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Original Article

Groin lymph node detection and sentinel lymph node biopsy in vulvar cancer

Chieko Sakae,[1] Ken Yamaguchi,[1] Noriomi Matsumura,[1] Hidekatsu Nakai,[2] Yumiko Yoshioka,[1] Eiji Kondoh,[1] Junzo Hamanishi,[1] Kaoru Abiko,[1] Masafumi Koshiyama,[1] Tsukasa Baba,[1] Aki Kido,[3] Masaki Mandai,[2] Ikuo Konishi[1]

[1]Department of Gynecology and Obstetrics, Kyoto University, Kyoto, Japan
[2]Department of Obstetrics and Gynecology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan
[3]Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Kyoto, Japan

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Correspondence to
Ken Yamaguchi
Department of Gynecology and Obstetrics, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail: soulken@kuhp.kyoto-u.ac.jp

ORCID
Chieko Sakae
http://orcid.org/0000-0001-9858-8049
Ken Yamaguchi
http://orcid.org/0000-0002-7669-1405
Hidekatsu Nakai
http://orcid.org/0000-0002-9994-2131
Yumiko Yoshioka
http://orcid.org/0000-0002-4654-0585
Eiji Kondoh
http://orcid.org/0000-0001-9399-1015
Junzo Hamanishi
http://orcid.org/0000-0002-7750-0623
Kaoru Abiko
http://orcid.org/0000-0001-9648-158X
Masafumi Koshiyama
http://orcid.org/0000-0003-2412-4430
Tsukasa Baba
http://orcid.org/0000-0003-0066-3747

ABSTRACT

Objective: To identify suitable diagnostic tools and evaluate the efficacy of sentinel lymph node (SLN) biopsy for inguinal lymph node metastasis in vulvar cancer.
Methods: Data from 41 patients with vulvar cancer were evaluated retrospectively, including magnetic resonance imaging (MRI) measurements, SLN biopsy status, groin lymph node metastasis, and prognosis.
Results: SLN biopsy was conducted in 12 patients who had stage I to III disease. Groin lymphadenectomy was omitted in five of the nine patients with negative SLNs. All SLN-negative patients who did not undergo groin lymphadenectomy showed no evidence of disease after treatment. On MRI, the long and short diameters of the inguinal node were significantly longer in metastasis-positive cases, compared with negative cases, in 25 patients whose nodes were evaluated pathologically (long diameter, 12.8 mm vs. 8.8 mm, p=0.025; short diameter, 9.2 mm vs. 6.7 mm, p=0.041). The threshold of >10.0 mm for the long axis gave a sensitivity, specificity, positive predictive value, and negative predictive value of 87.5%, 70.6%, 58.3%, and 92.3%, respectively, using a binary classification test. Decision tree analysis revealed a sensitivity, specificity, and accuracy of 87.5%, 70.6%, and 76.0%, respectively, with the threshold of >10.0 mm for the long axis on MRI. The criteria of >10.0 mm for the long axis on MRI predicted an advanced stage and poorer prognosis using a validation set of 15 cases (p=0.028).
Conclusion: Minimally invasive surgery after preoperative evaluation on MRI and SLN biopsy is a feasible strategy for patients with vulvar cancer.

Keywords: Groin; Lymph Node; Sentinel Lymph Node Biopsy; Vulvar Neoplasms

INTRODUCTION

Vulvar cancer accounts for approximately 3% to 5% of gynecologic malignancies and is rare in women aged <25 years [1,2]. However, because of the spread of human papilloma virus (HPV), the incidence is increasing, especially in young women [3]. Because lymph node metastasis is one of the most important prognostic factors in vulvar cancer, the standard treatment for early stage vulvar cancer is tumor excision with inguinofemoral lymphadenectomy [1,4]. One-third of patients with early stage disease have lymph node

Aki Kido
http://orcid.org/0000-0001-5131-2870

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

metastases and would benefit from inguinal lymphadenectomy [5]. However, 50% of patients experience complications after inguinal lymph node dissection, including groin wound infections, wound breakdown, lymphocyst formation, lymphedema, and cellulitis [6-9]. Therefore, accurate detection of groin lymph node metastases to determine the appropriateness of inguinofemoral lymphadenectomy could reduce the postoperative complication rate, which would likely improve prognosis.

The diagnosis of lymph node metastases before nodal resection includes preoperative imaging and intraoperative sentinel lymph node (SLN) biopsy. SLNs are the target nodes to which tumor cells primarily metastasize, because they are the initial site of tumor drainage. SLN mapping enables the omission of inguinofemoral lymphadenectomy for SLN-negative cases and can significantly decrease the complication rate. This technique is presently employed in patients with breast cancer, melanoma, and urological and gynecologic malignancies [10]. SLNs are identified using the radioactive tracer technetium-99m (^{99m}Tc), blue dye, and/or near-infrared fluorescence. The GROningen INternational Study on Sentinel nodes in Vulvar cancer (GROINSS-V) study showed that the risk of non-SLN metastases increases with size of the SLN metastasis [11], increasing the importance of considering SLN metastasis in vulvar cancer management. This factor had a negative predictive value (NPV) of 95% to 99%, suggesting that 1% to 5% of vulvar cancers metastasize to non-SLNS. However, a precise diagnostic methodology for determining the risks and benefits of omitting inguinal lymphadenectomy based on SLN biopsy data has not been established. Magnetic resonance imaging (MRI) is useful for preoperative assessment of gynecologic neoplasms. For vulvar cancer, the sensitivity and specificity of MRI for detecting lymph node metastasis varies widely, from 40% to 89% and 82% to 100%, respectively [4,12-15]. MRI has the potential to compliment SLN biopsy.

The purpose of this study was to retrospectively evaluate the feasibility of omitting inguinofemoral lymphadenectomy in SLN-negative cases and the diagnostic accuracy of MRI in patients with vulvar cancer.

MATERIALS AND METHODS

1. Patients

Forty-one patients with vulvar cancer treated at Kyoto University between February 2005 and September 2014, or at Kindai University between January 2001 and September 2014 (19 and 22 patients, respectively), were included in this retrospective study. Histological subtype was diagnosed via biopsy before any treatment. Clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) 2008 criteria was applied for all patients [16]. Malignant melanoma in the vulva was excluded in this study. Pathological tumor size and stromal invasion depth were also measured. No significant differences in the frequencies of clinical factors were identified between Kyoto University and Kindai University (data not shown).

2. SLN biopsy

SLN biopsy to omit groin lymphadenectomy was conducted with the approval of the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. All patients provided informed consent. The SLN procedure was performed using a radioactive tracer (radioisotope [RI] method), patent blue V (blue dye method), and/or indocyanine green (ICG method) based on the choice of the patients. At 18 to 20 hours before the operation, ^{99m}Tc-futin acid was

injected intradermally at 5-mm intervals around the primary tumor. Shortly before the start of surgery, ICG or blue dye was injected into the same positions used for the RI method. One hour after injection, the number and locations of the SLNs were confirmed using positron-emission tomography. SLNs were detected intraoperatively using an RI counter. A lymph node was considered sentinel when blue dye and/or ICG was detected, and/or radioactivity was ≥10× higher than the background radioactivity. If rapid frozen section analysis revealed SLN positivity, then bilateral inguinal lymphadenectomy was performed. If all SLNs were negative for malignant cells, groin lymphadenectomy was not conducted at Kyoto University. The pathological diagnoses of all lymph nodes that were submitted for intraoperative rapid frozen section analysis were confirmed postoperatively. Pathology was determined by a pathologist and a gynecological oncologist.

3. Preoperative evaluation of groin lymph nodes using MRI

The largest lymph node size was evaluated by using MRI data obtained within 1 month before treatment initiation. The MRI sequences used for the measurement of lymph nodes were axial and sagittal fast spin echo T2-weighted images (repetition time/echo time [TR/TE] = 4,500/83 msec, flip angle [FA] = 150°, slice thickness 4 mm at Kyoto University; TR/TE = 3,500/80 msec, FA = 90°, slice thickness 5 mm at Kindai University). The long and short axes of the groin nodes were compared between two groups according to whether they were SLN-negative or positive. The sensitivity, specificity, positive predictive value (PPV), and NPV of a binary classification test were calculated to determine the criteria for whether an SLN biopsy should be conducted. The decision tree was generated using Weka, a publically available data mining software (http://www.cs.waikato.ac.nz/ml/weka/). Histology, stage, length of the long and short axes of the lymph nodes, and the ratio of the short and long axes (S/L ratio) were applied to generate a strategy for the identification of groin lymph node metastasis.

4. Statistical analyses

Fisher exact test was used to determine differences in the distributions of patient characteristics. An unpaired t-test was used to determine differences between the SLN-positive and negative groups. The correlation coefficient was calculated using Pearson correlation analysis. Follow-up and survival data were calculated from the date of primary surgery to the date of the last examination or death. Prognosis was evaluated using Kaplan-Meier survival curve analysis conducted using GraphPad Prism (GraphPad, La Jolla, CA, USA). The prognostic significance of certain factors (age, histology, FIGO stage, tumor size, length of the long and short axes of the lymph nodes, and S/L ratio) was assessed using the Cox proportional hazards regression model with SPSS ver. 22 (IBM Co., Armonk, NY, USA). A $p<0.05$ was considered statistically significant.

RESULTS

1. Patients' clinical characteristics and treatments

The clinical background characteristics of the patients are listed in **Supplementary Table 1**. The mean age of vulvar cancer patients was 71 years (range, 28 to 91 years) (**Supplementary Table 2**). The FIGO staging distribution is as follows: stage I, 23 cases (56.1%); II, three cases (7.3%); III, 10 cases (24.4%); and IV, five cases (12.2%). Histological subtypes included squamous cell carcinoma (SCC), 32 cases (78.0%); invasive Paget's disease, five cases (12.2%); clear cell adenocarcinoma, one case (2.4%); basal cell carcinoma, one case (2.4%); Skene's adenocarcinoma, one case (2.4%); and neuroendocrine tumor, one case (2.4%).

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Table 1. The sensitivity, specificity, PPV, and NPV of the lengths of the long and short axes of groin lymph nodes

Variable	Pathological diagnosis of groin lymph nodes		Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
	Positive	Negative					
Long axis (mm)			87.5	70.6	76.0	58.3	92.3
>10.0	7	5					
≤10.0	1	12					
Short axis (mm)			87.5	41.2	56.0	41.2	87.5
>5.8	7	10					
≤5.8	1	7					

NPV, negative predictive value; PPV, positive predictive value.

HPV genotyping was performed for the youngest patient, who had SCC of the vulva, and who was undergoing steroid and immunosuppressive drug treatment for systemic lupus erythematosus. She tested positive for HPV 16, 51, 52, and 56 genotypes.

The standard treatment was surgery, except in nine patients who underwent radiation therapy for severe complications or advanced stage disease with multiple distant metastases (**Supplementary Table 2**). Adjuvant chemotherapy was administered after surgery for six patients, and radiation was administered after surgery for two patients.

2. Usefulness of SLN biopsy in the groin

SLN biopsy was conducted in 12 patients with stage I to III disease. All three detection methods were used in two patients, RI and blue dye were used in two, RI alone was used in one, blue dye alone was used in three, and ICG alone was used in four. Blue dye and RI did not detect the SLN for one patient, whereas the ICG method identified the SLNs in all patients. Of the 12 patients who underwent groin SLN biopsy, SLN-positivity was apparent in three patients; two patients underwent groin lymphadenectomy and one underwent adjuvant radiation therapy as an alternative treatment. The histological diagnosis for the three patients with positive SLNs was SCC. Of these three patients, two died of vulvar cancer and one

Table 2. Univariate and multivariate analyses for disease-free survival rate

Variable	No.	Univariate analysis			Multivariate analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Age (yr)		1.559	0.520–4.673	0.428			
<70	14						
≥70	20						
Histology		0.633	0.174–2.301	0.488			
SCC	26						
Non-SCC	8						
FIGO stage		32.744	4.160–257.740	0.001*	37.149	3.493–395.057	0.003*
I and II	19						
III and IV	15						
Tumor size (cm)		1.887	0.576–6.185	0.295			
≤3	13						
>3	21						
Long axis (mm)		5.871	1.309–26.328	0.021†	0.603	0.084–4.320	0.615
≤10	15						
>10	19						
Short axis (mm)		4.725	1.054–21.185	0.043†	1.554	0.249–9.700	0.637
<7	13						
≥7	21						
S/L ratio		0.997	0.345–2.889	0.997			
<0.75	13						
≥0.75	21						

Univariate and multivariate analyses were performed using the Cox regression model.

FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; SCC, squamous cell carcinoma; S/L, ratio of the short and long axes.

*p<0.005. †p<0.05.

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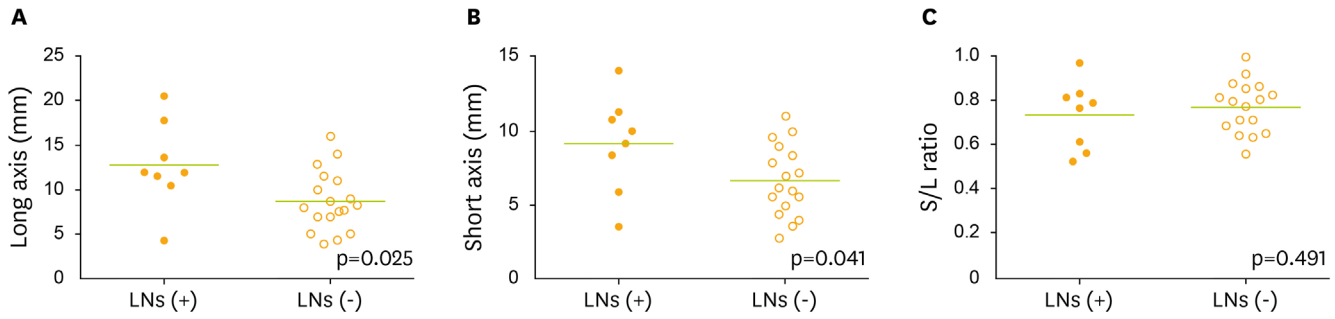

Fig. 1. (A) Long axis, (B) short axis, and (C) the ratio of the short to the long axis diameter (S/L ratio) of the inguinal lymph node (LN) on magnetic resonance imaging. Groin LN-positive cases showed significantly longer long and short axis diameters (p=0.025 and p=0.041, respectively). There were no significant differences with the S/L ratio (p=0.491).

remains alive and disease-free after inguinal lymphadenectomy. Nine patients did not have positive SLNs, and groin lymphadenectomy was omitted in five of them. All SLN-negative patients who did not undergo groin lymphadenectomy showed no evidence of disease after treatment. These findings suggest that the detection of groin metastasis by SLN biopsy to avoid inguinal lymphadenectomy is feasible and safe for the treatment of vulvar cancer.

3. Identification of the criteria to conduct SLN biopsy using MRI

The usefulness of preoperative MRI to select the cases that do not require SLN biopsy before surgery was assessed. Preoperative evaluation of groin lymph nodes using MRI was performed in 38 of the 41 patients. Of these 38 cases, groin node metastasis was evaluated pathologically in 25 patients. For groin lymph node metastasis-positive cases, the mean long axis was 12.8 mm, whereas for negative cases, it was 8.8 mm (p=0.025) (**Fig. 1A**). In addition, positive cases had significantly longer short diameters compared with negative cases (9.2 and 6.7 mm, respectively; p=0.041) (**Fig. 1B**). The S/L ratio was not significantly different between groin lymph node metastasis-positive and -negative cases (0.736 and 0.774, respectively; p=0.491) (**Fig. 1C**).

To evaluate if the long and short axes of groin lymph nodes could predict the need for SLN biopsy, the sensitivity, specificity, PPV, and NPV of a binary classification test were calculated using the 25 cases whose groin nodes were evaluated pathologically. Seven out of eight patients with groin node involvement and five patients without groin involvement were predicted using a threshold of >10.0 mm for the long axis. This algorithm gave a sensitivity, specificity, PPV, and NPV of 87.5%, 70.6%, 58.3%, and 92.3%, respectively (**Table 1**). For the short axis, a threshold of >5.8 mm gave a sensitivity, specificity, PPV, and NPV of 87.5%, 41.2%, 41.2%, and 87.5%, respectively (**Table 1**). These findings suggest that a long axis >10 mm might be useful as the criterion requiring SLN biopsy.

4. Preoperative prediction of groin lymph node metastasis in vulvar cancer

Because groin lymph node metastasis is a factor associated with poor prognosis, the correlation coefficient between the size of the primary tumor and the long axis of the inguinal lymph node on MRI was evaluated using 34 samples. The long axis of the groin lymph node was positively correlated with the primary tumor size, although this was not statistically significant (r=0.334, p=0.054) (**Fig. 2A**). Kaplan-Meier survival analyses showed that the 12 patients whose tumor size was 3 cm or smaller had a significantly more favorable overall survival compared with the 22 patients whose tumor was larger than 3 cm on MRI (p=0.006) (**Fig. 2B**).

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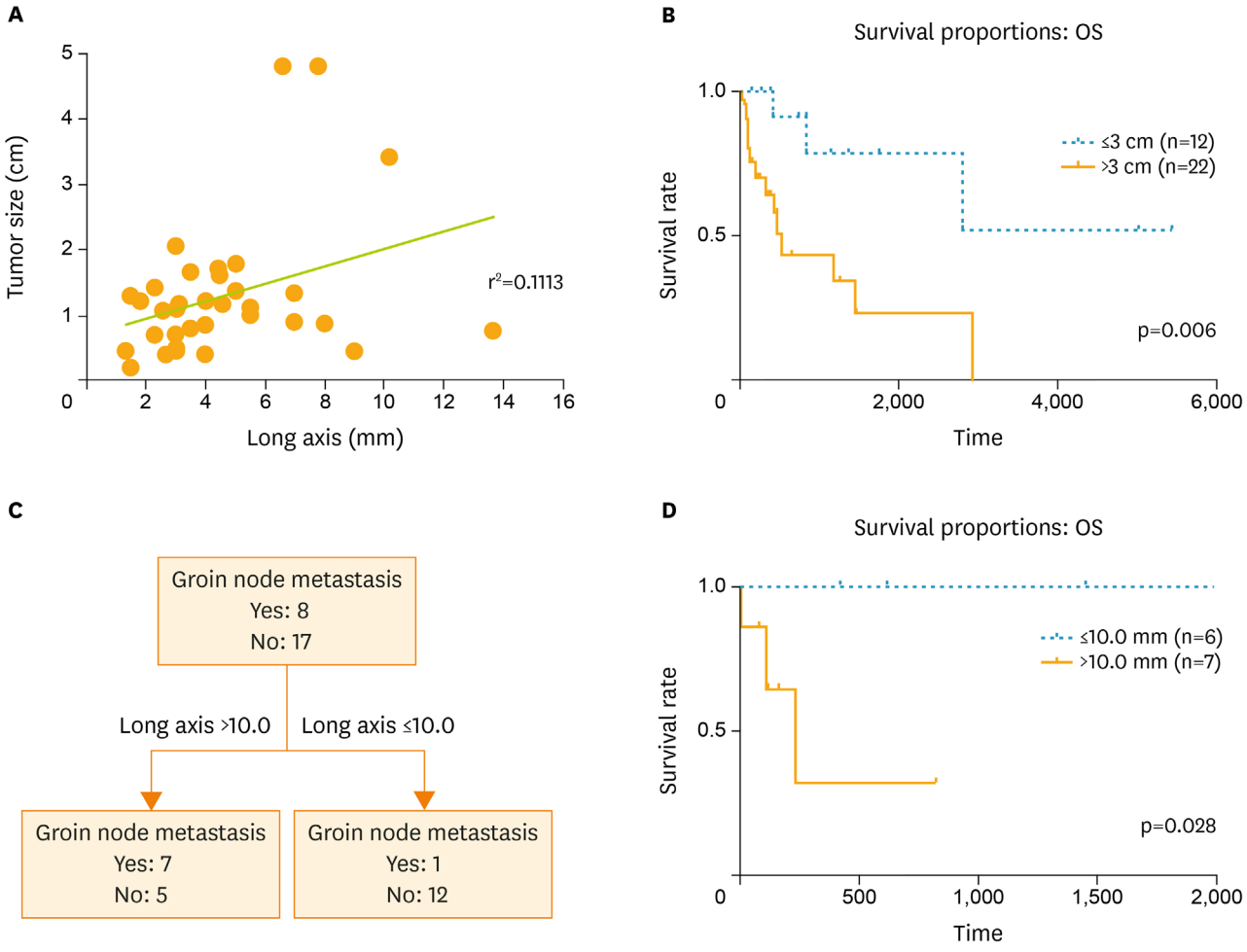

Fig. 2. (A) The long axis of the groin lymph node is positively correlated with the size of the primary tumor (p=0.054). (B) Kaplan-Meier survival analysis showed that patients with a primary tumor larger than 3 cm had a significantly poorer prognosis for overall survival (p=0.006). (C) Decision tree analysis revealed that a long axis diameter of 10.0 mm on magnetic resonance imaging was the threshold length for the prediction of groin node metastasis (n=25). This cut-off yields a sensitivity, specificity, and accuracy of 87.5%, 70.6%, and 76.0%, respectively. (D) Kaplan-Meier survival analysis showed a significantly poorer prognosis for patients with a long axis of the groin lymph node greater than 10 mm for overall survival (p=0.028).

To identify the criteria for preoperative detection of groin node metastasis, a decision tree analysis was conducted using histology, tumor size, long axis length (mm), short axis length (mm), and S/L ratio determined using MRI in the 25 patients whose groin nodes were analyzed pathologically. Only the long axis length was selected as a preoperative predictor by the decision tree analysis. Seven out of eight patients with pathological groin node metastasis and five patients without groin involvement were predicted using a threshold of >10.0 mm for the long axis. This algorism gave a sensitivity, specificity, and accuracy of 87.5%, 70.6%, and 76.0%, respectively (**Fig. 2C**).

To validate the usefulness of the predictive factors of groin node metastasis using 10.0 mm as the cut-off length for the long axis of the groin node on MRI, the clinical impact of the axis length was assessed in the 13 patients whose groin nodes were not analyzed pathologically. Five out of six cases with a groin node long axis less than 10 mm had stage I to II cancer, whereas six out of seven patients with a long axis greater than 10 mm had stage III to IV cancer. Kaplan-Meier survival analyses were applied to evaluate the contribution of the long axis cut-off of 10 mm to vulvar cancer prognosis. The seven patients whose groin node had a

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long axis >10 mm had significantly worse overall survival compared with the six patients who had a long axis ≤10 mm on MRI (p=0.028) (**Fig. 2D**).

The univariate analysis of disease-free survival showed that FIGO staging, and the lengths of the long and short axes of groin nodes were significant prognostic factors (p=0.001, p=0.021, and p=0.043, respectively) (**Table 2**). The multivariate analyses indicated that the FIGO stage was an independent prognostic factor associated with poor disease-free survival (p=0.003) (**Table 2**). For overall survival, no values were significant prognostic factors (**Supplementary Table 3**).

DISCUSSION

This retrospective study evaluated the feasibility of omitting groin lymphadenectomy in SLN-negative cases and the preoperative prediction of groin lymph node metastasis on MRI in patients with vulvar cancer. Ramanah et al. [17] reported that the average age of advanced vulvar cancer patients was 72 years, which is consistent with the average age in the present study. However, two of our patients were less than 35 years of age, and HPV infection causes up to half of the vulvar cancers in women under the age of 50 years [1]. We analyzed HPV genotyping in the youngest patient. Because this patient exhibited HPV positivity and was undergoing steroid treatment for an accompanying disease, immune suppression might have been related to the development of SCC of the vulva in this patient. According to the Japan Society of Obstetrics and Gynecology, Gynecologic Oncology Committee, the incidence of uterine cervical cancer related to HPV infection in young women (<40 years) has been increasing over recent decades (13.3% in 1982 and 24.0% in 2011). Therefore, similar to the epidemiology of cervical cancer, the spread of HPV in the younger generation might lead to a rise in the incidence of vulvar cancer in the future.

In 1979, DiSaia et al. [18] first declared that groin lymph nodes were the SLNs of vulvar cancer. In 1994, Levenback et al. [19] reported the first SLN biopsy for vulvar cancer using blue dye, using the SLN biopsy methodology used for malignant melanoma. A meta-analysis indicated that the SLN detection rate varied between studies depending on the methodology used, ranging from 76% to 100% for ^{99m}Tc alone, 53% to 88% for blue dye alone, and 84% to 100% for a combination of the two [1]. They suggested that, if an SLN biopsy is going to be performed, both methodologies should be used in each patient to reduce the risk of underdiagnosis [1,10]. Consistent with their reports, we also found that using only one methodology could result in false negatives for both the RI and blue dye methods. The sensitivity of SLN biopsy as well as the success of SLN detection is related to the mapping method used, with better results being obtained when RI and blue dye are both used and reduced sensitivity with blue dye alone [10]. Fortunately, our results showed sensitivity and specificity of 100% for both. These findings might be caused for the limitation of sample size in this study.

In cases with negative SLNs, inguinal lymphadenectomy can be omitted while still providing a low recurrence rate and good prognosis [1]. SLN biopsy to omit inguinal lymphadenectomy shows significantly fewer complications compared with precautionary inguinal lymphadenectomy [2]. In 2008, the International Sentinel Lymph Node Society stated that groin SLN biopsy performed by a skilled multidisciplinary team was feasible for well-selected patients with SCC of the vulva, whose primary tumors had an invasion depth >1 mm, a tumor

size < 4 cm, and no obvious metastatic disease [20]. The findings of the present study are consistent with the accuracy of SLN detection and a favorable prognosis in the follow-up period for patients with SCC who underwent SLN biopsy, suggesting that groin SLN biopsy is an acceptable alternative for lymphadenectomy in patients with early vulvar cancer.

During SLN biopsy, minimal excision is important to reduce the rate of postoperative complications, such as wound breakdown. Recently, intraoperative near-infrared fluorescence imaging using ICG was applied as a new technique for SLN biopsy in gynecological malignancies [21,22]. In vulvar cancer, three technical feasibility studies reported that this new method showed similar accuracy to the RI method and was superior to the blue dye method [21,23,24]. In our patients, the SLN biopsy excision size could be minimized because SLNs could be accurately detected using the ICG method.

To avoid postoperative complications and improve the prognosis of patients with vulvar cancer, the evaluation of inguinal lymph node status is important. Therefore, multicenter or larger studies are needed for a more accurate estimation of the test accuracy for detection of groin lymph node metastasis in this rare disease. Of note, reports describing SLN biopsy in Asian patients, including Japanese patients, with vulvar cancer have not been published.

Groin lymph node status can be evaluated in the pre- and intraoperative settings. Although there is no consensus on the appropriate node diameter lengths to use when determining a cut-off value for MRI analysis, using a short axis diameter length >1 cm for MRI, Singh et al. [15] showed a sensitivity, specificity, PPV, and NPV of 85.7%, 82.1%, 64.3%, and 93.9%, respectively. Furthermore, another study using a minimal short axis diameter length of ≥8 mm detected lymph node involvement in vulvar cancer with a sensitivity, specificity, PPV, and NPV of 52%, 85% to 89%, 46% to 52%, and 87% to 89%, respectively [13]. These results are consistent with the findings of the present study. Kataoka et al. [4] reported that, to detect lymph node metastases, the S/L ratio should be ≥0.75, yielding a sensitivity, specificity, PPV, and NPV of 81.3%, 89.7%, 81.3%, and 89.7%. However, we found that a higher S/L ratio tended to indicate less groin node metastasis in the present study. The disagreement between the present study and that of Kataoka et al. [4] might be due to the difficulty in measuring the lymph node diameter on MRI when the node is small. Other reasons might include the limited number of patients with groin metastasis in our analysis or a different slice thickness.

Evaluation of groin node metastasis using MRI might lead to a decreased need for SLN biopsy itself. Clinical factors were assessed to determine whether MRI could replace SLN biopsy. Although primary tumor size and invasion depth have been found to contribute to inguinal lymph node metastases [3], we did not find any significant relationship between these features and groin lymph node metastases (data not shown), perhaps owing to the limited number of patients in our study. The prevalence of groin lymph node metastasis is approximately 19% in patients with vulvar cancer tumors <2 cm in diameter, whereas 30% to 55% of patients with larger tumors have groin node metastasis [3]. Furthermore, if the invasion depth is <2 mm, then the rate of groin lymph node positivity was <10%, and as the extent of invasion increases, the frequency of groin lymph node involvement increases [3]. However, a true evaluation of invasion depth is not possible using MRI. This study showed that the patients whose tumor size was 3 cm or smaller had a significantly more favorable overall survival compared with the patients whose tumor was larger than 3 cm on MRI. A long axis >10 mm had a favorable sensitivity of 87.5% and NPV of 92.3%, suggesting that only 7.8% of cases with a long axis of the groin node <10 mm will experience recurrence

when an SLN biopsy is not performed. For the short axis, the threshold of 5.8 mm indicated a value of 87.5% for both sensitivity and NPV. Taken together, these findings suggest that MRI is useful for the preoperative prediction of inguinal lymph node metastases, although it is necessary to recognize that such limitations could lead to underdiagnosis in approximately 10% of patients with inguinal node metastases from vulvar carcinoma. These findings suggest that groin lymphadenectomy could be omitted when the long axis of the groin lymph node is less than 10 mm and the size of the primary tumor is equal to or less than 3 cm on preoperative MRI.

In summary, SLN biopsy combined with clinical follow-up for SLN-negative cases led to a favorable prognosis in patients with early-stage vulvar cancer. ICG is a promising methodology for accurate SLN detection in patients with vulvar cancer. SLN detection in patients with early-stage vulvar cancer resulted in decreased postoperative morbidity without compromising groin recurrence and survival outcomes. MRI was useful for the preoperative prediction of inguinal lymph node metastases. Further analysis using more vulvar cases is needed to evaluate whether MRI complements SLN biopsy.

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