 patients, 653 (4.5%) had recurrences and 14179 (95.5%) did not. Table 3 shows the relationship between positive surgical margins and recurrence according to the age group. There were significant differences between the incidences of positive surgical margins and recurrence in patients in their 20s, 30s, 40s, 50s, and 60s (p = 0.003, 0.0001, 0.0001, 0.04, and 0.004, respectively).

Following conization, there were 561 pregnancies in women in their 20s, 1037 in those in their 30s, and 82 in those in their 40s (data not shown). The rates of preterm birth according to age group were 17% in women in their 20s, 14% in those in their 30s, and 16% in those in their 40s (Table 2). Table 4 shows the pregnancy outcomes in patients who had undergone cerclage after conization during their pregnancies. There were no significant differences between patients in all age groups who had and had not undergone cerclage and pregnancy outcomes.

4. Discussion

The incidence of CIN2 and CIN3 is increasing in the same manner in Japan as it is in the USA, where the incidence is reportedly 1.5 per 100 women, with the peak prevalence occurring in 25- to 35-year-old women [17]. However, the incidence of high-grade CIN in Japan remains unknown. It is important to determine the incidence of high-grade CIN and of conization in Japan to enable clarification of the indications for conization. In the present study, the median patient age was 37 years (Table 1). However, the study cohort included 1838 ≥ 50-year-old women, and these women accounted for 12.4% of the 14832 participants (Table1). Chen et al. reported that 4.3% of 1113 women with CIN3 were post-menopausal [18]. Although the rate of ≥50-year-old women in this study was higher than that in previously reported studies, these data suggest that high-grade CIN and invasive cancer are common in ≥50-year-old women.

Although CIN3 was the most common histological diagnosis both pre- and post-operatively in all age groups (Figure 1 and data not shown), the rate of post-operative detection of more advanced lesions increased with increasing age (Table 2). In particular, the rate was significantly higher in women aged >50 years than in those aged ≤50 years (Figure 2C). Colposcopy-directed biopsy is the gold standard for the diagnosis of cervical cancer and its precursors [19]. However, cervical atrophy, retraction of the squamo-columnar junction, and reduced cellular exfoliation in post-menopausal women can lead to an unsatisfactory colposcopic biopsy and a discrepancy between preoperative biopsy and post-operative conization findings [20]. Previous studies have found that surgical margin status is the most important predictor for CIN recurrence after conization [21, 22]. In the present study, recurrence occurred in 9.2% and 3.4% of patients with positive and negative surgical margins, respectively (p = 0.04). Regarding analyzing the relationship between recurrence and surgical margin status according to age, although there were no significant differences between recurrence and surgical margins in patients in their 10s, 70s, and 80s, the relationship differed significantly in those in their 20s, 30s, 40s, 50s, and 60s (Table 3). This apparent discrepancy may be attributable to the small numbers of patients in their 10s, 70s, and 80s (n = 23, 196, and 21, respectively). Therefore, in agreement with other studies, our data confirm that a positive surgical margin is the most important predictor of recurrence after conization. Therefore, close follow-up is essential for early detection of recurrence after conization with positive surgical margins. Arbyn et al. reported that high-risk human papillomavirus (HPV) post-treatment predicts residual or recurrent CIN2+ more accurately than surgical status [23]. Moreover, previous studies have suggested that the presence of high-risk HPV was lowest among older patients before conization and was highest among these patients post-conization. The pre- and post-conization HPV distributions in high grade cervical lesions were affected by patient age. Therefore, HPV distribution according to age could be a risk factor for post-conization lesion recurrence [24, 25, 26]. However, the relationship between pre-/post-operative HPV status and clinical outcomes after conization remains unclear, and further prospective studies are needed to evaluate this relationship.

The optimal management of high-grade CIN and early invasive cervical cancer in post-menopausal women has not yet been reliably established [27]. Generally, simple hysterectomy is frequently selected as the primary treatment for post-menopausal women. In agreement with other studies, the rates of positive surgical margins, post-operative detection of more advanced lesions, recurrence, and invasive cancer were significantly higher in women aged >50 years than in those aged ≤50 years, in this study (Figure 2B, C, D and E) [28, 29]. Thus, the possible disadvantages of simple hysterectomy are that it is unnecessary for the treatment of high-grade CIN and inadequate for invasive cervical cancer. Moreover, Giannella et al. reported that women aged 50 years and older with CIN3 showed a significant reduction of high-grade lesion predictors, such as HPV16 infection, high-grade colposcopic impression, and high-grade cytological changes along with physiologically-confounding cervical changes [30]. Therefore, conization provides more precise and reliable pathological information than colposcopy-directed biopsy and other predictors, and conization may be particularly indicated for diagnostic purposes in women aged >50 years. Diagnostic conization can provide guidance for selecting the most appropriate type of subsequent hysterectomy in post-menopausal women. However, an important consideration is that conization can be difficult to perform in older women because the cervix is sometimes small.

Previous studies have suggested that conization is associated with a significantly increased risk of preterm birth [31, 32, 33, 34, 35, 36, 37, 38]. The rates of preterm birth were 17% in women in their 20s, 14% in those in their 30s and 16% in those in their 40s in this study (Table 2). These rates are three-fold greater than the 5.6% reported for the general population in Japan [39]. As with previous studies, our data suggest that conization is associated with an increased risk of preterm birth in all age groups. Moreover, we investigated whether cervical cerclage can reduce

the incidence of preterm birth among women who have undergone conization. Although previous studies have reported that cervical cerclage significantly reduced the incidence of preterm birth in women with previous spontaneous preterm birth [40], the efficacy of cervical cerclage in reducing the incidence of preterm birth in women who have undergone conization remains controversial. In our study, cervical cerclage did not reduce the incidence of either preterm birth or preterm premature rupture of the membranes (PROM) among women who had undergone conization in all age groups (Table 4). These results suggest that cervical cerclage is ineffective in preventing preterm birth in pregnant women who have undergone conization. Moreover, although the rates of preterm birth tended to be higher in women who had undergone cerclage following conization than in those who had not undergone cerclage in all age groups, these differences were not statistically significant. Cho et al. reported that women who have undergone conization and cerclage are at higher risk of preterm birth than those who have not undergone cerclage [41]. The authors proposed that the higher risk may be attributable to inflammation after cervical cerclage and repeated trauma induced by conization. Given the increasing number of women choosing late childbearing in Japan, the number of women who have undergone conization before pregnancy is increasing. Although we analyzed the efficacy of cervical cerclage in each age group, further prospective studies are needed to evaluate the relationship between cerclage and preterm birth in women who have undergone conization before pregnancy.

As with other retrospective studies, the current study also has limitations, namely that it was a retrospective study, the lack of a randomized-controlled prospective design, and the short follow-up duration. In addition, some patients' compliance was poor, and some patients were lost to follow-up, resulting in selection bias that may have affected the statistical results. In conclusion, this is the first large study of conization in Japan to identify the risk factors potentially involved in CIN recurrence or persistence, additional treatment after conization, the effects of conization on pregnancy, and the actual status of conization in Japan. Post-conization management of patients aged $\geq$50 years requires considering the high rates of detection of more advanced lesions postoperatively, positive surgical margins, and recurrence. Therefore, conization may be particularly indicated for diagnostic purposes in women aged >50 years. Diagnostic conization can provide guidance for selecting the most appropriate type of subsequent hysterectomy in postmenopausal women. Cerclage should not be performed post-conization without careful consideration. Further prospective studies with a larger sample size, evaluating HPV status, and involving longer follow-up periods are needed to establish the indications for conization and to develop guidelines for CIN.

Declarations

Author contribution statement

M. Ikeda, M. Mikami, Y. Kobayashi, S. Nagase, M. Yokoyama, T. Enomoto and H. Katabuchi: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

I. Murakami: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

A. Ohno and H. Yamashita: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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