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ORIGINAL ARTICLE

Investigation of the clinicopathological features of squamous cell carcinoma of the vulva: a retrospective survey of the Tohoku Gynecologic Cancer Unit

Masayuki Futagami · Yoshihito Yokoyama · Kaori Iino · Masahiko Aoki · Tadahiro Shoji · Toru Sugiyama · Hisanori Ariga · Hideki Tokunaga · Tadao Takano · Yoh Watanabe · Nobuo Yaegashi · Keiichi Jingu · Naoki Sato · Yukihiro Terada · Akira Anbai · Tsuyoshi Ohta · Hirohisa Kurachi · Yuuki Kuroda · Hiroshi Nishiyama · Keiya Fujimori · Takafumi Watanabe · Hisashi Sato · Toru Tase · Hitoshi Wada · Hideki Mizunuma

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Abstract
Background This multi-institutional study was conducted to clarify the clinicopathological features of squamous cell carcinomas of the vulva.
Methods The medical records of vulvar cancer patients treated between 2002 and 2012 were retrospectively reviewed following approval by the Institutional Review Board of each institution.
Results One hundred and eleven patients with vulvar malignancies were included. Of these, 63 patients had squamous cell carcinoma (57 %). Initial treatment was surgery, radiation therapy (RT), and concurrent chemoradiotherapy (CCRT) in 34 (54 %), 15 (24 %), and 11 (17 %) patients, respectively. Nineteen, 11, 26, and 7 patients had stage I, II, III, and IV disease, respectively. Of the 34 patients who had surgical treatment, 50 % had stage I disease, while 74 % of those who received CCRT had stage

M. Futagami · Y. Yokoyama (✉) · K. Iino · H. Mizunuma
Department of Obstetrics and Gynecology, Hirosaki University Graduate School of Medicine, 5-Zaifu-cho, Hirosaki, Aomori 036-8562, Japan
e-mail: yokoyama@cc.hirosaki-u.ac.jp

M. Aoki
Department of Radiology and Radiation Oncology, Hirosaki University Graduate School of Medicine, 5-Zaifu-cho, Hirosaki, Aomori 036-8562, Japan

T. Shoji · T. Sugiyama
Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Morioka, Japan

H. Ariga
Department of Radiation Oncology, Iwate Medical University School of Medicine, Morioka, Japan

H. Tokunaga · T. Takano · Y. Watanabe · N. Yaegashi
Department of Obstetrics and Gynecology, Tohoku University Graduate School of Medicine, Sendai, Japan

K. Jingu
Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan

N. Sato · Y. Terada
Department of Obstetrics and Gynecology, Akita University Graduate School of Medicine, Akita, Japan

A. Anbai
Department of Radiology and Radiation Oncology, Akita University Graduate School of Medicine, Akita, Japan

T. Ohta · H. Kurachi
Department of Obstetrics and Gynecology, Yamagata University Faculty of Medicine, Yamagata, Japan

Y. Kuroda
Department of Radiation Oncology, Yamagata University Faculty of Medicine, Yamagata, Japan

H. Nishiyama · K. Fujimori · T. Watanabe
Department of Obstetrics and Gynecology, Fukushima Medical University School of Medicine, Fukushima, Japan

H. Sato
Department of Radiation Oncology, Fukushima Medical University School of Medicine, Fukushima, Japan

T. Tase
Department of Gynecology, Miyagi Cancer Center, Natori, Japan

H. Wada
Department of Radiation Oncology, Miyagi Cancer Center, Natori, Japan

III or IV disease. Complete response (CR) rates for the surgery, RT, and CCRT groups were 73, 60, and 64 %, respectively. The 5-year survival rates for stage I/II and III/IV disease were 64 and 39 %, respectively ($P = 0.019$). The 5-year survival rates for the surgery, RT, and CCRT groups were 53, 38, and 50 %, respectively, and the prognosis of patients treated with surgery or CCRT was significantly better than that of patients who received RT ($P < 0.05$). In multivariate analysis, clinical response to initial treatment was an independent prognostic factor ($P < 0.001$).

Conclusions Although many patients had advanced-stage disease in the CCRT group, the therapeutic outcome for the surgery and CCRT groups was similar. Thus, CCRT may be a promising treatment for squamous cell carcinoma of the vulva.

Keywords Squamous cell carcinoma of the vulva · Surgery · CCRT · Prognosis

Introduction

Malignancies of the vulva are relatively rare, accounting for 3–5 % of all gynecological cancers [1]. The median age of patients at diagnosis is 60–70 years. The incidence of malignancies of the vulva is increasing and the disease affects women of all ages, not just those who are elderly [2]. To our knowledge, there are no Japanese reports over the last 2 decades describing the clinical features of this disease using large numbers of patients. Thus, it would be helpful to determine recent morbidity and mortality rates.

Surgery is considered the standard therapy for malignancies of the vulva worldwide. The surgical procedure involves en-bloc radical vulvectomy with bilateral inguinofemoral lymphadenectomy, and may be accompanied by complications related to surgery, such as wound infection, wound breakdown, urinary incontinence, lymphocele, lymphedema, and psychosocial or sexual dysfunction [3–5]. Wound complications are the most common and serious causes of morbidity and mortality in patients who underwent this type of surgical treatment. Furthermore, most patients with malignancies of the vulva are elderly, and may have severe medical complications such as uncontrollable diabetes mellitus and hypertension. Consequently, some of these patients are not eligible for surgery. In addition to surgical treatment, radiation therapy (RT) or concurrent chemoradiation therapy (CCRT) can be used to eliminate this disease. However, the treatment efficacy and prognosis of patients treated by CCRT must be clarified.

The most common histological subtype of vulvar malignancies is squamous cell carcinoma. Furthermore, the majority of uterine cervical cancer histological subtypes are also squamous cell carcinomas. Some clinical trials have shown that the therapeutic effect of CCRT on uterine cervical cancer was superior to that of RT alone [6–8]. Furthermore, therapeutic outcomes of surgical treatment and CCRT were equal in stage I and II uterine cervical cancer [9]. Moore [10] reported that CCRT for locally advanced-stage vulvar cancers resulted in a favorable outcome. Therefore, while it may be important to compare the outcomes of vulvar cancer patients treated with surgery or CCRT, we decided to focus on squamous cell carcinomas of the vulva, as to our knowledge no retrospective or prospective studies have been carried out on this subgroup.

This multi-institutional study was conducted to clarify the clinicopathological features of squamous cell carcinoma of the vulva in Japanese patients.

Patients and methods

The medical records of vulvar cancer patients treated between 2002 and 2012 were retrospectively reviewed after approval from the Institutional Review Board of the 7 participating institutions. The histological type of vulvar cancer was classified by expert pathologists from each of the institutions. A database form was constructed to collate the medical records from all of the institutions. The medical records included age, gravidity, parity, menstrual history, initial chief complaint, histological type, the International Federation for Obstetrics and Gynecology (FIGO) stage (2008), initial treatment, complications related to treatment, site of recurrence, clinical assessment of initial treatment, and prognosis. Information on surgical procedure, lymph node dissection, surgical margin status, and use of surgical flap was also present. RT was performed according to the RT guidelines of the Japanese Society for Radiation Oncology (JASTRO). The target margins were consisted as follows: clinical target volume (CTV) was gross tumor volume (GTV) plus 2 cm margin in all directions; planning target volume (PTV) was CTV plus 0.5 cm margin in all directions. A leaf margin was also taken 0.5 cm around the PTV. For cases with inguinal lymph node metastasis, the radiation field was expanded to the whole pelvic area. The dose of RT for microscopic disease was 45–50 Gy and for gross disease was 60–70 Gy with conventional fractionation (1.8–2.0 Gy per fraction, 5 days a week). RT consisted of external beam radiation using AP-PA opposed beams generated by a linear accelerator with 10 MV X-ray. Electrons were used for boosting the inguinal node region. For CCRT, 30 mg/m^2 of nedaplatin or 40 mg/m^2 of cisplatin was administered weekly during RT. Clinical response was assessed according to the revised Response Evaluation Criteria in Solid Tumors guidelines (version 1.1) [11]. Complete response (CR) was defined as no lesions on biopsy or cytology and imaging

assessments. Overall survival (OS) was calculated from the date of the start of treatment to the date of death or last follow-up. The cumulative survival curves by clinical stage, type of initial treatment, and clinical response to initial treatment were estimated using the Kaplan–Meier method. Comparison between the curves was determined using the log-rank test. *P* values <0.05 were considered statistically significant. Five variables were chosen to test their value as prognostic factors for patient survival: age, serum squamous cell carcinoma antigen (SCC) level, clinical stage, clinical response to initial treatment, and lymph node status. Serum SCC levels were measured before the initial treatment. For statistical analysis of serum SCC levels, the cases were divided into 2 groups (serum SCC level <2.0 ng/ml and ≥2.0 ng/ml). All variables with a *P* value <0.05 in univariate analysis were further evaluated by multivariate Cox regression analysis. All statistical analyses were conducted using SPSS software version 21 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

One hundred and eleven patients were included in this retrospective study. Of these, 63, 20, 10, 4, 4, 3, 2, and 3 had squamous cell carcinoma, Paget disease, sarcoma, basal cell carcinoma, malignant melanoma, adenocarcinoma, verrucous carcinoma, and other cancers, respectively. The median age of the patients was 69.8 years (range 16–95 years). Most of the patients had stage I or III disease (70 %). The characteristics of patients with squamous cell carcinoma of the vulva are shown in Table 1. The median age of the patients was 71.3 years (range 30–91 years). Chief complaints included vulvodynia, genital bleeding, and pruritus in 28 (44 %), 9 (14 %), and 9 patients (14 %), respectively. Stage I and III diseases were also more common (71 % of patients). Initial treatment involved surgery, RT, and CCRT in 54, 24, and 17 % of cases, respectively. Table 2 shows the characteristics of the vulvar squamous cell carcinoma patients according to the type of treatment they received. The median age of the surgery and CCRT groups was 10 years younger than that of the RT group. With regard to treatments, 50, 13, and 0 % of stage I patients had surgery, RT, and CCRT, respectively, while 41, 60, and 74 % of stage III and IV patients had surgery, RT, and CCRT, respectively. The rates of complications associated with surgery, RT, and CCRT were 30, 0, and 45 %, respectively. There were no fatal complications in any of the groups. Wound problems such as infection and breakdown occurred in 7 (21 %) of the surgery group patients (Table 2). Radiation dermatitis of more than grade 2 occurred in 2 (18 %) of the CCRT group patients and in none of the RT group (Table 2).

Table 1 Characteristics of patients with squamous cell carcinoma of the vulva

Clinical factors	No. of patients
Squamous cell carcinoma of the vulva	63
Age (years), median (range)	71.3 (30–91)
Gravidity (mean)	2.8
Parity (mean)	2.3
Age of menopause (mean)	49.8
Chief complaint	
Vulvodynia	28 (44 %)
Genital bleeding	9 (14 %)
Pruritus	9 (14 %)
Others	17 (28 %)
FIGO stage	
I	19 (30 %)
II	11 (17 %)
III	26 (41 %)
IV	7 (12 %)
Initial treatment	
Surgery	34 (54 %)
RT	15 (24 %)
CCRT	11 (17 %)
Chemotherapy alone	3 (5 %)

Analysis of surgical procedures used for squamous cell carcinoma of the vulva showed that simple or radical vulvectomies were performed in 6 (18 %) or 14 (41 %) of 34 patients, respectively, while lymph node dissection was performed in 28 (82 %). Bilateral inguinal node dissection was performed in 19 patients (68 %). A positive surgical margin was found in 10 (29 %) of 34 patients, and a surgical flap was used in 9 (26 %). Postoperative therapy was administered to 14 patients (41 %), and 12 (86 %) of these received radiotherapy. The median irradiation dose to the vulva in the RT group was 60.0 Gy (50–70 Gy). Of the 15 patients treated with RT alone, 3 simultaneously received boost irradiation to inguinal regions at a dose of 20–25 Gy. The median irradiation dose to the vulva in CCRT group was 60.0 Gy (50–69 Gy). Of the 11 patients treated with CCRT, 2 simultaneously received boost irradiation to inguinal node regions at a dose of 10.8–15 Gy. Nedaplatin and cisplatin were used weekly in 6 and 5 patients, respectively. The median number of weekly chemotherapy cycles was 4.6.

Patient outcome

The CR rates for the surgery, RT, and CCRT groups were 73, 60, and 64 %, respectively (Table 3). The CR and

Table 2 Clinical characteristics and complications according to the kind of treatment in squamous cell carcinoma of the vulva

	Surgery ($n = 34$)	RT ($n = 15$)	CCRT ($n = 11$)
Age (years), median (range)	68.8 (30–91)	79.0 (61–89)	69.5 (51–80)
Gravidity (mean)	2.6	3.2	3.1
Parity (mean)	2.4	2.6	2.1
FIGO stage			
I	17 (50 %)	2 (13 %)	0
II	3 (9 %)	4 (27 %)	3 (26 %)
III	14 (41 %)	8 (53 %)	4 (37 %)
IV	0	1 (7 %)	4 (37 %)
Complications			
Wound infection	6 (18 %)	0	0
Wound breakdown	1 (3 %)	0	0
Radiation dermatitis*	0	0	G2 1 (9 %) G3 1 (9 %)
Hematological toxicity	0	0	G1 2 (18 %)
Others	3 (9 %)	0	1 (9 %)

G grade, * adverse event of more than grade 2

Table 3 Clinical evaluation and recurrent sites according to the kind of treatment in squamous cell carcinoma of the vulva

	Surgery ($n = 34$)	RT ($n = 15$)	CCRT ($n = 11$)
Clinical response			
Complete response	25 (73 %)	9 (60 %)	7 (64 %)
Partial response	2 (6 %)	4 (27 %)	4 (36 %)
Progressive disease	2 (6 %)	2 (13 %)	0
Unknown	5 (15 %)	0	0
Recurrence number	10 (29 %)	5 (33 %)	5 (45 %)
Recurrent sites			
Vulva	2	2	3
Vagina	0	2	0
Inguinal lymph node	0	0	2
Pelvic lymph node	2	0	0
Para-aortic lymph node	2	0	0
Lung	1	1	0
Others	3	0	0

In surgery, CR was defined as a case where a complete resection was performed. PR was defined as a case where the residual tumor existed after surgery. PD was defined as a case where new lesions appeared or a residual tumor grew immediately after surgery

partial response (PR) rates totaled 100 % in the CCRT group. The recurrence rates for the surgery, RT, and CCRT groups were 29, 33, and 45 %, respectively (Table 3). While 8 of the 10 relapsed cases in the surgery group suffered from distant metastasis, 5 cases in the CCRT group relapsed at local sites such as the vulva and inguinal lymph nodes (Table 3). The 5-year OS curves according to clinical stage, type of initial treatment, and clinical response to treatment are shown in Fig. 1. The 5-year OS of stage I/II disease (64 %) is significantly better than that of stage III/IV (39 %) ($P = 0.019$). The 5-year OS rates for surgery, RT, and CCRT were 48, 33, and 50 %, respectively. Surgery and CCRT significantly prolonged OS compared to RT ($P < 0.05$). The 5-year OS rate for patients who experienced CR was 61 %, which was significantly better than that of patients with PR or progressive disease (PD) ($P = 0.001$, $P < 0.001$).

Determination of factors predicting OS in squamous cell carcinoma of the vulva

In univariate analysis, FIGO stage, clinical response to initial treatment, and positive lymph nodes were found to be statistically significant for OS (Table 4). No significant differences were observed for age or serum SCC levels. Furthermore, multivariate analysis showed that PD as a clinical response to initial treatment was an independent prognostic factor for OS (Table 4).

Discussion

There have been no Japanese reports using large numbers of patients describing the clinical features of malignancies of the vulva over the last 2 decades. Most research has been based on case reports or treatment studies from a single Japanese institution. This multicenter retrospective study showed similar 5-year OS rates following surgery or CCRT for vulvar squamous cell carcinoma patients, although FIGO stage I/II patients accounted for 59 % of the surgery group and stage III/IV patients for 74 % of the CCRT group. Furthermore, this study also revealed a high clinical response for patients who underwent CCRT, and all achieved CR or PR.

The median age of patients with vulvar malignancies was 69.8 years, which was consistent with a previous report [12]. The most common histological type of vulvar cancer was squamous cell carcinoma. Therefore, we studied the clinicopathological features of squamous cell carcinoma of the vulva. Of the 63 vulvar squamous cell carcinoma patients, 19 (30 %), 11, 26 (41 %), and 7 had stage I, II, III, and IV disease, respectively. In earlier reports, FIGO stage I accounted for 20 to 50 % and stage III for 40 to 65 % of patients [13–15].

In this study, surgery was selected as initial treatment in 34 (54 %) of 63 patients with squamous cell carcinomas of the vulva. Surgery is regarded as the gold standard treatment modality for malignancies of the vulva. In total, 24

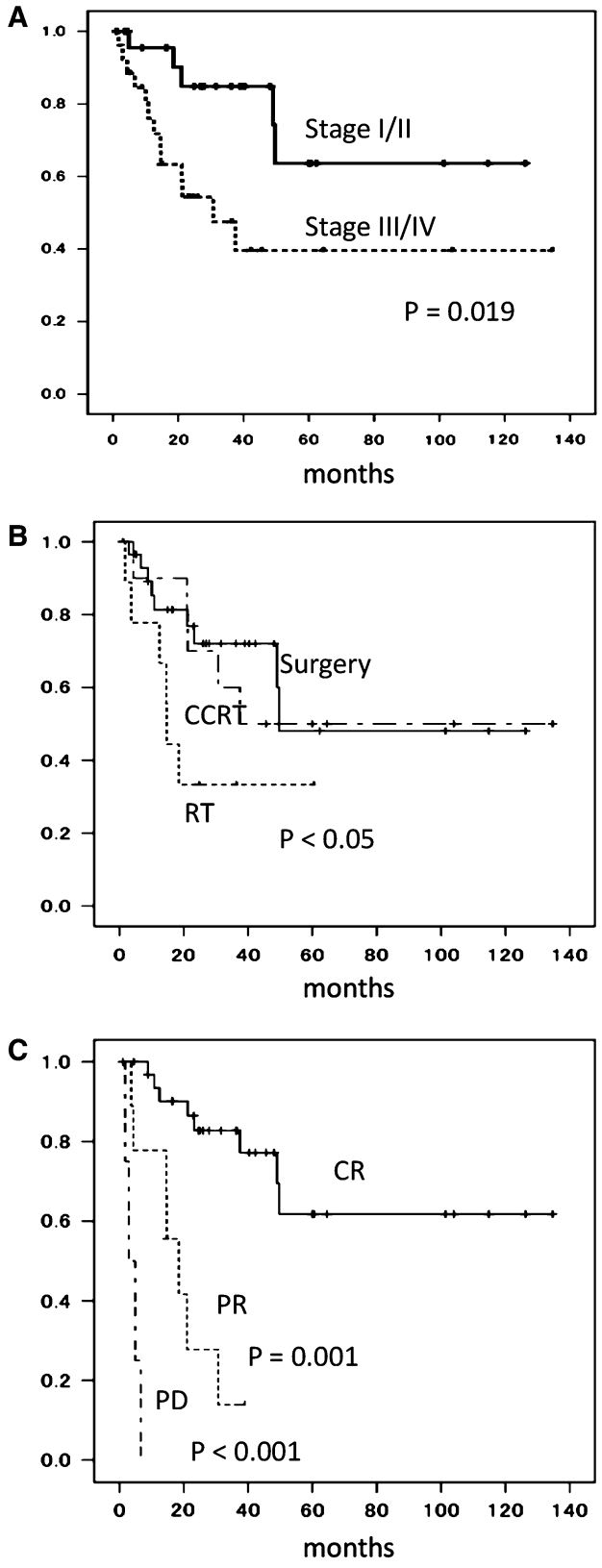

Fig. 1 Kaplan–Meier analysis of the association between stage (**a**), type of initial treatment (**b**), and clinical response to treatment (**c**) and overall survival

or 17 % of vulvar squamous cell carcinoma patients were treated with RT alone or CCRT, respectively. The median age of the RT group was 10 years higher than that of the surgery and CCRT groups. The ratios of FIGO stage III and IV disease in the RT and CCRT groups were higher than that of the surgery group (60 %, 74 vs. 41 %). Patients in the RT group may have been inoperable because of age, medical complications, or FIGO stage. The median age of the CCRT group was the same as that of the surgery group. Of the CCRT group, 74 % had stage III or IV disease and none had stage I. It is evident from these results that CCRT was used because of the advanced nature of the disease in these cases.

There were no fatal complications related to treatment in any of the groups. In this study, surgical complications such as infection and breakdown occurred in 30 %. A recent systematic review showed that the frequency of wound breakdown or dehiscence was 12.5–39 % [5]. In spite of advancements in surgical techniques, the rate of wound breakdown or dehiscence is still high, and this is supported by our data. In our study, although radical vulvectomy was performed in 41 % of vulvar squamous cell carcinoma patients and bilateral inguinal lymph node dissection in 68 %, a surgical flap was used in only 26 %. The low frequency of surgical flaps may lead to wound complications, which can adversely affect patients' quality of life (QOL), since it can prolong hospital stays and result in severe wound pain or scar contracture. On the other hand, radiation dermatitis of more than grade 2 was present in 0 and 18 % of the RT and CCRT groups, respectively, and hematological toxicity of grade 1 was found in 18 % of the CCRT group. Because the severe complication rate was very low in the RT and CCRT groups, respectively, this did not affect hospital stay and QOL.

Clinical responses including CR and PR following surgery, RT, and CCRT were 79, 87, and 100 %, respectively. In this study, while 8 of the 10 patients with relapse in the surgery group showed distant metastasis, 5 in the CCRT group showed relapse at local sites such as the vulva and inguinal lymph nodes. According to previous reports, the majority of recurrence sites involved the vulva, vagina, and inguinal lymph nodes [13, 15]. Differences in the location of the relapsed sites between the surgery and CCRT groups suggest that CCRT is more effective at controlling distant metastasis in advanced squamous cell carcinoma of the vulva. Three of the 5 patients who locally relapsed in the CCRT group were able to receive a surgically complete resection of the relapsed mass.

The 5-year survival rates for the surgery and CCRT groups were similar (48 and 50 %). Although FIGO stage III/IV disease accounted for 74 % of the CCRT group, it was effective for the treatment of advanced vulvar

Table 4 Univariate and multivariate analyses for determining prognostic factors of overall survival in squamous cell carcinoma of the vulva

Variables	Univariate analysis for overall survival (OS)			Multivariate analysis for OS (Cox proportional hazards model)		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age						
Continuous	1.004	0.970–1.039	0.826			
SCC value						
<2.0	1					
≧2.0	1.702	0.440–6.585	0.441			
FIGO stage						
I/II	1			1		
III/IV	3.129	1.203–8.141	0.019	0.651	0.048–8.843	0.747
Clinical response						
CR	1			1		
PR	1.270	2.366–22.336	0.001	2.042	0.422–9.872	0.375
PD	86.708	13.344–563.430	<0.001	75.983	11.047–522.615	<0.001
Lymph node						
Positive	3.055	1.281–7.284	0.006	4.510	0.969–18.435	0.258

HR hazard ratio, *CI* confidence interval

squamous cell carcinoma. There have been reports that CCRT was an effective treatment for locally advanced squamous cell carcinoma of the vulva [10, 16–18]. The chemotherapy regimens used in those studies were cisplatin-based. Although a small cohort was analyzed in our retrospective study, CCRT using nedaplatin was as effective as CCRT with cisplatin-based drugs in squamous cell carcinoma of the vulva. We have already reported that 30 mg/m^2 of weekly nedaplatin with concurrent radiotherapy is an effective and well-tolerated regimen for advanced squamous cell carcinoma of the uterine cervix [19]. It remains to be clarified whether CCRT can be a promising alternative treatment for squamous cell carcinoma of the vulva via a phase II prospective trial of CCRT using weekly nedaplatin.

Many reports have examined the prognostic factors for survival of vulvar squamous cell carcinoma [13–15, 20–25]. Factors such as age, lymph node metastasis, tumor size, depth of invasion, and involvement of resection margins were related to OS [25]. In particular, lymph node status appears to be the most important independent prognostic factor [25]. In our univariate analysis, clinical stage, clinical response to initial treatment, and lymph node status were statistically significant for 5-year OS. Multivariate analysis showed that only clinical response to initial treatment was an independent prognostic factor for 5-year OS. FIGO stage and lymph node status were not independent prognostic factors in our retrospective study, and this is possibly due to the small sample size. Recently, tumor size, stromal invasion, and positive resection margins were found to be prognostic factors for recurrence. Furthermore, Baiocchi et al. [22] reported that patients with more than 3 positive lymph nodes had a worse prognosis. In this study, the number of positive inguinal lymph nodes, spread beyond regional lymph nodes, and tumor size were not reviewed because histological analysis could not be performed to determine the inguinal lymph node status in the RT and CCRT groups. To the best of our knowledge, there has been no other study comparing the effects of surgery and CCRT in squamous cell carcinoma of the vulva. Since the number of patients in this study is small, a larger scale retrospective study or a prospective study is required to evaluate the clinical outcomes following surgery and CCRT in this disease.

Conflict of interest The authors declare that they have no conflict of interest.

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