Gynecologic Oncology Reports 49 (2023) 101268

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Margin status in vulvovaginal melanoma: Management and oncologic outcomes of 50 cases

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ARTICLE INFO

Keywords:
Vulvovaginal melanoma
Surgery
Margin status

ABSTRACT

Objectives: To determine the influence of margin status, including preinvasive disease at the margin, on local recurrence and overall survival (OS) in patients with vulvovaginal melanoma.
Methods: All patients with Stage 0-III vulvovaginal melanoma treated with primary surgical management between 1/2010–12/2019 were included. Margin status was categorized as negative, preinvasive disease (atypical junctional melanocytic hyperplasia and melanoma in situ), and invasive melanoma. Kaplan-Meier analyses were performed for local progression free survival (PFS) and OS. The impact of clinical and pathologic factors on local PFS and OS were assessed with Cox-regression analyses.
Results: Fifty patients with a median follow-up of 48 months (range 3–119) were included. The median age was 63 years (range 20–83). Twenty percent (N = 10) had Stage 0 disease, 18% (N = 9) had Stage I, 46% (N = 23) had Stage II, and 16% (N = 8) had Stage III. Forty-four percent (N = 22) of patients had negative surgical margins, 46% (N = 23) had preinvasive disease at the margins, and 10% (N = 5) had invasive melanoma at the margins. The 5-year local PFS was 63% (95% CI: 42–78%) and OS was 60% (95% CI: 42–74%). Age, Breslow depth, stage, margin status, and re-resection did not significantly impact local PFS. In patients with preinvasive disease at the margin, all who recurred locally had Stage I-II disease.
Conclusion: Preinvasive disease at the surgical margins may play an important role in local recurrence in patients with Stage I-II vulvovaginal melanoma. Patients with early (Stage 0) and advanced (Stage III) disease rarely recur locally and may not benefit from re-resection.

1. Introduction

Vulvovaginal melanomas are rare tumors of the genital tract. While they are the second most common type of vulvar cancer, they account for only 5% of all vulvar malignancies and less than 3% of all melanomas diagnosed in female patients. (Albert et al., 2020; Blank et al., 2019; Garbe et al., 2016; Gershenwald et al., 2017) Most tumors are diagnosed in postmenopausal patients with a median age at diagnosis of 68 years. (Grewal et al., 2021) These are aggressive tumors that have an estimated 5-year survival rate ranging from 10 to 47%, (Albert et al., 2020; Hanauer et al., 2015; Irvin et al., 2001; Janco et al., 2013; Leitao et al., 2014) which is drastically different than the 5-year survival for localized cutaneous melanomas of 93.7%. (Melanoma of the Skin - Cancer Stat Facts, 2021) Due to the paucity of data on pathogenesis and management of this rare tumor, most management strategies are extrapolated from the broader mucosal melanoma literature.

The preferred primary treatment of vulvovaginal melanoma is surgery with wide local excision of the primary tumor and regional lymph node assessment. (Grewal et al., 2021) Accepted surgical margins range from 0.5 to 2.0 cm depending on Breslow depth, with the goal of achieving negative margins. (Merkel and Gerami, 2017) On histopathology, these tumors resemble other mucosal melanomas irrespective of anatomic site and have a broad lentiginous pattern of spread. (Mert et al., 2013; Mitra et al., 2022) Preinvasive melanocytic proliferations have been described under different terminologies, including melanoma in situ, atypical intraepidermal melanocytic proliferation (AIMP), and atypical junctional melanocytic hyperplasia (AJMH); these have uncertain malignant potential and clinical meaning. (Blank et al., 2019; Ragnarsson-Olding et al., 1993) Further, there is clinical uncertainty for management of preinvasive changes when present at the margins of invasive melanomas. As such, the primary objective of this study is to determine the influence of margin status, including preinvasive disease

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https://doi.org/10.1016/j.gore.2023.101268
Received 15 June 2023; Received in revised form 29 August 2023; Accepted 30 August 2023

at the margin, on local progression free survival (PFS) and overall survival (OS) in patients with vulvovaginal melanoma.

2. Methods

All patients age 18 years and older who were diagnosed with vulvovaginal melanoma between January 1, 2010 and December 31, 2019 were identified using the University of Michigan's Electronic Medical Record Search Engine (EMERSE). (Saida et al., 2004) Patients were included if they underwent primary surgical management for vulvar or vaginal melanoma and their surgical specimen was reviewed by our institution's pathologists. Patients were staged using the American Joint Committee on Cancer (AJCC) Staging eighth edition and patients with Stage 0-III were included. (Tcheung et al., 2012) Patients with distant metastatic disease or those who underwent a pelvic exenteration for primary management were excluded.

Demographic, clinical, and histopathologic data was collected from the electronic medical records. Operative reports were reviewed to collect the dictated margin obtained at the time of primary surgery. The pathologic margin status following primary surgical management was categorized as negative, preinvasive disease (AJMH and melanoma in situ) (Fig. 1), or invasive melanoma. Histopathologic data collected included tumor thickness (Breslow depth), the presence of ulceration, mitotic rate, lymphovascular space invasion, perineural involvement, and lymph node status. Primary vulvar cancers were those that involved the vulva only, while vaginal cancers included vaginal with or without vulvar involvement.

Descriptive statistics were used to summarize the demographic, clinical, and histopathologic characteristics of the cohort. The local progression free survival (PFS) was calculated from the date of diagnosis to the date of local progression at the primary site of disease to the date of last follow-up or the date of death. The progression free survival (PFS) was calculated from the date of diagnosis to the date of progression as diagnosed by pathologic findings or radiologic evidence to the date of last follow-up or the date of death. OS was calculated from the date of diagnosis to the date of death or last follow-up. Kaplan-Meier analyses were performed for local PFS, PFS and OS rates. Univariate analyses were used to compare clinical and pathologic factors and surgical margins. Due to the sample size, multivariate analyses were not performed. Cox proportional hazard models were created to evaluate the association between clinicopathologic characteristics and local PFS, PFS and OS. This project was approved by our Institutional Review Board (HUM00153403). Stata 17 was used for all statistical analyses.

3. Results

During the 10-year period, 56 patients were identified; three were excluded due to having metastatic disease and three did not have their pathology reviewed at our institution. In total, 50 patients met inclusion criteria with a median follow-up of 48 months (range 3–119). The median age was 63 years (range 20–83). Ninety percent (N = 45) of patients had vulvar melanoma and 10% (N = 5) had vaginal melanoma. The median Breslow depth was 2 mm (range 0.2–13). Twenty percent (N = 10) of patients had Stage 0 disease, 18% (N = 9) had Stage I, 46% (N = 23) had Stage II, and 16% (N = 8) had Stage III. Forty-four percent (N = 22) of patients had negative surgical margins, 46% (N = 23) had preinvasive disease at the margins, and 10% (N = 5) had invasive melanoma at the margins (Table 1).

Age at diagnosis, BMI, Breslow depth, mitotic rate, presence of ulceration, microscopic satellitosis, perineural involvement, lymphovascular space invasion, the primary location of the tumor, gross surgical margins as dictated by the surgeon, and stage did not have a significant impact on margin status ($p > 0.05$). Patients who underwent a second surgical procedure were more likely to have positive (preinvasive or invasive) margins at the time of primary surgery (p less than 0.001) (Table 2).

Age at diagnosis, stage, Breslow depth, preinvasive disease at the margins, and reoperation did not have a significant impact on local recurrence ($p > 0.05$). Margins positive for invasive melanoma were associated with a risk of local recurrence (Hazard ratio 5.94, 95% CI 1.08–32.6). Stage and Breslow depth had a significant impact on PFS and OS, while age at diagnosis, preinvasive disease at the margins, and reoperation did not have a significant impact on PFS and OS ($p > 0.05$) (Table 3).

The 5-year local PFS was 63% (95% CI: 42–78%) for the entire cohort, 78.8% (95% CI: 43.2–93.4%) for negative margins, and 56.6% (95% CI: 28.7–77.2%) for preinvasive disease at the margins. The 5-year OS was 60% (95% CI: 42–74%) for the entire cohort, 66.6% (95% CI: 39.5–83.7%) for negative margins, and 48.7% (95% CI: 24.0–69.6%) for preinvasive disease at the margins (Fig. 2). For patients with local disease (Stage 0-I), the 5-year PFS was 48.6% (95% CI 30.9–64.8%) and OS was 68.9% (95% CI 49.7–82.0%).

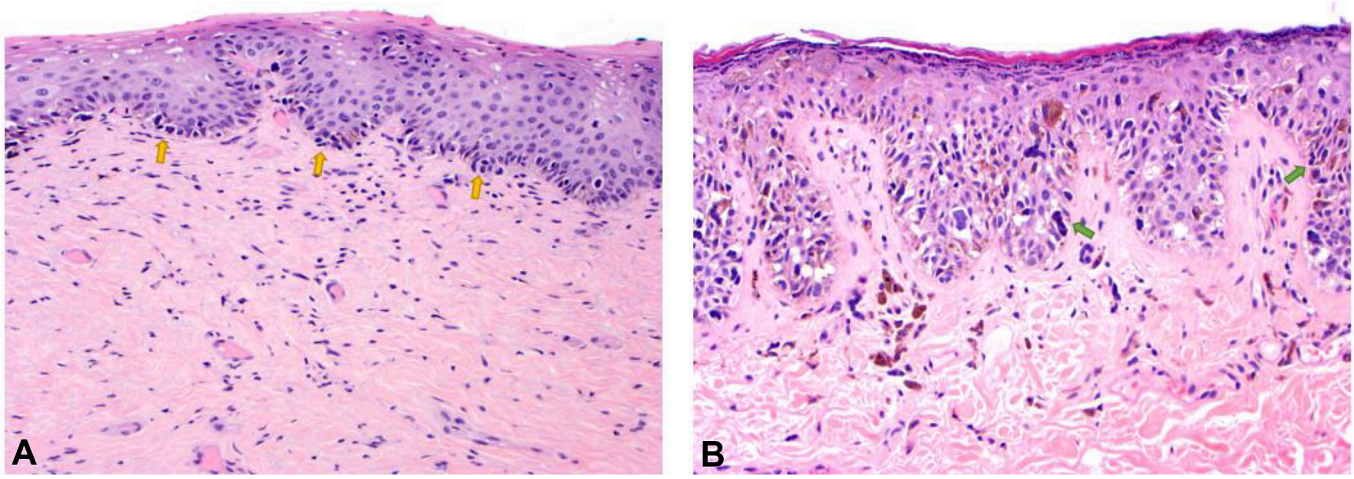

Fig. 1. Atypical junctional melanocytic hyperplasia (AJMH) and melanoma in situ (MIS) involving the vulva. A. Atypical junctional melanocytic hyperplasia (AJMH) involving the vulva. An increased number of atypical melanocytes are singly disposed along the basal epidermis (yellow arrows). These melanocytes are enlarged with angulated and hyperchromatic nuclei. (Hematoxylin-eosin stain, original magnification x200). B. Melanoma in situ (MIS) involving the vulva. There is a marked increase in the number of melanocytes in the epidermis. These melanocytes are present singly and in loose aggregates, with frequent pagetoid (upward) spread into the upper epidermis (green). Severe nuclear atypia and pleomorphism is readily seen.(Hematoxylin-eosin stain, original magnification x200). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic and clinical characteristics of patients with vulvovaginal melanomas (N = 50).

Characteristic	n (%) or median (range)
Age at diagnosis, years	63 (20–83)
BMI, kg/m^2	28 (17.5–53)
Race	
White	46 (92.0)
Black	2 (4.0)
Asian	1 (2.0)
Not reported	1 (2.0)
Primary tumor location	
Vulva	45 (90.0)
Vagina	5 (10.0)
Primary tumor characteristics*	
Breslow depth, millimeters (range)	2 (0.2–13)
Mitotic rate	7 (0–31)
Ulceration present	24 (70.6)
Microscopic satellitosis	1 (3.1)
Lymphovascular space invasion	4 (11.8)
Procedure	
Simple vulvectomy	33 (66.0)
Radical vulvectomy	14 (28.0)
Vaginectomy	3 (6.0)
Urethrectomy	1 (2.0)
Sentinel lymph node biopsy	26 (52.0)
Full lymph node assessment	6 (12.0)
AJCC staging	
Stage 0	10 (20.0)
Stage I	9 (18.0)
Stage II	23 (46.0)
Stage III	8 (16.0)
Surgeon's dictated gross margin, cm	1.5 (0–3)
Pathologic margins after resection	
Negative	22 (44.0)
Preinvasive disease	23 (46.0)
Melanoma	5 (10.0)

BMI, body mass index; AJCC, American Joint Committee on Cancer.
*Data not available in 6 patients with invasive cancer.

Table 2
Univariant analyses evaluating factors associated with the margin status following primary surgery (N = 50).

Characteristic	Negative margins N = 22	Preinvasive[a] N = 23	Melanoma N = 5	P value
Age at diagnosis, years	58.5 (43–68)	65 (57–73)	60 (59–68)	0.28
BMI	27.1 (21.2–32.0)	30.3 (26.2–33.5)	30.2 (24.4–35.9)	0.41
Breslow depth, mm	1.65 (1.2–3.9)	2.0 (0.95–6.4)	2.04 (0.91–8.0)	0.83
Mitotic rate*	4.5 (1–12)	7 (2–13)	11 (6.5–17.5)	0.40
Ulceration*	13 (76)	7 (54)	4 (100)	0.16
Microscopic satellitosis*	1 (6)	0 (0)	0 (0)	0.63
Perineuronal involvement*	0 (0)	1 (9)	0 (0)	0.43
LVSI*	2 (12)	1 (8)	1 (25)	0.64
Primary location				0.47
Vulva	21 (95.5)	20 (87.0)	4 (80.0)	
Vagina	1 (4.5)	3 (13.0)	1 (20.0)	
Margins dictated[b], cm	2 (1–2)	1.5 (1–2)	1 (0–2)	0.63
Stage				0.92
0	4 (18.2)	6 (26.1)	0 (0)	
I	4 (18.2)	4 (17.4)	1 (20.0)	
II	10 (45.5)	10 (43.5)	3 (60.0)	
III	4 (18.2)	3 (13.0)	1 (20.0)	
Reoperation Yes	1 (4.5)	7 (30.4)	4 (80.0)	**0.001**

Data are presented as median (IQR) for continuous measures, and N (%) for categorical measures.
*Data missing in 6 patients.
LVSI: lymphovascular space invasion.
[a] Margins obtained as dictated by surgeon at time of primary surgery.
[b] Preinvasive disease includes atypical junctional melanocytic hyperplasia and melanoma in situ.

Table 3
Univariant Cox regression analysis assessing association between clinicopathologic characteristics and oncologic outcomes in patients with vulvovaginal melanoma.

Characteristic	Local PFS Hazard Ratio (95% CI)	PFS Hazard Ratio (95% CI)	OS Hazard Ratio (95% CI)
Age at diagnosis	1.02 (0.99–1.06)	1.03 (0.99–1.07)	1.03 (0.99–1.07)
Stage	1.05 (0.58–1.90)	**2.63 (1.36–5.10)**	**3.6 (1.68–7.71)**
Breslow depth, millimeters	1.15 (0.96–1.38)	**1.16 (1.00–1.34)**	**1.29 (1.09–1.53)**
Pathologic margins after primary surgery			
Preinvasive disease*	2.46 (0.80–7.61)	2.13 (0.82–5.53)	1.42 (0.54–3.76)
Melanoma present	**5.94 (1.08–32.6)**	3.27 (0.66–16.2)	
Reresection	1.59 (0.54–4.67)	1.10 (0.40–3.03)	0.61 (0.17–2.12)

*Preinvasive disease includes atypical junctional melanocytic hyperplasia and melanoma in situ.
Local PFS: Progression free interval at primary site; PFS: Progression free interval; OS: Overall survival.

Twenty-three patients had preinvasive disease at the margins. Of these, 16 (69.9%) were observed and seven (30.4%) underwent re-resection. In the observation group, three patients (18.8%) developed a local recurrence, all of whom had Stage II disease. Patients with Stage 0 and Stage III disease did not recur locally (Stage III patients developed distant recurrences). In the patients who underwent re-resection due to the margin status, those with Stage 0 and most with Stage II disease did not recur locally (Table 4).

4. Discussion

Surgical management with a wide local excision and clinically negative margins is the preferred primary treatment for vulvar and vaginal melanomas. Margin status has been shown to be an important prognostic factor for locoregional control. (Verschraegen et al., 2001) To the best of our knowledge, this is the largest series to date that examines the importance of preinvasive disease at the margins and its clinical implications. Re-resection for pervasive disease at the margins may impact local regional recurrence in patients who have Stage I or Stage II disease.

Several studies have described the diagnosis of noninvasive melanocytic changes at the time of melanoma diagnosis. Tcheung et al evaluated 36 melanomas of the female genital tract and found 15 patients who had atypical melanocytic hyperplasia adjacent to the primary melanoma, the presence of which did not impact survival, nor did they comment on locoregional recurrence. (Wechter et al., 2004) Another retrospective study evaluated 1127 biopsies of AJMP and its synonyms (atypical junctional melanocytic proliferation/hyperplasia, atypical melanocytic proliferation, lentiginous junctional melanocytic proliferation, and proliferation of solitary units of melanocytes at the dermoepidermal junction). The authors found that 8.2% of patients were diagnosed with a concurrent melanoma in situ or invasive melanoma. Notably, this study also showed that 39% of patients had a prior diagnosis of melanoma or melanoma in situ. (Ragnarsson-Olding et al., 1993) These data suggest that preinvasive disease is associated with melanoma and may be an important clinical marker.

The oncologic outcomes in the present study are consistent with other published studies. For patients with local disease, the 5-year PFS

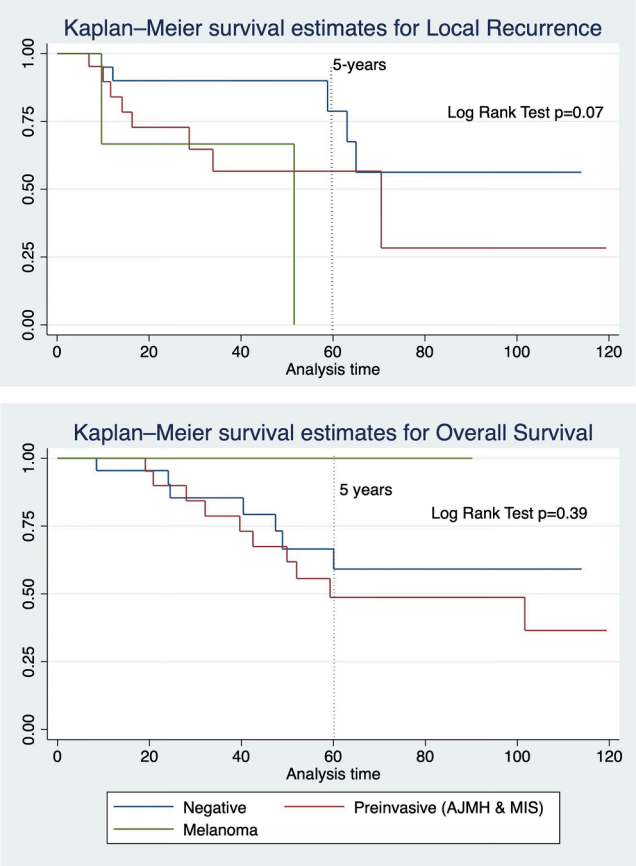

Fig. 2. Kaplan-Meier estimates for the effect of margin status on local recurrence and overall survival. AJMH: atypical junctional melanocytic hyperplasia; MIS: melanoma in situ.

was 48.6% and OS was 68.9%, which is consistent with a study evaluating 1917 patients with vulvovaginal melanoma in the National Cancer Database, where the local disease had a 5-year OS of 55.8%. (Weinstock, 1994) In a study evaluating 124 patients with vulvar and vaginal melanoma, the actuarial 4-year local control was 46%; however, 27% of this cohort was patients with vaginal melanoma, which historically has a poorer prognosis. (Wohlmuth et al., 2020).

A notable trend in the present study showed that patients with melanoma in situ, 60% of whom had preinvasive changes at the margins, had a very good prognosis. Mohs surgery has been described as a possible treatment strategy for treatment of melanoma in situ once more advanced disease has been ruled out. (Wohlmuth and Wohlmuth-Wieser, 2021) Future studies may evaluate this surgical modality in vulvar melanoma.

This study is limited in that it is retrospective in nature. While the time period covered is relatively short for this rare tumor, the small sample size did not allow for more robust modeling. It is important to note that margin status did not impact local recurrence and overall survival and these data should be interpreted within this context.

In conclusion, this study demonstrates that preinvasive changes in vulvovaginal melanoma are common and may play an important role in recurrence and disease management. The development of a national registry for these cancers, with pathologic review evaluating margin status, may facilitate treatment guidelines.

Funding

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers U24CA204863 and P30CA046592, as well as the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Numbers UL1TR000433 and UL1TR002240. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funders played no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Table 4
Summary of outcomes for the sub-cohort of patients who had preinvasive disease at the surgical margins (N = 23).

Management	Developed local recurrence	Age at diagnosis, years	Breslow depth, mm	Stage	Margin	Time to local progression or last follow-up, months	Location of local recurrence	OS (Months)	State of disease
		65	0	0	AJMH	59	–	59.0	NED
		81	0	0	AJMH	50.9	–	50.9	NED
		62	0	0	MIS	7.2	–	7.2	NED
		80	0	0	AJMH	39.6	–	39.6	DOC
	No	33	0.4	IA	AJMH	119.4	–	119.4	NED
	N = 13 (81.3%)	59	0.2	IB	AJMH	62	–	62.0	NED
		50	0.95	IB	MIS	119.5	–	119.5	NED
Observation		64	4	IIB	AJMH	20.7	–	20.7	NED
N = 16		78	15	IIC	MIS	8.1	–	32.1	DOD
(69.6%)		57	6.2	IIC	AJMH	22.0	–	22.0	AWD
		72	7.2	IIIB	MIS	5.1	–	19.0	DOD
		76	2.35	IIIB	AJMH	25.8	–	28.0	DOD
		71	7.5	IIIB	AJMH	58.9	–	59.3	DOD
	Yes	55	1.6	IB	AJMH	14	Vulva	118.8	NED
	N = 3 (18.8%)	68	0.81	IIB	MIS	34.9	Vagina	49.9	DOD
		44	8.2	IIC	MIS	10	Vulva	20.8	DOD
		57	0	0	MIS	8.7	–	8.7	NED
	No	53	0	0	AJMH	69.7	–	69.7	NED
	N = 5 (71.4%)	81	0.8	IIC	AJMH	68.3	–	68.3	NED
Re-resection		65	4.7	IIC	AJMH	19.2	–	19.2	NED
N = 7		66	6.4	IIC	AJMH	33.5	–	52.0	DOD
(30.4%)	Yes	80	9	IIC	MIS	28.7	Vagina	42.5	DOD
	N = 2 (28.6%)	73	2.13	IIA	MIS	70.5	Vulva	101.6	DOD

AJMH: atypical junctional melanocytic hyperplasia; MIS: melanoma in situ; OS: overall survival in months; NED: no evidence of disease; DOC: died other cause; DOD: died of disease.

Disclosures

Dr. Straubhar has a patent (W02019195097A1) issued outside of this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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