Clinicopathological Demographics of Malignant Melanoma of the Vulva and Vagina in Japan

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Abstract

Objective: Malignant melanomas of the vulva (VuM) and vagina (VaM) represent a unique subgroup of rare malignant melanomas with critical biological properties and treatment differing from that of other cancers. In Japan, adequate surveys on these have not been performed. The objective of this study was to elucidate the clinicopathological demographics and the outcomes of VuM and VaM in Japan.

Methods: This retrospective observational study included women with invasive VuM or VaM, identified from older medical records in Japan. Clinical data were collected and the Kaplan-Meier method was used to analyze progression-free survival (PFS) and overall survival (OS). Univariate and multivariate regression models were used to identify factors significantly related to survival.

Results: A total of 217 patients were identified: 109 (50.2%) with VuM and 108 (49.8%) with VaM. The median PFS was 16.8 months in patients with VuM (95% confidence interval [CI] 23.1-87.7) and 15.6 months in patients with VaM (95% CI 8.4-12.6). The median OS was 43.9 months (95% CI 60-138) and 31.1 months (95% CI 24.8-45.3) in patients with VuM and VaM, respectively. Multivariate analysis showed that a >III American Joint Committee on Cancer (AJCC) disease stage (hazard ratio [HR] = 2.063; 95% CI = 0.995-4.278) was associated with poorer PFS, and unknown surgical margin was the only independent factor influencing OS (HR = 2.188; 95% CI = 1.203-3.977).

Conclusions: The overall outcomes of VuM and VaM remain poor in Japan. The AJCC stage and the surgical margin are significant predictors of survival.

1. Introduction

Vulvar melanoma (VuM) and vaginal melanoma (VaM) are rare carcinomas with an annual age-adjusted reported incidence rate of 1.03 cases per million female population in Asians and Pacific Islanders and 1.90 cases per million in non-Hispanic Whites [1]. They represent only 1–3% of all melanoma cases diagnosed in women [2], as a result of which, epidemiological studies are scarce and evidence-based guidelines for disease management are lacking. Staging and management for VuM and VaM have therefore been extrapolated from cutaneous melanoma [3]; however, significant differences exist in terms of their biology, surgical considerations, and treatments. VuM and VaM are characterized as mucosal melanomas with more aggressive behavior and poorer survival rates than skin melanomas. The reported 5-year overall survival (OS) for mucosal melanoma is significantly worse than that for cutaneous melanomas [4] (34% versus 89%) [5]. A small number of retrospective studies evaluated the clinicopathological characteristics of VuM and VaM in specific populations, confirming clinical differences and worse survival prediction in comparison to cutaneous melanomas [6–12]. However, these retrospective studies were limited to a single center with a limited number of patients, due to the rarity of the disease. According to a nomogram model presented in a recent SEER population-based study, patients diagnosed with VuM can be divided into high-risk and low-risk groups based on age, race, tumor site, depth of tumor invasion, lymph node status, distant metastasis, tumor size, surgery, chemotherapy, and radiotherapy [8]. To date, only one prospective study in 1994 followed the evolution of patients with VuM who underwent radical hemivulvectomy and led to the conclusion that the American Joint Committee on Cancer (AJCC) staging system was the only independent prognostic factor [13].

The essential first-line therapy for vulvovaginal melanomas is surgery [14–15]; however, it could be challenging to preserve continence and sexual function. Moreover, compared to other malignant melanomas, vulvar and vaginal melanomas have high recurrence rates of 60% and 80%, respectively [16]. Adjuvant radiotherapy does not seem to improve survival outcomes after surgery [17]. For vulvar melanoma with a depth of invasion greater than 1 mm

without the presence of metastasis, sentinel lymph node mapping should be considered. In cases of vaginal melanoma with additional risk factors, resection of the lesion itself is difficult, and sentinel lymph node mapping is not performed [18]. According to a retrospective study by Lopez et al., the sentinel lymph node procedure is capable of identifying occult lymph node metastases in patients with vulvar and vaginal melanoma; however, its clinical application needs to be further validated [19].

Currently, postoperative adjuvant therapies and management of recurrences of VuM and VaM follow the guidelines for cutaneous melanoma [20]. However, recent studies have demonstrated that the molecular profile of urogenital melanomas differs from other melanoma types [21] and seems to show more similarity to mucosal melanomas than cutaneous melanomas [22].

Retrospective studies are showing the potential benefit of immunotherapy in adjuvant setting in improving the overall survival, especially for patients with distant metastatic disease [7]. The most common mutation in cutaneous melanomas is BRAF V600E; however, it is not present at all in VuM and VaM [23] or is less frequent (7–26%) [24–25, 21]. In contrast, the NRAS mutation and c-KIT amplification are present in 27.6% of cases of these rare melanomas [24], and the NRAS mutation is associated with poorer survival (33.5 vs. 14.0 months) [26]. C-KIT expression [27] and PARP1 expression [28] have therefore been identified as valuable predictors of prognosis and survival. Furthermore, somatic variant analysis of 27 vulvovaginal mucosal melanomas identified SF3B1 as the most commonly mutated gene (22% cases) [29]. The knowledge of clinicopathological features and the molecular background of these melanomas would pave the way for targeted therapy and improved survival.

There have been no previous Japanese reports on multiple cases of VuM and VaM. Therefore, the objective of the study was to conduct a survey in Japan to obtain data on patient characteristics and current treatment. However, since it is a rare carcinoma, it required multicentered investigations to accumulate data on a substantial number of cases. Moreover, vulvar and vaginal melanoma were treated by skin cancer specialists in many facilities. Participation was thus requested among member facilities of the Japan Skin Cancer Society (JSCS) along with members of the Japanese Gynecologic Oncology Group (JGOG) in order to collect data on more patients for a coordinated inter-group study. Access to more extensive data on the current status and treatments for vulvar and vaginal melanoma in Japan should provide more references necessary for planning an effective prospective clinical trial in the future.

2. Materials And Methods

2.1. Data resource

This was an inter-group study of the JGOG and JSCS on vulvar and vaginal melanoma. This retrospective observational study included patients diagnosed with and treated for vulvar and vaginal melanoma between January 1, 1995, and December 31, 2015. The survey period was between December 1, 2016, and December 31, 2017, with a target sample size of 200 cases. The study was conducted in accordance with the Declaration of Helsinki and “Ethical Guidelines for Medical and Health Research Involving Human Subjects”. Informed consent was waived by the ethics committee of the Kurume University School of Medicine because of the retrospective observational nature of the study. Patient data obtained for the purposes of this study were anonymized and were not disclosed to any third party. The present study was reviewed and approved by the ethics committee of the Kurume University School of Medicine served as the host institution (Institutional Review Board approval registration number: 16132), and each participating institution obtained approval as appropriate. The JGOG-1078S protocol was registered in the University Hospital Medical Information Network (UMIN) (protocol number: UMIN000025968).

2.2. Study eligibility

The following patient data were collected: age; site; Breslow thickness; TNM staging; presence or absence of ulcers; mitotic rate; microsatellite; tumor depth; histological subtype; AJCC 7th staging; treatment-related factors (initial treatment, date of initiation of treatment, and date of completion of treatment); surgery; sentinel lymph node dissection status; preoperative, initial or postoperative radiotherapy and concurrent chemotherapy (radiation field, method of radiation, total dose, duration of treatment, treatment completion rate); and preoperative, initial, and postoperative chemotherapy (regimen, number of cycles).

The patient outcome was recorded in terms of recurrence, date of confirmation of recurrence, treatment for recurrence, survival, and the last confirmed surviving date.

2.3. Statistical analysis

The collected data were analyzed for survival by using the Kaplan-Meier method, and the effects of the clinical factors on OS were investigated using a Cox regression model. In the univariate analysis, we included the following factors: physician in charge (dermatologist or gynecologist), organ (vagina/vulva), age, lymph node metastases, microsatellites, histology (nodular melanoma, superficial spreading melanoma, mucosal lentiginous melanoma, and others), AJCC staging (IA/IB, IIA/IIB/IIC, IIIA/IIIB/IIIC, IV), surgical margin, and surgery. Factors with $P < 0.10$ in univariate analysis were included to the multivariate model. The magnitude of effect was expressed as hazard ratio (HR) and 95% confidence interval (CI). All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). A $P < 0.05$ value was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 217 patients were identified; 109 (50.2%) had VuM, and 108 (49.8%) had VaM. The median age of the subjects was 67 years (range, 29–96 years). Surgery was performed in 84.3% of the women with VuM and 83.3% of those with VaM. The median depth of invasion was 4.5 mm (range, 0.1–12 mm). Ulceration was documented in 47.9% (104/217) of the lesions. Nodal status was positive in 60 patients (27.6%), negative in 149 patients (68.7%), and unknown in 8 (3.7%) patients. According to the AJCC staging system, 37 patients (17.1%) were in stage I, 106 patients (48.8%) in stage II, 46 patients (21.2%) in stage III, and 28 patients (12.9%) in stage IV. Nodular melanoma was the most common subtype (48.8%) (Table 1). There were no statistical differences in patient characteristics between VuM and VaM.

Table 1
Patient Characteristics (n = 217)

	All	VuM	VaM
	217	108	109
Age (range)	67 (29–96)	68 (30–89)	66 (29–96)
Physician			
Gynaecologist	158	75	83
Dermatologist	59	33	26
Breslow thickness (range)	4.5 (0.1–12)	4.0 (0.1–11)	5.0 (0.1–12)
TNM classification			
T			
IA	26	12	14
IB	11	7	4
2A	18	6	12
2B	12	8	4
3A	29	16	13
3B	13	6	7
4A	30	11	19
4B	78	42	36
N			
0	126	64	62
1	8	1	7
1A	9	8	1
1B	10	7	3
2	6	3	3
2A	3	1	2
2B	14	8	6
2C	2	0	2
3	9	7	2
X	30	9	21
M			
0	184	93	91
1	9	4	5

	All	VuM	VaM
1A	6	3	3
1B	3	1	2
1C	7	4	3
X	8	3	5
AJCC classification			
IA	24	12	12
IB	13	7	6
IIA	27	15	12
IIB	37	14	23
IIC	42	19	23
IIIA	9	5	4
IIIB	19	11	8
IIIC	18	12	6
IV	28	13	15
Ulcer			
presence	104	55	49
absence	113	53	60
Microsatellite			
presence	55	20	35
absence	162	88	74
Lymph node metastases			
positive	60	35	25
negative	149	70	79
unknown	8	3	5
Histology			
mucosal lentiginous melanoma	36	10	26
nodular melanoma	107	45	52
superficial spreading melanoma	47	39	8
others	27	14	13
Surgery			
performed	183	92	91

	All	VuM	VaM
Not performed	34	16	18
Surgical margin			
positive	46	19	27
negative	137	73	64
unknown	34	16	18
Chemotherapy			
performed	136	66	70
Not performed	81	42	39
Radiation therapy			
performed	34	14	20
Not performed	183	94	89

3.2. Survival outcome

The median progression-free survival (PFS) was 16.8 months in patients with VuM (95% confidence interval [CI] 23.1–87.7) and 15.6 months in patients with VaM (95% CI 8.4–12.6) (Fig. 1A). The median OS was 43.9 months (95% CI 60–138) in patients with VuM and 31.1 months (95% CI 24.8–45.3) in patients with VaM (Fig. 1B).

We performed independent analyses of the factors associated with survival for VuM and VaM. The univariate analysis (for VaM and VuM combined) showed that the presence of lymph node metastasis, grade > IIIA according to the AJCC classification, positive or unknown surgical margins, and the lack of previous surgery were factors related to both OS and PFS, whereas histology type other than nodular melanoma, superficial spreading melanoma, or mucosal lentiginous melanoma, was related only to OS (Tables 2 and 3).

Table 2
Univariate Cox proportional hazards model of overall survival

	All (217)			VaM (109)			VuM (108)		
	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value
Physician									
Dermatologist	1			1			1		
Gynecologist	0.942	0.633–1.403	0.7693	1.792	0.932–3.445	0.0805	0.564	0.329–0.967	0.0374*
Age	1.007	0.992–1.022	0.3433	0.985	0.965–1.006	0.1605	1.027	1.004–1.051	0.0203*
Organ									
Vagina	1								
Vulva	0.884	0.617–1.267	0.5025						
Presence of lymph node metastasis	2.217	1.514–3.246	0.0001*	1.520	0.852–2.710	0.1562	3.327	1.944–5.693	< .0011*
Presence of ulcer	1.295	0.903–1.858	1.1599	1.396	0.843–2.313	0.1951	1.183	0.702–1.991	0.5284
Presence of microsatellites	1.346	0.899–2.013	0.1486	0.908	0.522–1.579	0.7324	2.168	1.184–3.970	0.0122*
Histology									
Nodular melanoma	1			1			1		
Superficial spreading melanoma	0.641	0.385–1.067	0.0871	0.693	0.243–1.977	0.4933	0.603	0.324–1.120	0.1094
Mucosal lentiginous melanoma	0.936	0.563–1.558	0.7997	1.136	0.628–2.055	0.6742	0.509	0.154–1.679	0.2673
Others	1.723	1.032–2.878	0.0377*	1.723	0.813–3.650	0.1558	1.633	0.805–3.313	0.1742
AJCC classification									
IA/IB	1			1			1		
IIA/IIB/IIC	0.92	0.533–1.589	0.7649	1.124	0.528–2.391	0.7616	0.700	0.311–1.573	0.3873
IIIA/IIIB/IIIC	2.063	1.155–3.684	0.0144*	1.563	0.634–3.850	0.3320	2.620	1.194–5.752	0.0163*
IV	3.271	1.760–6.080	0.0002*	2.580	1.113–5.979	0.0271*	5.645	2.181–14.612	0.0004*

All (217)			VaM (109)			VuM (108)			
Surgical margin									
negative	1			1			1		
positive	1.978	1.295–3.020	0.0016*	2.139	1.191–3.839	0.0109*	1.728	0.910–3.283	0.0946
unknown	2.386	1.477–3.855	0.0004*	3.101	1.588–6.054	0.0009*	1.892	0.932–3.841	0.0775
Surgery performed	0.558	0.346-0.900	0.0166*	0.539	0.284–1.022	0.0582	0.575	0.279–1.186	0.1340

Table 3
Univariate Cox proportional hazards model of progression free survival

	All (217)			VaM (109)			VuM (108)		
	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value
Physician									
Dermatologist	1			1			1		
Gynecologist	1.221	0.854–1.747	0.2731	1.594	0.932–2.727	0.0889	0.970	0.589–1.597	0.9040
Age	1.005	0.993–1.018	0.4006	0.991	0.974–1.007	0.2745	1.020	1.001–1.040	0.0425
Organ									
Vagina	1								
Vulva	0.719	0.524–0.988	0.0421						
Presence of lymph node metastasis	1.559	1.099–2.210	0.0128*	1.126	0.661–1.918	0.6611	2.288	1.399–3.741	0.0010*
Presence of ulcer	1.182	0.861–1.622	0.3013	1.266	0.817–1.959	0.2909	1.129	0.708–1.800	0.6099
Presence of microsatellites	1.174	0.823–1.674	0.3768	0.798	0.497–1.280	0.3489	1.724	0.986–3.016	0.0562
Histology									
Nodular melanoma	1			1			1		
Superficial spreading melanoma	0.790	0.525–1.190	0.2599	0.586	0.249–1.381	0.2216	0.951	0.567–1.596	0.8495
Mucosal lentiginous melanoma	0.830	0.530–1.299	0.4143	1.003	0.603–1.670	0.9894	0.332	0.101–1.089	0.0689
Others	1.513	0.919–2.491	0.1033	2.464	1.213–5.006	0.0126*	1.207	0.587–2.482	0.6090
AJCC classification									
IA/IB	1			1			1		
IIA/IIB/IIC	1.148	0.723–1.823	0.5582	1.230	0.660–2.292	0.5142	0.969	0.480–1.954	0.9288
IIIA/IIIB/IIIC	1.524	0.906–2.564	0.1124	1.038	0.472–2.284	0.9260	2.096	1.016–4.324	0.0453*
IV	3.087	1.734–5.494	0.0001*	2.957	1.358–6.436	0.0063*	3.379	1.422–8.027	0.0058*

	All (217)			VaM (109)			VuM (108)		
Surgical margin									
negative	1			1			1		
positive	1.579	1.076–2.317	0.0197*	1.814	1.090–3.020	0.0220*	1.213	0.655–2.243	0.5392
unknown	1.672	1.057–2.645	0.0279*	1.678	0.901–3.123	0.1026	1.584	0.799–3.141	0.1876
Surgery performed	0.666	0.433–1.025	0.0648*	0.757	0.410–1.400	0.3750	0.578	0.314–1.062	0.0776

In the multivariate analysis, an unknown surgical margin was identified as a risk factor for OS (HR = 2.288, 95% CI = 1.203–3.977), and an AJCC grade > IV, for PFS (HR = 2.063, 95% CI = 0.995–4.278) (Tables 4 and 5).

Table 4
Multivariate Cox proportional hazards model of overall survival

	All (217)			VaM (109)			VuM (108)		
	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value
Physician									
Dermatologist	1			1			1		
Gynecologist				2.235	1.127–4.433	0.0213*	0.826	0.416–1.640	0.5854
Age							1.022	0.998–1.048	0.0759
Presence of lymph node metastasis	1.365	0.643–2.895	0.4180				2.489	0.744–8.329	0.1390
Presence of microsatellites							2.104	1.071–4.131	0.0308*
Histology									
Nodular melanoma	1								
Superficial spreading melanoma	0.711	0.410–1.234	0.2260						
Mucosal lentiginous melanoma	0.970	0.569–1.654	0.9109						
Others	1.567	0.918–2.675	0.0994						
AJCC classification									
IA/IB	1			1			1		
IIA/IIB/IIC	0.937	0.535–1.640	0.8192	1.065	0.477–2.375	0.8786	0.700	0.304–1.611	0.4011
IIIA/IIIB/IIIC	1.563	0.630–3.874	0.3352	2.032	0.788–5.240	0.1423	1.067	0.264–4.315	0.9275
IV	1.809	0.815–4.016	0.1452	1.767	0.686–4.554	0.2387	2.503	0.740–8.468	0.1402
Surgical margin									
negative	1			1			1		
positive	1.590	0.980–2.581	0.0605	2.013	1.061–3.817	0.0322*	1.512	0.739–3.094	0.2580

	All (217)			VaM (109)			VuM (108)		
unknown	2.188	1.203– 3.977	0.0102*	2.814	1.138– 6.960	0.0251*	1.691	0.736– 3.881	0.2156
Surgery performed	0.953	0.531– 1.711	0.8729	0.892	0.381– 2.088	0.7924			

Table 5
Multivariate Cox proportional hazards model of progression free survival

Multivariate Cox proportional hazards model of progression free survival									
All (217)				VaM (109)			VuM (108)		
	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value	Hazard risk	95% CI	p-value
Physician									
Dermatologist				1					
Gynecologist				1.531	0.843–2.782	0.1622			
Age							1.014	0.993–1.036	0.1993
Organ									
Vagina	1								
Vulva	0.775	0.560–1.073	0.1240						
Presence of lymph node metastasis	1.603	0.812–3.163	0.1738				3.275	0.984–10.903	0.0532*
Presence of microsatellites							1.422	0.787–2.569	0.2435
Histology									
Nodular melanoma				1			1		
Superficial spreading melanoma				0.525	0.207–1.330	0.1742	1.306	0.742–2.298	0.3553
Mucosal lentiginous melanoma				1.228	0.711–2.121	0.4605	0.360	0.108–1.197	0.0955
Others				1.804	0.825–3.945	0.1391	1.469	0.669–3.228	0.3378
AJCC classification									
IA/IB	1			1			1		
IIA/IIB/IIC	1.103	0.687–1.771	0.6842	1.203	0.620–2.334	0.5855	1.111	0.535–2.305	0.7780
IIIA/IIIB/IIIC	0.989	0.436–2.243	0.9780	1.051	0.439–2.519	0.9103	0.777	0.203–2.977	0.7123
IV	2.063	0.995–4.278	0.0516*	2.322	1.012–5.327	0.0469*	1.938	0.632–5.944	0.2471
Surgical margin									

	All (217)			VaM (109)			VuM (108)		
negative	1			1					
positive	1.413	0.941– 2.122	0.0957	1.776	0.972– 3.247	0.0620			
unknown	1.369	0.799– 2.343	0.2527	1.664	0.866– 3.198	0.1264			
Surgery performed	0.757	0.463– 1.237	0.2665				0.696	0.353– 1.375	0.2973

3.3. VaM-specific outcome

Specifically, for VaM in the univariate analysis, we identified AJCC grade > IV and positive or unknown surgical margin as the only prognostic factors for OS, and histology type other than nodular melanoma, superficial spreading melanoma or mucosal lentiginous melanoma, AJCC grade > IV, and positive surgical margin as prognostic factors for PFS (Tables 2 and 3). The multivariate analysis identified that the treatment by a gynecologist as opposed to a dermatologist (HR = 2.235, 95% CI = 1.127–4.433) together with a positive surgical margin (HR = 2.013, 95% CI = 1.061–3.817) or unknown surgical margins (HR = 2.814, 95% CI = 1.138–6.960) as predictors of OS, and AJCC grade > IV as a prognostic factor for PFS (HR = 2.322, 95% CI = 1.012–5.327) (Tables 4 and 5).

3.4. VuM-specific outcome

With regard to VuM, the univariate analysis identified that the treatment by a dermatologist instead of a gynecologist, age, the presence of lymph node metastasis and microsatellites, and AJCC grade > III are factors related to OS. Only the presence of microsatellites and AJCC grade > III are related to PFS (Tables 2 and 3). According to the multivariate analysis in VuM, the presence of microsatellites was identified as a prognostic factor for OS (HR = 2.104, 95% CI = 1.071–4.131) and the presence of lymph node metastasis as a prognostic factor for PFS (HR = 3.275, 95% CI = 0.984–10.903) (Tables 4 and 5).

4. Discussion

Only a handful of studies have evaluated the clinicopathological features of the rare cancers VuM and VaM, and none of them was conducted in the Japanese population. Therefore, in this retrospective observational study, we analyzed 109 cases of VuM and 108 cases of VaM treated over a period of 20 years at various centers in Japan and aimed to characterize those cases and identify predictors for OS and PFS. According to our study, the OS for VuM and VaM in Japan were 43.6 months and 31.1 months respectively, which is comparable to a US population-based study (53 months for VuM and 16 months for VaM) [30] and to a Canadian study (45 months for VuM and 10.48 months for VaM) [15]. The median PFS was 16.8 months in patients with VuM (95% CI 23.1–87.7) and 15.6 months in patients with VaM (95% CI 8.4–12.6). Even though both the OS and PFS in our study were worse for VaM, the observed differences were not significant. As there were no significant differences between VuM and VaM in patient characteristics in terms of staging according to AJCC, age, or the treatment received, we can conclude that the poorer OS and PFS observed in patients with VaM can be attributed to the melanoma subtype and that it needs to be studied further.

Various studies have evaluated the risk factors for OS and PFS in VaM and VuM with different results. A study by Sinasac et al. reported that clinical stage, maximum tumor size, tumor thickness, lymphovascular space invasion status, clinically enlarged lymph nodes, sentinel lymph nodes, lymph node status, and radiation treatment are

associated with OS [15], and Huang Q et al. reported that macroscopic tumor growth and the treatment method are independent prognostic factors for OS [31]. Multivariate progression analysis in a retrospective review of 100 cases of VuM identified the tumor thickness, dermal mitotic rate, lymphovascular invasion, microscopic satellite, and absence of precursor nevus as predictors of poor survival [32].

In order to understand the risk factors in the Japanese population, we performed independent analyses of the factors associated with the OS and PFS for VuM and VaM. In a multivariate analysis, we identified that an AJCC stage > 4 is associated with poor PFS and that an unknown surgical margin is associated with poorer OS. Even though the management and treatment of VuM and VaM follow the same guidelines, there are clear differences in the OS, PFS, and risk factors associated with each subtype. Due to the nature of the cancer type, both subtypes are treated either by a dermatologist or a gynecologist. However, multivariate analysis showed that management by a gynecologist significantly decreased the OS of VaM (HR = 2.235, 95% CI = 1.127–4.433). In contrast, the univariate analysis demonstrated that the management by a gynecologist in the VuM significantly increased the OS (HR = 0.564, 95% CI = 0.329–0.967). According to multivariate analysis, factors that are associated with the OS and PFS in each subtype also differ. The positive and unknown surgical margin, and the presence of microsatellites are the factors associated with poor OS in VaM and VuM respectively. Factors associated with poor PFS are an AJCC stage > 4 and the presence of lymph node metastasis in VaM and VuM, respectively.

In our study, surgery was performed in 84.3% of the women with VuM and 83.3% of those with VaM; the study demonstrated the selection of surgery as a first-line treatment regardless of the disease stage. Moreover, surgery was identified as a positive prognostic factor for OS in VaM (HR = 0.539, 95% CI = 0.284–1.022) and negative surgical margins as a prognostic factor for better OS and PFS in all groups. However, the survival benefits of radical initial surgery for primary VaM have not been demonstrated yet [33]. Adjuvant chemotherapy and radiotherapy were used in 62.7% and 15.7% of cases, respectively. The relationship between the selected therapy and survival rates was not the objective of this study, and may be explored in further studies.

Overall, we have demonstrated that the survival rates for VuM and VaM remain poor in Japan, and that there are significant differences between these subtypes.

Our study has several limitations, the primary one being the inherent limitations of its retrospective design. Salient unmeasured biases that could impact outcomes include medical comorbidities, pathological diagnoses, performance status, surgeons' experiences, patient compliance, and the decision-making processes at multiple participating institutions; all of these factors could affect the treatment approach, operational performance, and survival. In addition, while this study included a diverse range of hospitals in Japan, not all hospitals in Japan participated, which may have resulted in a selection bias. Furthermore, due to the relatively long duration of the study (21 years), there may have been changes in treatment methods resulting in non-uniformity that could have affected the overall survival.

In conclusion, we conducted a large-scale survey and a detailed review of the treatment and clinicopathological features of malignant melanomas of the vulva (VuM) and vagina (VaM) in Japan. Our results show that the overall outcomes of VuM and VaM remain poor in Japan, and that the AJCC stage and surgical margin are significant predictors of survival. The results of this study could be used as a basis for decision-making in routine clinical practice and as data for future prospective clinical trials.

Declarations

Conflicts of interest

The authors have no conflicts of interest to declare

Author Contributions:

Study concept and design: Dai Ogata, Shin Nishio, Mikio Mikami, Yoshio Kiyohara, Takayuki Enomoto, Provision of materials or patients: Shin Nishio, Dai Ogata, Acquisition of data: Shin Nishio, Dai Ogata, Naohito Hatta, Tatsuya Kaji, Kazuyasu Fujii, Analysis and interpretation of data: Shin Nishio, Manuscript writing: All authors, Final approval of manuscript: All authors.

Ethical Approval/Informed Consent

The present study was reviewed and approved by the ethics committee of the affiliated facility of the lead principal investigator. Informed consent was not required because of the retrospective observational nature of the study.

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Figures

Figure 1

(A). Progression free survival. Kaplan Meier curve demonstrates the survival probability of PFS in patients with VaM and VuM. (B). Overall survival. Kaplan Meier curve demonstrates the survival probability of OS in patients with VaM and VuM.