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Outcomes and complications of total laparoscopic hysterectomy after conization

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Objective: High-grade squamous intraepithelial lesion (HSIL)/cervical intraepithelial neoplasia (CIN) 3, and stage IA1 cervical cancer are often diagnosed after cervical conization. Additional resection is required in some cases, and total laparoscopic hysterectomy (TLH) after conization requires attention due to the postoperative changes around the cervix. *Methods*: This single-center retrospective study investigated the perioperative outcomes and complications of TLH with or without conization. Patients diagnosed with CIN or stage IA1 cervical cancer were grouped according to whether conization was performed before TLH. The perioperative outcomes, complications, and oncological outcomes were compared for 32 patients who underwent TLH after conization (cone-TLH group) and 18 patients who underwent TLH alone (TLH group). *Results*: The mean interval between conization and TLH was 14.8 $\pm$ 5.2 weeks. There were no significant differences between the cone-TLH and TLH groups in terms of surgical time (186.3 $\pm$ 48.1 min vs. 179.8 $\pm$ 34.6 min, $P = 0.61$), blood loss (100 [5-500] mL vs. 100 [5-560] mL, $P = 0.79$), length of hospital stay (4.7 $\pm$ 1.4 days vs. 4.6 $\pm$ 1.0 days, $P = 0.86$), or recurrence rate. One patient in the cone-TLH group experienced a ureter injury. *Conclusions*: Although the outcomes were comparable between TLH alone and TLH after conization, care is needed to avoid ureter complications.

Keywords

Conization; Total laparoscopic hysterectomy; TLH; Cervical intraepithelial neoplasia; CIN; Cervical cancer; Uterine manipulator

1. Introduction

Cervical cancer is the fourth most common cancer among women worldwide, with estimates of 570,000 newly diagnosed cases and approximately 311,000 related deaths during 2018 [1, 2]. In Japan, annual incidences are approximately 7,300 cases for cervical cancer, 2,900 deaths related to cervical cancer, and 13,000 cases of precancerous lesions, such as high-grade squamous intraepithelial lesion (HSIL)/cervical intraepithelial neoplasia (CIN) 3 [3, 4]. Conization is standard therapy for precancerous lesions, as approximately one-third of HISL/CIN3 cases progress to carcinoma within 30 years [5], and as in about 6-12% of women diagnosed with HSIL on cervical biopsy, an occult invasive carcinoma can be detected in the final cone specimen [6]. However, recurrence can occur after conization and is linked to high-risk HPV infection and the presence of atypical cells at the resection or endocervical curettage margins [7–10]. Therefore, re-conization or hysterectomy may be performed after conization, and total laparoscopic hysterectomy (TLH) can be performed in cases of CIN3 or stage IA1 cervical cancer (based on the 2018 FIGO classification system). In such cases, patients should be informed regarding the oncological risk and potential short-term benefits of the different surgical approaches.

Inflammation or scarring can occur at the parametrium after conization, and the complications of TLH after conization are related to the interval between the conization and hysterectomy procedures [11–17]; for example, infectious complications or urinary tract injuries are relatively common when TLH is performed within 6 weeks after conization. Therefore, this study retrospectively evaluated perioperative and oncological outcomes of TLH after conization at our institution, as well as summarized the reported evidence regarding complications from hysterectomy after conization.

2. Methods

This retrospective study was approved by the appropriate institutional review board (300696); all participants provided written informed consent. Consecutive patients were considered eligible if they underwent TLH after conization, based on diagnoses of CIN or stage IA1 cervical cancer (according to the 2008 and 2018 FIGO systems), between April 2012 and May 2020 at our institution. Patients were excluded if they did not undergo TLH within 6 months after conization (based on patient preference) or if they were diagnosed with CIN recurrence at $>$ 6 months after conization. Thus, we included 32 patients who had undergone TLH after conization (the cone-TLH group) and compared their characteristics to those of 18 patients who underwent TLH without conization (the TLH group) during the same period based on a diagnosis of CIN. We retrospectively reviewed patients' medical records and surgical videos to collect data regarding

Table 1. Baseline characteristics

	Cone-TLH group (n = 32)	TLH group (n = 18)	*P*-value
Age (years)	47.0 ± 9.4	61.1 ± 9.6	< 0.01
BMI (kg/m^2)	21.9 ± 3.4	21.6 ± 3.1	0.85
Parity	2.2 ± 0.9	2.0 ± 0.9	0.5
No. of TVDs	2.1 ± 0.8	1.5 ± 1.0	0.04
Uterine length (cm)	7.3 ± 1.0	6.5 ± 1.6	0.63
Interval (weeks)	14.8 ± 5.2	NA	NA

Data are presented as mean ± standard deviation.

TLH, total laparoscopic hysterectomy; BMI, body mass index; TVDs, transvaginal deliveries; interval, interval between conization and total laparoscopic hysterectomy; NA, not applicable.

Table 2. Pre-operative and post-operative diagnoses in the cone-TLH group (n = 32)

Pre-TLH diagnosis			Post-TLH diagnosis	
CIN2	Endocervical margin (+)	5	CIN2	4
			CIN3	1
CIN3	Endocervical margin (+)	19	CIN3	19
	Ectocervical margin (+)	1	CIN3	1
	Surgical margin (-)	2	CIN3	2
Cervical cancer stage IA1	Surgical margin (-)	1	Cervical cancer stage IA1	1
AIS	Endocervical margin (+)	1	AIS	1
	Surgical margin (-)	3	AIS	3

Data are presented as the number of patients.

TLH, total laparoscopic hysterectomy; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma *in situ*.

perioperative outcomes (surgical time, blood loss, postoperative inflammatory markers, and hemoglobin concentrations), length of hospital stay, complications, and oncological outcomes.

The indications for TLH after conization were: 1) CIN2-3 with positive surgical margins; 2) CIN2-3 and the patient wishing to undergo hysterectomy; 3) adenocarcinoma in situ; and 4) stage IA1 cervical cancer. The indications for TLH without conization were: 1) CIN2-3 diagnosed by cervical biopsy under colposcopy; 2) being judged unsuitable for safe conization due to a narrow vagina; and 3) magnetic resonance imaging showing no visible cervical cancer.

As TLH for large myoma is more difficult, takes longer, and causes more blood loss, this was inadequate as the control group in this study; therefore, we selected these 18 cases who had undergone TLH for CIN. We performed 326 cases of TLH procedures for benign diseases and 488 cases of conizations during the study period.

2.1 Surgical technique

2.1.1 Conization

Cold knife conization was performed and repaired using Sturmdorf and Emmet sutures. Endocervical and endometrial curettage specimens were subjected to histological examination.

2.1.2 Pre-operative preparation for the TLH

Bowel preparation was performed using magnesium citrate on the day before surgery. An antimicrobial agent was administered intravenously before the surgery and was added every 3 h during the surgery. Thromboprophylaxis was also performed according to the patient's risk. We performed a colposcopy or Schiller's test immediately before the surgery to confirm the extent of the lesions in all cases in both groups.

2.1.3 Tlh

The TLH procedure involved an extrafascial hysterectomy that was performed by the attending gynecological surgeon. The surgeons had comparable experience between the two groups. Under general anesthesia, the patient was placed in a moderate Trendelenburg position (10-15°) with carbon dioxide pneumoperitoneum (8-12 mmHg). A 12-mm trocar was placed at the umbilicus to accommodate the laparoscope and three 5-mm trocars were placed in a line at the lower abdomen (a 12-mm trocar was occasionally substituted for one of the 5-mm trocars). Use of a uterine manipulator for traction was based on the surgeon's discretion. If a uterine manipulator was not used, one additional trocar was placed at the upper abdomen for uterine traction or the uterus was pulled up toward the abdomen using a suture. The bilateral uterine arteries and ureters were exposed as much as possible. A vaginal pipe was used to clarify the vaginal incision line, the incision was made using a monopolar system or a vessel sealing system, and then the vaginal wall was sutured intraperitoneally.

2.2 Statistical analysis

All statistical analyses were performed using EZR software, which is a graphical user interface for R software (version 2.12; The R Foundation for Statistical Computing, Vienna, Austria) [18]. The groups were compared using the Mann-Whitney U test, Student's *t*-test, or Chi-squared test, as appropriate. Differences were considered statistically significant at *P*-values of < 0.05.

3. Results

The patients' baseline characteristics are shown in Table 1. Relative to the TLH group, patients in the cone-TLH group were younger (47.0 ± 9.4 years vs. 61.1 ± 9.6 years, $P < 0.01$) and had more transvaginal deliveries (2.1 ± 0.8 vs. 1.5 ± 1.0, $P = 0.04$). There were no significant inter-group differences in body mass index, parity, and uterine length. The mean interval between conization and TLH was 14.8 ± 5.2 weeks. A cervical cytology examination had been performed during the interval for 22 cases (68.8%), although worsening of the disease was not suspected in any case.

The diagnoses before TLH are shown in Table 2 and Table 3. The pre-TLH diagnoses in the cone-TLH group were CIN2 with positive endocervical margins (5 cases) and CIN3 (22 cases). Among the 22 patients with CIN3, 19 cases involved positive endocervical margins; 1 case involved positive ectocervical margins. One case was stage IA1 cervical cancer (squamous cell carcinoma) and 4 cases were adenocarcinoma in situ (including 1 case with positive endocervical margins). The pre-TLH diagnoses in the TLH group were CIN2 (7 cases), CIN3 (9 cases), and lobular endocervical glandular hyperplasia (LEGH, 2 cases).

Table 3. Pre-operative and post-operative diagnoses in the TLH group (n = 18)

Pre-TLH diagnosis		Post-TLH diagnosis	
CIN2	7	CIN2	4
		CIN3	3
CIN3	9	CIN3	8
		cervical cancer stage IA1	1
LEGH	2	LEGH	1
		tunnel cluster	1

Data are presented as the number of patients.
TLH, total laparoscopic hysterectomy; CIN, cervical intraepithelial neoplasia; LEGH, lobular endocervical glandular hyperplasia.

3.1 Perioperative outcomes

The perioperative outcomes are shown in Table 4. There were no significant inter-group differences in terms of surgical time, blood loss, decreased hemoglobin concentration, inflammatory response (white blood cell count and C-reactive protein [CRP] concentration), and length of hospital stay. One patient from each group experienced blood loss of > 500 mL. In the cone-TLH group, 1 patient experienced ureter injury at the point where the ureter and uterine artery cross; this injury was intraoperatively repaired. Vaginal cuff dehiscence occurred in 1 patient from each group.

In the cone-TLH group, a uterine manipulator was used in 19 cases (59.4%). The perioperative outcomes according to manipulator use/non-use are shown in Table 5. There were also no significant inter-group differences in terms of surgical time, blood loss, decreased hemoglobin concentration, or inflammatory response (white blood cell count and CRP concentration). However, uterine manipulator use was associated with a shorter length of hospital stay; 1 patient in the non-manipulator group experienced ureter injury.

3.2 Oncological outcomes

In the cone-TLH group, 1 case was upgraded from CIN2 to CIN3 after TLH (Table 3). The initial diagnosis after conization was CIN2 with positive endocervical margins and the interval between the conization and TLH procedures was 149 days. A cervical cytology test was performed at 92 days after conization and the results revealed a high-grade squamous intraepithelial lesion. One patient who was originally diagnosed with CIN3 had a positive vaginal margin (CIN1) after TLH. Another patient's surgical margins were free from atypical cells.

In the TLH group, among the 7 patients with pre-TLH diagnoses of CIN2, 3 patients were diagnosed with CIN3 after TLH. Moreover, among the 9 patients with pre-TLH diagnoses of CIN3, 1 patient was diagnosed with stage IA1 cervical cancer (squamous cell carcinoma) after TLH. All surgical margins were free from CIN or carcinoma cells.

The mean follow-up periods were 91.8 ± 79.8 weeks for the cone-TLH group and 89.5 ± 80.2 weeks for the TLH group (Table 6). Three patients in the cone-TLH group and 1 patient in the TLH group developed vaginal intraepithelial neoplasia (VAIN) 1 during the follow-up periods and have been followed-up via only vaginal cytology or pathology examinations. The first case involved conization followed by TLH without a uterine manipulator; the final diagnosis was CIN3, and the vaginal surgical margin was positive for CIN1. This patient's vaginal cytology findings were negative soon after TLH, although vaginal pathology findings revealed VAIN 1 at 37 months after TLH. The second case involved conization followed by TLH with a uterine manipulator; the final diagnosis was CIN3, and the vaginal surgical margin was negative. Vaginal pathology findings revealed VAIN 1 at 13 months after TLH. The third case involved conization followed by TLH with a uterine manipulator; the final diagnosis was CIN3, and the vaginal surgical margin was negative. Vaginal pathology findings revealed VAIN 1 at 3 months after TLH. The fourth case involved only TLH with a uterine manipulator; the final diagnosis was CIN3, and the vaginal surgical margin was negative. Vaginal pathology findings revealed VAIN 1 at 34 months after TLH.

Table 4. Perioperative outcomes in the cone-TLH and TLH groups

	Cone-TLH group (n = 32)	TLH group (n = 18)	*P*-value
Surgical time (min)	186.3 ± 48.1	179.8 ± 34.6	0.61
Blood loss in mL, median (range)	100 (5-500)	100 (5-560)	0.79
Decrease in Hb on POD1 (g/dL)	1.2 ± 0.7	1.7 ± 1.0	0.07
WBCs on POD1 (μL)	7,765.6 ± 2,704.7	7,188.9 ± 1,965.5	0.73
CRP on POD1 (mg/dL)	2.5 ± 1.8	3.3 ± 2.6	0.5
Length of hospital stay (days)	4.7 ± 1.4	4.6 ± 1.0	0.86
Complications (n)			
Blood loss of > 500 mL	1	1	NA
Infection	0	0	NA
Ureter injury	1	0	NA
Vaginal cuff dehiscence	1	1	NA
Repeat surgery	1*	1*	NA

Data are presented as mean ± standard deviation, median (range), or number of patients.

TLH, total laparoscopic hysterectomy; WBCs, white blood cells; CRP, C-reactive protein; POD, postoperative day; NA, not applicable.

* Repair of vaginal cuff dehiscence.

Table 5. Peri-operative outcomes in the manipulator and non-manipulator groups

	Manipulator group (n = 19)	Non-manipulator group (n = 13)	*P*-value
Surgical time (min)	117.5 ± 35.4	119.2 ± 61.6	0.21
Blood loss in mL, median (range)	57 (5-500)	150 (5-350)	0.16
decrease of Hb on POD1 (g/dL)	1.1 ± 0.6	1.5 ± 0.7	0.08
WBCs on POD1 (μL)	7,778.9 ± 2,848.7	7,746.2 ± 2,693.1	0.95
CRP on POD1 (mg/dL)	2.1 ± 1.1	3.1 ± 2.3	0.16
Length of hospital stay (days)	4.2 ± 1.1	5.4 ± 1.6	0.01
Complications (n)			
Blood loss of > 500 mL	1	0	NA
Infection	0	0	NA
Ureter injury	0	1	NA
Vaginal cuff dehiscence	0	1	NA
Repeat surgery	0	1*	NA

Data are presented as mean ± standard deviation, median (range), or number of patients.

TLH, total laparoscopic hysterectomy; WBCs, white blood cells; CRP, C-reactive protein; POD, postoperative day; NA, not applicable.

* Repair of vaginal cuff dehiscence.

Table 6. Oncological outcomes

	Cone-TLH group (n = 32)	TLH group (n = 18)	*P*-value
Follow-up periods (weeks)	91.8 ± 79.8	89.5 ± 80.2	0.87
Recurrence (n)			
VAIN 1	3	1	0.56

Data are presented as mean ± standard deviation or number of patients. The recurrence rates were compared using the chi-squared test.

TLH, total laparoscopic hysterectomy; VAIN, vaginal intraepithelial neoplasia.

4. Discussion

Cases of CIN and stage IA1 cervical cancer are often diagnosed after conization. In addition, hysterectomy after conization is difficult due to inflammatory changes and vascular granulation tissue accumulation [14], which may increase perioperative complications such as infection, urinary tract injury, bleeding, and prolonged surgical time [14, 17]. Some reports have indicated that hysterectomy is best performed 3-6 weeks after conization [13, 14, 17]; however, Kim *et al.* have reported that TLH can be performed when the patient is in sufficiently good condition to tolerate the procedure [19]. Thus, we typically performed TLH at 3 months after conization. The present study failed to detect significant differences between the cone-TLH and TLH groups; we therefore believe that this supports 3 months as an adequate interval between conization and TLH. One patient experi-

Table 7. Reported complications from hysterectomy after conization

Report	Ref.	Route	Interval	Urinary tract injury	Other complications
Cavanagh, D. *et al.* (1960)	[11]	TAH TVH	7-120 days	NS	UTI: 18/66 (27.3%) Parametritis: 1/66 (1.5%) Wound infection: 5/66 (7.6%) Pneumonia: 1/66 (1.5%) Bowel fistula: 1/66 (1.5%)
Malinak, L.R. *et al.* (1964)	[14]	TAH TVH	2-150 days	NS	Wound infection: 5/124 (4.0%) Pelvic abscess: 3/124 (2.4%) Death: 1/124 (0.8%)
DeCenzo, J.A. *et al.* (1971)	[12]	TAH TVH	within 220 days	NS	FUO: 14/200 (7.0%) UTI: 57/200 (28.5%) Vaginal cuff infection: 34/200 (17.0%) Wound infection: 3/200 (1.5%)
Tae Kim, Y. *et al.* (2005)	[19]	TAH	0-6 weeks	Urinary injury: 1/298 (0.3%)	UTI: 6/298 (2.0%) Wound infection: 22/298 (7.4%) Abdominal wall hematoma: 1/298 (0.3%)
Tanaka, H. *et al.* (2013)	[27]	TLH	NS	0/3 (0%)	0/3 (0%)
Phongnarisorn, C. *et al.* (2016)	[16]	TLH	27-284 days	Bladder injury: 1/26 (3.8%) Ureter injury: 1/26 (3.8%)	Blood transfusion: 1/26 (3.8%) UTI: 3/26 (11.5%) Subcutaneous emphysema: 2/26 (7.7%)
Yin, X. *et al.* (2018)	[17]	TAH TLH	1-2 weeks	NS	Infection: 20/60 (33.3%) (TAH) Infection: 21/35 (60.0%) (TLH)
Hoshino, K. *et al.* (present report)		TLH	14.8 ± 5.2 weeks	Ureter injury: 1/32 (3.1%)	Vaginal cuff dehiscence: 1/32 (3.1%)

Interval: interval between conization and hysterectomy, TAH: total abdominal hysterectomy, TVH: transvaginal hysterectomy, TLH: total laparoscopic hysterectomy, UTI: urinary tract infection, FUO: fever of unknown origin, NS: not stated.

enced ureter injury, although she had severe deep infiltrating endometriosis; it may have been difficult to avoid this injury even if conization was not performed.

Another challenge for TLH after conization is the determination of the vaginal margin, as conization can make it difficult to recognize the vaginal fornix. The uterus must be removed with a sufficient vaginal margin; therefore, it is necessary to clarify the lesion's extent using colposcopy or Schiller's test. However, it's unlikely that a colposcopy with Schiller's test alone could provide information on the real extension of the lesion, as it could not indicate the possible presence of an underlying severe intraepithelial neoplasia or invasive carcinoma. Conization performed before the hysterectomy should be considered the correct approach, especially if the margins and the apex of the sample are negative, unlike a simple biopsy, it could provide information on possible lymphovascular spaces invasion. Unfortunately, this aspect was not investigated in this study; however, it could guide the surgeon regarding the type of surgery to be performed, especially when faced with the choice of performing a pelvic lymphadenectomy or a sentinel lymph node biopsy.

Oncological outcomes are another important factor, as many gynecologists exercise caution when choosing minimally invasive surgery for early-stage cervical cancer based on the results from the LACC trial [20]. However, some replication studies have indicated that tumor size or surgical procedure might be the source of the undesirable outcomes in the LACC trial [21–23]. Moreover, Bogani *et al.* [24] reported that conization might overcome the local recurrence risk after laparoscopic hysterectomy for early-stage cervical cancer. Thus, as none of our cases had visible lesions, we believe it was appropriate to perform laparoscopic surgery.

It is also worth considering whether a uterine manipulator could help to avoid intraoperative complications in cases with precancerous lesions. In our study, a uterine manipulator was not used for the only patient who experienced a ureter injury, although that patient had severe endometriosis and the ureter was displaced. We suspect that using a uterine manipulator may have aided in avoiding this complication. A uterine manipulator was used during TLH for 3 of 4 cases with VAIN 1; however, we suspect that the VAIN was related to HPV infection, rather than the surgical procedure. HPV infection is the most common cause of VAIN, which can occur after total abdominal hysterectomy for benign uterine diseases [25, 26]. Thus, our findings suggest that using a uterine manipulator did not worsen the oncological outcomes; we suggest that it can be used at the surgeon's discretion based on the intraabdominal findings to help avoid intraoperative complications.

The previous reports regarding hysterectomy after conization are summarized in Table 7 and Table 8. Infectious complications were significant during the 1950-1970s, and hysterectomy after conization was associated with a higher risk of infection than hysterectomy without conization. However, urinary tract injuries tended to increase as laparoscopic surgery replaced laparotomy and antimicrobial treatments were developed [11, 12, 14–17, 19, 27]. To

Table 8. Summary of complications from hysterectomy according to whether conization was performed

Report	Ref.	Route	Hysterectomy after conization	Hysterectomy without conization
Cavanagh, D. *et al.* (1960)	[11]	TAH	UTI: 18/66 (27.3%)	UTI: 4/62 (6.5%)
		TVH	Parametritis: 1/66 (1.5%)	Pneumonia: 2/62 (3.2%)
			Wound infection: 5/66 (7.6%)	Vaginal cuff hematoma: 1/62 (1.6%)
			Pneumonia: 1/66 (1.5%)	Wound infection: 1/62 (1.6%)
			Bowel fistula: 1/66 (1.5%)	
Malinak, L.R. *et al.* (1964)	[14]	TAH	Wound infection: 5/124 (4.0%)	Wound infection: 3/124 (2.4%)
		TVH	Pelvic abscess: 3/124 (2.4%)	
			Death: 1/124 (0.8%)	
DeCenzo, J.A. *et al.* (1971)	[12]	TAH	Serious febrile morbidity: 35/200 (17.5%)	Serious febrile morbidity: 9/100 (9.0%)
		TVH	FUO: 14/200 (7.0%)	
			UTI: 57/200 (28.5%)	
			Vaginal cuff infection: 34/200 (17.0%)	
			Wound infection: 3/200 (1.5%)	
Hoshino, K. *et al.* (present report)		TLH	Ureter injury: 1/32 (3.1%)	Vaginal cuff dehiscence: 1/18 (5.6%)
			Vaginal cuff dehiscence: 1/32 (3.1%)	

TAH, total abdominal hysterectomy; TVH, transvaginal hysterectomy; TLH, total laparoscopic hysterectomy; UTI, urinary tract infection; FUO, fever of unknown origin; NS, not stated.

the best of our knowledge, ours is the first report to compare operative outcomes between TLH with and without conization.

The surgical time and length of hospital stay in this study was considerably long. As mentioned in the Methods section 2.1.3, we exposed the bilateral uterine arteries and ureters as much as possible for safety; we believe this to be the reason our TLH procedure took longer. Additionally, the length of hospitalization after surgery in Japan is longer than in Western countries; in this regard, the length of hospital stay in this study was normal for Japan.

This study is limited by the small sample size, retrospective design, and relatively short follow-up period. Longer follow-up periods are needed to confirm the oncological outcomes. Furthermore, it would be useful to consider high-risk HPV infections, as these infections can cause precancerous lesions in the cervix and vagina, which would influence oncological outcomes.

5. Conclusions

Our results indicate that TLH after conization is a safe and effective surgical treatment for CIN and early-stage cervical cancer; however, we do not have enough data regarding the safest surgical approach in early-stage cervical cancer. Further prospective studies are thus needed to evaluate the perioperative and oncological outcomes, as well as to provide more accurate answers. Nevertheless, the conization procedures could be considered mandatory; they do not seem to significantly alter the safety and feasibility of the TLH procedure, while guiding the gynecologist regarding their choice for the best type of surgery. Although TLH after conization was not inferior to TLH without conization, care is needed to avoid ureter injury; a uterine manipulator might be useful in this setting.

Author contributions

Kaori Hoshino, Yasuyuki Kinjo and Hiroshi Harada designed the research study. Kaori Hoshino, Yoko Aoyama and Midori Murakami collected the data. Kaori Hoshino, Taeko Ueda, Seiji Kagami and Yusuke Matsuura analyzed the data. Kaori Hoshino and Kiyoshi Yoshino wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All patients had provided written informed consent for their treatment. The retrospective study protocol was approved by the institutional review board of the University of Occupational and Environmental Health (300696).

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Conflict of interest

The authors declare no competing interests.

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