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Glandular Involvement by Carcinoma in Situ of the Uterine Cervix

Akira GOTO[1], Shoji KODAMA[2], Hiroaki KASE[2], Mari SAITO[2], Kenichi TANAKA[2], and Miwako ISHII[3]

[1]Department of Obstetrics and Gynecology, Niigata Prefectural Yoshida Hospital, [2]Department of Obstetrics and Gynecology, Niigata University School of Medicine, [3]Department of Obstetrics and Gynecology, Kido Hospital, Niigata, Japan

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Summary. **Assessment of the extent of glandular involvement by carcinoma in situ (CIS) of the uterine cervix is important when treatment by the laser conization is considered. A total of 67 subjects consisting of 28 cases of therapeutic conization (Group A), 16 cases of diagnostic conization plus simple hysterectomy (Group B), and 23 cases of simple hysterectomy (Group C) were reviewed histologically. Glandular involvement was observed 82.1% of all the patients, and 14.5% of them had no lesion in the surface squamous epithelium located upwards of the glandular involvement. Negative cases of the resected surgical margins of conization were found in 87.5% of Group A and 58.3% of Group B in surface squamous CIS, and 100% of Group A and 78.6% of Group B in lesions of glandular involvement. In the negative cases of the resected surgical margins of conization, average distances from the lesion in the surface squamous cell layer to the margins were 4532.7 μm and 5394.1 μm in Groups A and B, respectively. On the other hand, average distances from glandular involvement to the margins were found to be shorter being 3465.1 μm and 4021.2 μm in Groups A and B, respectively. In six cases of positive margins in Group B, three cases had glandular involvement in the margins of conization and also in the removed uterus. In five cases with a residual lesion in the removed uterus, four had glandular involvement and two of those had the same lesions at the margins of conization. The results suggest that the conization for CIS should be performed under careful management in consideration of the possibility of residual glandular involvement, even if the squamous lesion of the surgical margins is negative.**

Key words—glandular involvement, carcinoma in situ, uterine cervix.

Correspondence: Akira Goto, Department of Obstetrics and Gynecology, Niigata Prefectural Yoshida Hospital, Yoshida 1001, Niigata 959-02, Japan.

INTRODUCTION

For the treatment of carcinoma in situ (CIS) of the uterine cervix, it has recently become possible to select of several kinds of therapies such as perspiration and conization with laser instruments, and loop electrosurgical excision procedure (LEEP), including preservation of uterus. Vaginal hysterectomy is popular as the treatment for CIS in U.S.A., while conization has been widely performed in Europe.[1,2] In Japan, hysterectomy has been mainly conducted, whereas conization only was carried out in 19.6% of CIS.[3] Though a preservative operation of uterus such as conization has many advantages, it was reported that the residual lesion was observed in 6.3% of operated cases and recurrence in more or less than 0.6%.[1] Thus, follow-up of the patients should be done regularly. Studies on risk factors for recurrence after conization so far have mainly focused on the presence of residual lesions at the surgical margins;[1,2,4,5] few studies on glandular involvement have been reported. In cervical intraepithelial neoplasia (CIN), the same lesion is often observed in glandular duct and surface squamous epithelium. Glandular involvement was detected in 88.4%[6] of CIN III and 78.8%[7] of CIS. In this study, we carried out a histological study to evaluate whether glandular involvement is a risk factor for recurrence after conization.

MATERIALS AND METHODS

The subjects were 67 patients with squamous cell carcinoma in situ of the uterine cervix, all patients being operated on at the Department of Obstetrics and Gynecology, Niigata University Hospital from

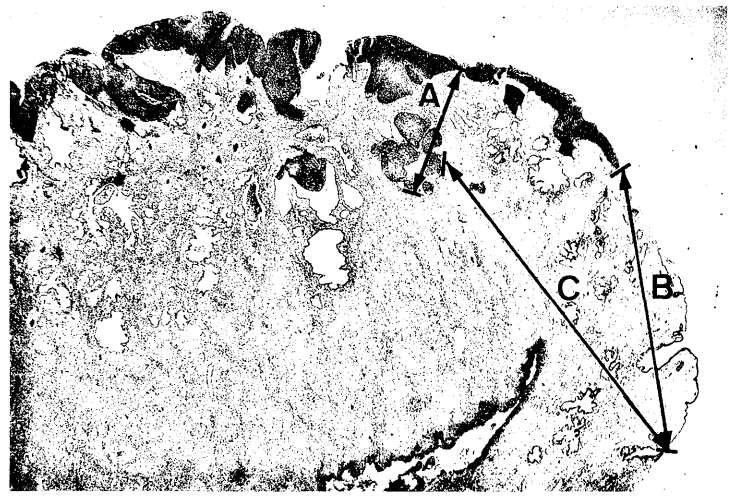

Fig. 1. Measurements made on a section from a cervical conization. (H & E ×40). **A:** Depth of the deepest glandular involvement; **B:** Distance from the surface lesion to the surgical margin of the endocervix. **C:** Distance from the glandular involvement to the surgical margin of the endocervix.

Table 1. Histological study for carcinoma in situ of the uterine cervix

1. Extent of surface squamous cell carcinoma in situ
2. Lesions of the glandular involvement
3. Depth of glandular involvement
4. Lesions of the surface squamous epithelium over the glandular involvement
5. Lesions of the surgical margins of the surface squamous epithelium by conization (Group A, B)
6. Distance from the surface lesion to the surgical margin of the endocervix by conization
7. Distance from the surface lesion to the glandular involvement (Group A, B)
8. Distance from the glandular involvement to the surgical margin of the endocervix by conization (Group A, B)
9. Residual lesions of the removed uterus (Group B)

Group A: conization; Group B: conizaton+total abdominal hysterectomy (TAH)

Table 2. Age distribution and glandular involvement

Age	No. of cases	No. of cases of glandular involvement	(%)
20-29	3	2	66.7%
30-39	22	19	86.4%
40-49	24	20	83.3%
50-	18	14	77.8%
Total	67	55	82.1%

Table 3. Age distribution and glandular involvement by each surgery

Age	Type of operation			Total
	Group A	Group B	Group C	
20-29	3 (2)	0	0	3 (2)
30-39	13 (10)	1 (1)	8 (8)	22 (19)
40-49	9 (6)	5 (5)	10 (9)	24 (20)
50-	3 (1)	10 (8)	5 (5)	18 (14)
Total	28 (19)	16 (14)	23 (22)	67 (55)
(%)	67.9%	87.5%	95.7%	82.1%

Group A: conization only; Group B: conization+TAH; Group C: TAH; ( ): No. of cases of glandular involvement

January 1, 1988 to December 31, 1993. With regard to the selection of the operation method, conization was performed in principle for young patients in age, or for those who wished to preserve fertility and those who could be followed-up. Hysterectomy was conducted for the other patients. Therapeutic conization was employed when the results of cytology, colposcopy and histologic diagnosis were consistent. Diagnostic conization was conducted when the results of cytology did not coincide with those of histologic diagnosis or when the entire lesion could not be observed because of unsatisfactory colposcopic findings (UCF). Hysterectomy was carried out in those lesions which were worse than CIS on pathologic diagnosis of conization. The therapeutic con-

Table 4. Surface squamous lesions and glandular involvement

Type of operation	No. of cases	Surface CIS		Glandular involvement	
		Positive (%)	Negative	Positive	Negative
Group A	28	24 (85.7%)	4	19 (67.9%)	9
Group B	16	12 (75.0%)	4	14 (87.5%)	2
Group C	23	23 (100%)	0	22 (95.7%)	1
Total	67	59 (88.1%)	8	55 (87.1%)	12

Group A: conization; Group B: conization+TAH

ization consisted of 28 cases (Group A), 16 cases of hysterectomy after diagnostic conization (Group B) and 23 cases of hysterectomy (Group C). Surgery of conization was performed with light amplification by stimulated emission of radiation (LASER), leaving the conization bed open to natural healing. An incision, ensuring the removal of all the abnormal area by colposcopy, was made into the mucous membrane over the lesion to at least 5 mm of the ectocervix. Specimens from more than 10 sections of the cervix after conization or hysterectomy were histologically examined, and those with CIS were chosen for this study. Subjects with CIS observed only in specimens of preoperative biopsy were excluded.

Histological findings were referred to the nine items shown in Table 1, and on the histogram in Fig. 1. The distance of the histological lesions was measured by microscopic analysis with computer graphics.

RESULTS

The incidence of glandular involvement in CIS of the uterine cervix by age is shown in Table 2. The incidence was two of three cases (66.7%) for patients in their 20s, 19 of 22 (86.4%) for those in their 30s, 20 of 24 (83.3%) for those in their 40s, 14 of 18 (77.8%) for those in their 50s, and 55 of 67 (82.1%) in total. No difference in incidence by age was observed.

The incidence of glandular involvement by each operation group is shown in Table 3. The frequency was observed in 19 of 28 cases (67.9%) in Group A, 14 of 16 (87.5%) in Group B and 22 of 23 (95.7%) in Group C, and lesions of glandular involvement were found to exist at a high incidence.

The number of cases with surface squamous lesions of CIS and glandular involvement of the uterine cervix is shown in Table 4. Surface squamous lesions were observed in 24 of 28 cases (85.7%) in Group A, 12 of 16 (75.0%) in Group B and 23 of 23 (100%) in Group C. Glandular involvement was observed in 19 (67.9%) in Group A, 14 (87.5%) in Group B and 22 (95.7%) in Group C, respectively.

Table 5. Correlation between surface lesions and glandular involvement

Surface lesion	Glandular involvement		Total
	+	−	
CIS +	47 (85.5%)	12 (100%)	59 (88.1%)
CIS −	8 (14.5%)	0 (0%)	8 (11.9%)
Total	55 (100%)	12 (100%)	67 (100%)

Table 6. Age distribution and depth of glandular involvement

Age	No. of cases	Distribution	Mean	Standard deviation
20-29	2	269-1008	638.5	369.5
30-39	19	192-1625	955.9	471.8
40-49	20	429-1656	1047.9	409.2
50-	14	581-3156	1149.1	716.8
Total	55	192-3156	1026.7	535.6

Depth: μm

Table 7. Distance from the surface lesions to the surgical margin of the endocervix by conization

Lesions of the surgical margin and distance	Group A	Group B
Negative	21 cases (87.5%)	7 cases (58.3%)
Distance		
Distribution (μm)	59-9610	1495-9308
Mean (μm)	4532.7	5394.1
Standard Deviation (μm)	3130.9	2401.6
Positive	3 cases (12.5%)	5 cases (41.7%)
Total	24 cases (100%)	12 cases (100%)

The relation between surface squamous lesions and glandular involvement is shown in Table 5. Both surface squamous lesions and glandular involvement were observed in 47 (70.1%) of all cases, and glandular involvement without any surface lesion in 8

Table 8. Distance from glandular involvement to the surgical margin of the endocervix by conization

Lesions of the surgical margin and distance	Group A	Group B
Negative	19 cases(100%)	11 cases(78.6%)
Distance		
Distribution (μm)	437-9270	1347-10872
Mean (μm)	3465.1	4021.2
Standard deviation (μm)	2337.8	3027.7
Positive	0 cases(0%)	3 cases(21.4%)
Total	19 cases(100%)	14 cases(100%)

Table 9. Cases with a positive endocervical surgical margin by conization and uterine residual lesion (Group B)

Case	Age	Conization		Uterus	
		Surface	Glandular Involvement	Surface	Glandular Involvement
1.	48	+	+	+	+
2.	68	+	+	−	−
3.	56	+	−	+	+
4.	35	+	−	+	−
5.	53	+	−	−	−
6.	77	−	+	+	+

+: Positive lesion of the carcinoma in situ

Table 10. Cases with uterine residual lesions and lesions of the endocervical surgical margin by conization (Group B)

Case	Age	Conization		Uterus	
		Surface	Glandular Involvement	Surface	Glandular Involvement
1.	48	+	+	+	+
2.	56	+	−	+	+
3.	35	+	−	+	−
4.	77	−	+	+	+
5.	56	−	−	+	+

+: Positive lesion of the carcinoma in situ

(14.5%) of those cases.

The depth of glandular involvement was measured for each age group (Table 6). The depth from the surface epithelium or basement membrane of the surface squamous lesion was 192-3156 μm (mean; 1026.1 μm, standard deviation; 535.6 μm). The mean depth was 638.5 μm for patients in their 20s, 955.9 μm for those in their 30s, 1047.9 μm for those in their 40s, 1149.1 μm for these in their 50s and 2106 μm for those in their 70s. There was a tendency for elder patients to have a deeper lesion.

The distance was measured from the surface squamous lesion with CIS of the uterine cervix to the surgical margins with negative lesions in the conization cases (Table 7): 59-9610 μm (mean; 4532.7 μm, standard deviation; 3130.9 μm) in 21 cases (87.5%) from Group A, and 1495-9308 μm (mean; 5394.1 μm, standard deviation; 2401.6 μm) in 7(58.3%) from Group B.

The distance from the glandular involvement to the surgical margins with negative lesions in the conization cases is shown in Table 8: 437-9270 μm (mean; 3465.1 μm, standard deviation; 2337.8 μm) in all 19 cases of Group A, and 1347-10872 μm (mean; 4021.2 μm, standard deviation; 3027.7 μm) in 11 (78.8%) cases from Group B.

Six cases with positive surgical margins by conization in Group B are shown in Table 9. Three of five cases in which the lesions were found in the surface squamous layer of the surgical margins of the conization also had a lesion in the surface squamous layer of the uterus. In one case (Case 6), no lesion was discovered in the surface squamous layer of the margins of the conization, but was found in the surface layer of the uterus. Likewise, two (Case 1, 6) of three (Case 1, 2, 6) in which glandular involvement was found in the margins of the conization also had a lesion in the surface squamous layer of the uterus. In one case (Case 6), no lesion was detected in the surface layer of the margins of the conization, but glandular involvement was found in the removed uterus.

On the other hand, five cases with a residual lesion in the removed uterus were observed in Group B (Table 10). Four (Case 1, 2, 3, 4) of them were positive with the surgical margins of the conization as mentioned above, and in one case (Case 2), without glandular involvement, lesions were found in superficial epithelium of the removed uterus and gland. However, in Case 5, only glandular involvement was observed in materials of the conization and the surgical margin at the distance of 1657 μm was negative; retained lesions in the superficial layer of the removed uterus and glandular involvement were discontinuously found.

DISCUSSION

Hysterectomy is a popular treatment for carcinoma in situ of the uterine cervix in Japan.[3] As hysterec-

tomy is "radical", a preservative operation for uterus is recommended except for several conditions such as complications of leiomyoma, or the impossibility of follow-up for the patients.[1] Though preservative operations for the uterus such as conization have many advantages, residual lesions and recurrence have been reported to be observed in 6.3% of the operations and 0.6%, respectively.[1] We had one experience of recurrence after conization, and investigated the risk factor for recurrence.[8] As a result, a residual lesion in the gland and squamous lesion were noted in the recurrent case and in the removed uterus.

CIN III is often observed in the glandular duct as well as surface squamous epithelium. Glandular involvement was found in 88.4%[6] of CIN III, 78.8%[7] of CIS of the uterine cervix and 82.1% of our cases. This suggests that glandular involvement might be a risk factor for recurrence after a preservative operation for uterus.

The excision of a large area is required in conization, and an index of the depth for excision has been reported. Anderson et al.[6] have reported that glandular involvement was located an average of 1.24 mm from the surface squamous epithelium and at a maximum depth of 5.22 mm; thus, 99.7% of glandular involvement could be removed when the tissue was excised up to 3.8 mm in depth, and the excision of the tissue at least up to 4 mm from surface epithelium should be required for conservative treatment due to the deepening of glandular involvement by aging. Abdul-Karim et al.[9] mentioned that the depth from the superficial epithelium to glandular involvement was 7.60 ± 4.32 mm, and 99.7% of glandular involvement could be extirpated by an excision of 4.8 mm in depth from surface epithelium. In our cases, the depth from the lesion of glandular involvement was 1026.1 μm on average and 3156 μm at maximum when it was measured from the basement membrane. From these results, it is considered that 5 mm as the depth of excision for therapeutic conization might be sufficient.

In the meantime, the range of excision required for conization has been controversial when glangular involvement is take into account. Sakaguchi et al.[10] reported that no presence of glandular involvement was found when no glandular involvement was detected within 3.1 mm from the surgical margins, or the distance from the lesion-free area in the surgical margin to the CIS lesion was over 3.1 mm. According to our results, no glandular involvement was detected at the margins of therapeutic conization, and the mean distance from the surgical margins to the nearest glandular involvement was 3465.1 μm; 78.6% of hysterectomies after conization showed negative surgical margins, and the mean distance from the negative surgical margins to the nearest glandular involvement was 4021.2 μm. Therefore, it was difficult to evaluate the presence of residual lesions by the distance from glandular involvement to the resection margins. However, the high incidence of 21.4% of positive surgical margins in our diagnostic conization cases might be due to the following reasons: the subjects who received hysterectomy and diagnostic conization were rather elderly, and many cases were invisibile by colposcopy, with the lesion mainly in the small cervical canal and unsuitable for large conization.

When the lesion is retained at the surgical margins of the uterus after preservation treatment, a recurrence does not always occur. It has been demonstrated that the recurrence rate is less than the residual rate of the lesion after hysterectomy following conization.[1,5] However, residual lesions in the uterine cervix may be present when the lesion exists at the surgical margins. Creasman et al.[11] reported that the lesion was retained in 22% of the removed uterus and indicated that association with glandular involvement appeared in 40% of recurrent uteruses. According to Burghart et al.,[12] a high residual rate of the lesions of 42% was observed. Our results show that surface squamous lesions were retained in three of five cases with positive resection margins, and a residual lesion of glandular involvement was also detected in the removed uterus in two of three cases with positive glandular involvement at the surgical margins. In four of five cases in which the residual lesion was found in the removed uterus, glandular involvement was noticed, and the residual lesion in the uterus was suspected in cases with positive surgical margins.

On the other hand, a recurrence or new lesion developed at the rate of 0.3%[12]-3.8%[15] even if the lesion was negative at the surgical margins of conization. Furthermore, it is suggested that recurrence might be related to the existence of glandular involvement even without any lesion of CIS at the surface squamous region in the uterine cervix.

Thus, for patients who underwent conization, careful follow-up for a long time of period is necessary with a full understanding of the limits of conization.

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