REVIEW ARTICLE

Vulvar Melanoma: Molecular Characteristics, Diagnosis, Surgical Management, and Medical Treatment

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Abstract

Ten percent of all women have pigmented vulvar lesions. Fortunately, most of these are benign but 1% of all melanomas in women affect the vulva. While the mortality rate of cutaneous melanoma has dropped by 7% annually during the last 5 years, the prognosis of vulvar melanoma remains dismal: the 5-year overall survival rate is 47% compared with 92% for cutaneous melanoma. The current evidence suggests that this likely results from a combination of delayed diagnosis and different tumor biology, treatment strategies, and treatment response. Although many landmark trials on checkpoint inhibitors included mucosal and vulvar melanomas, the results were often not reported separately. Post-hoc analyses indicate overall response rates between 19 and 37% for checkpoint inhibitors. A recently published retrospective study on vulvar melanomas suggests an objective response in 33.3% with a similar safety profile to cutaneous melanoma. Tyrosine kinase inhibitors may be considered in recurrent disease if a *c-KIT* mutation is present.

Key Points

Compared with skin melanomas, vulvar melanomas are associated with a poor prognosis resulting from delayed diagnosis and different tumor biology, treatment strategies, and treatment response.

Novel treatment modalities include checkpoint inhibitors and targeted therapies and recent evidence shows that these are also effective in vulvar melanomas.

Vulvar melanomas have a different tumor biology with frequent *c-KIT* mutations, which provides an additional therapeutic target in recurrent disease.

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1 Introduction

One in 41 (2.4%) women will develop a malignant melanoma at some point during their life, making it the sixth most common cancer in women in the USA [1]. Vulvar melanomas (VMs) account for 1% of all melanomas in women and 5% of all vulvar malignancies [2]. The majority of VMs are diagnosed in postmenopausal women, the median age at diagnosis is 68 years, but VMs have also been reported in children [2–7]. Strikingly, up to 10% of women have pigmented vulvar lesions [8, 9]. Obviously, the majority of these are benign, but in view of the advanced stage and melanoma size at diagnosis and associated poor prognosis, there appears to be room for improvement in terms of early detection and treatment initiation. While the overall mortality rate of cutaneous melanoma has dropped by 7% annually during the last 5 years, this did not apply for VMs: for all stages combined, the 5-year overall survival rate for cutaneous melanoma is 92%, compared with only 47% in VM; and there was no significant improvement over time [1, 2]. These somber numbers may in part be explained by the delayed diagnosis compared with cutaneous melanomas. A recent US population-based study of 1863 women has shown that 38% of women with staged VM had advanced disease at the time of diagnosis with regional involvement and/or distant metastases. The mean size of the primary tumor at

diagnosis was 31 mm and more than 46% had a Breslow's thickness > 2 mm [2]. This puts them at very high risk and large single-center series suggest that 52–63% of non-metastatic patients will eventually develop distant metastases [10–12]. The advanced stage at diagnosis may in part be explained by the location itself with potentially lower self-awareness, social awareness, and public awareness and the fact that most early-stage VMs are oligosymptomatic or asymptomatic [11, 13–15]. However, an analysis of the Dutch cancer registry has shown that even if matched for sex, age, tumor ulceration status, Breslow thickness, lymph node status, and distant metastases, VMs have a significantly worse prognosis compared with cutaneous melanomas [16]. This could be attributable to a different tumor biology and treatment approach or response. The latter is especially critical because of the lack of specific treatment guidelines for vulvovaginal melanomas, which in turn may increase treatment heterogeneity.

This comprehensive review aims to raise awareness among medical professionals and to provide up-to-date evidence on the molecular characteristics and the diagnosis and treatment of VMs, including surgery and medical therapy.

2 Cancerogenesis and Molecular Biology of VM

By definition, melanomas are cancers arising from melanocytes. The pathogenesis of VM remains largely unknown. Unlike cutaneous melanomas, VMs are unrelated to chronic sun exposure and damage from ultraviolet light. Chronic dermatoses such as lichen sclerosus have been discussed as potential risk factors based on findings from a population-based study, but this warrants validation in larger scaled and prospective studies [17, 18].

Molecular characterization of VMs may shed more light on the carcinogenesis. Table 1 provides an overview of mutations in VMs summarizing previously published studies, where the location "vulva" was explicitly stated. The mitogen-associated protein kinase pathway is a signaling pathway that is commonly activated in malignant melanomas. The *c-KIT* gene encodes KIT (CD117), which is a class III transmembrane receptor tyrosine kinase and is expressed in a variety of cells [19, 20]. While *c-KIT* mutations are rare in cutaneous melanomas [21, 22], 21.6% of women with VMs harbor a *c-KIT* mutation. The high rate of *c-KIT* mutations appears to be characteristic for VMs,

Table 1 Overview of molecular characteristics in malignant VMs

Study, year	VM (*n*)	*BRAF*, % (*n*)	*NRAS*, % (*n*)	*c-KIT*, % (*n*)
Edwards (2004) [115]	8	0% (0/8)	n.a.	n.a.
Cohen (2004) [116]	8	0% (0/8)	n.a.	n.a.
Wong (2005) [117]	3	33.3% (1/3)	0% (0/3)	n.a.
Torres-Cabala (2009) [118]	11	n.a.	n.a.	27.3% (3/11)
Handolias (2010) [119]	5	n.a.	n.a.	40.0% (2/5)
Omholt (2011) [24]	23	8.7% (2/23)	0% (0/23)	34.8% (8/23)
Abu-Abed (2012) [120]	17	n.a.	n.a.	5.9% (1/17)
Aulmann (2014) [121]	50	0% (0/39)	11.9% (5/42)	17.9% (7/39)
Rouzbahman (2015) [30]	13	7.7% (1/13)	23.1% (3/13)	23.1% (3/13)
Pappa (2015) [122]	10	10.0% (1/10)	0% (0/10)	0% (0/10)
Tseng (2015) [34]	12	0% (0/12)	25.0% (3/12)	16.7% (2/12)
Yelamos (2016) [123]	11	0% (0/11)	0% (0/11)	27.3% (3/11)
Saleh (2017) [37]	13	0% (0/13)	7.7% (1/13)	30.8% (4/13)
Udager (2017) [124]	19	0% (0/19)	5.3% (1/19)	15.8% (3/19)
Hou (2017) [23]	37	27.3% (9/33)	0% (0/19)	26.5% (9/34)
Wylomanski (2018) [125]	15	33.3% (5/15)	6.7% (1/15)	6.7% (1/15)
Shi (2019) [126]	4	0% (0/4)	50.0% (2/4)	25.0% (1/4)
Wohlmuth (2020) [11]	28	8.0% (2/25)	13.3% (2/15)	13.6% (3/22)
Zarei (2020) [25]	20	0% (0/20)	20.0% (4/20)	40.0% (8/20)
Studies combined	307	8.2% (21/256)	10.2% (22/216)	21.6% (58/268)

Summary of molecular characteristics of VMs from previously published studies evaluating melanoma mutations, where the vulvar location was specified. Single case reports were not included

BRAF v-raf murine sarcoma viral oncogene homolog B1 mutations, *c-KIT* tyrosine-protein kinase Kit mutations, *n* number, *n.a.* not assessed, *NRAS* neuroblastoma RAS viral oncogene mutations, *VMs* vulvar melanomas

which also distinguishes them from vaginal melanomas. In one of the largest series, Hou et al. noted that *c-KIT* was the only molecular marker of interest that varied significantly between vulvar and vaginal sites, with 27% of vulvar samples harboring the mutation compared with only 8% of vaginal samples [23]. Similarly, Omholt et al. reported eight *c-KIT* mutations in 23 women with VM vs no mutations in seven women with vaginal melanomas [24]. No difference in the mutational profile between the hair-bearing and glabrous skin of the vulva appears to be present [25]. KIT activates downstream signaling cascades of the Ras/Raf/MEK/ERK pathway, a key regulator of melanoma cell regulation [26]. The most common *c-KIT* mutation in VMs is the L576P substitution accounting for 26.2% (Fig. 1A). This mutation is located on exon 11 and affects the juxta-membrane domain of KIT, promoting dimerization of the protein and its constitutive activation [21]. W557R accounted for 11.9% and is also located in the juxta-membrane domain on exon 11. K642E, which accounted for another 16.7%, lies within the tyrosine kinase domain 1 on exon 13, and results in constitutive phosphorylation of KIT and activation of downstream signaling [27, 28]. The remaining rarer mutations were observed in exons 9, 11, 13, and 17 (Fig. 1A).

Further downstream, the NRAS enzyme has a GTP/GDP binding and GTPase activity resulting in the activation of RAF proteins. Mutations may result in reduced intrinsic GTPase activity resulting in constitutive activation [29, 30]. *NRAS* mutations occur in 10.2% of VMs (Table 1), which is less common than in cutaneous and vaginal melanomas [23, 26, 31]. A meta-analysis has shown that *NRAS* mutations are more frequent in patients with nodular melanomas, which account only for a smaller portion of VMs and are more common in vaginal melanomas [2, 32]. Mutations most commonly affect the regions G12, G13 (exon 2), and Q61 (exon 3), both resulting in abnormal phosphorylation of downstream molecules (Fig. 1B) [31, 33].

BRAF mutations have been reported in up to 70% of cutaneous melanomas and represent a therapeutic target for BRAF inhibitors alone or in combination with MEK inhibitors [26]. Combining previously published studies, *BRAF* mutations are found in only 8.2% of VMs, most of which affect codon 600 (Fig. 1C). In contrast, *BRAF* mutations are common in typical and atypical nevi of the vulva [34, 35]. The same has been reported in the remaining skin, where up to 80% of benign nevi harbor activating *BRAF* mutations [26]. Studies have suggested that p16^{INK4a} expression in benign nevi induces senescence by preventing the progression from the G1 to the S phase. For a malignant transformation of nevi, additional alterations accompanying *BRAF* mutations must therefore be present [26]. The high discrepancy between *BRAF* mutations found in benign vulvar nevi and VMs, however, further supports the hypothesis that VMs develop independently from pre-existing nevi.

Cancer immunobiology is another important aspect that has fundamentally improved our understanding of cancerogenesis and provided us with new treatment modalities with ground-breaking success in melanoma. T cells recognize foreign antigens loaded on the major histocompatibility complex. At the same time, activating and inhibiting costimulatory signals regulate the T-cell immunity preventing
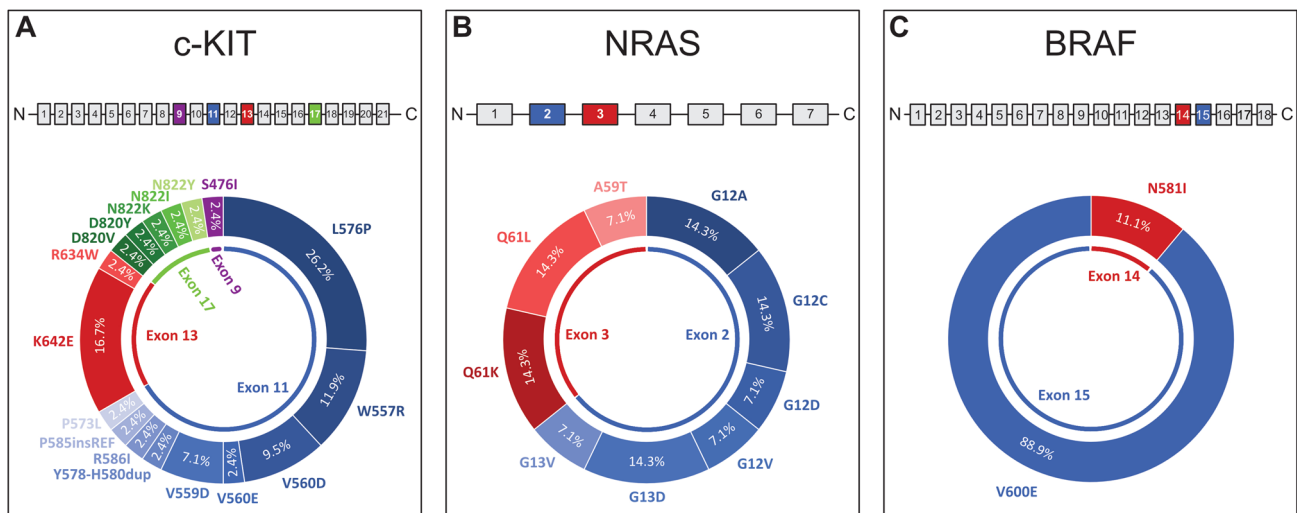
Fig. 1 **A–C** Summary of the frequencies of *c-KIT*, *NRAS*, and *BRAF* mutations from previously published studies that reported details on vulvar melanomas. The affected exons are highlighted in blue, red, and green and the corresponding mutations are shown in different gradations of blue, red, and green. **A** In *c-KIT*, 66.7% of the mutations were located on exon 11, 19.0% on exon 13, 11.9% on exon 17, and 2.4% on exon 9. **B** In *NRAS*, 64.3% of the mutations were located on exon 2 and 35.7% on exon 3. **C** In *BRAF*, 88.9% were located on exon 15 and 11.1% on exon 14

autoimmunity under physiological conditions [36]. One of the key negative regulating mechanisms (immune checkpoints) is the B7:CD28 family, which includes CTLA-4, PD-1, and its ligands PD-L1 and PD-L2. During cancerogenesis, cancer cells must acquire mechanisms to escape immune surveillance and destruction, in which CTLA-4 and PD-1 with their ligands B7 and PD-L1 play a significant role in melanoma [36]. Studies have shown that PD-L1 is frequently expressed in VMs and checkpoint inhibitors represent a treatment option (see below) [37, 38].
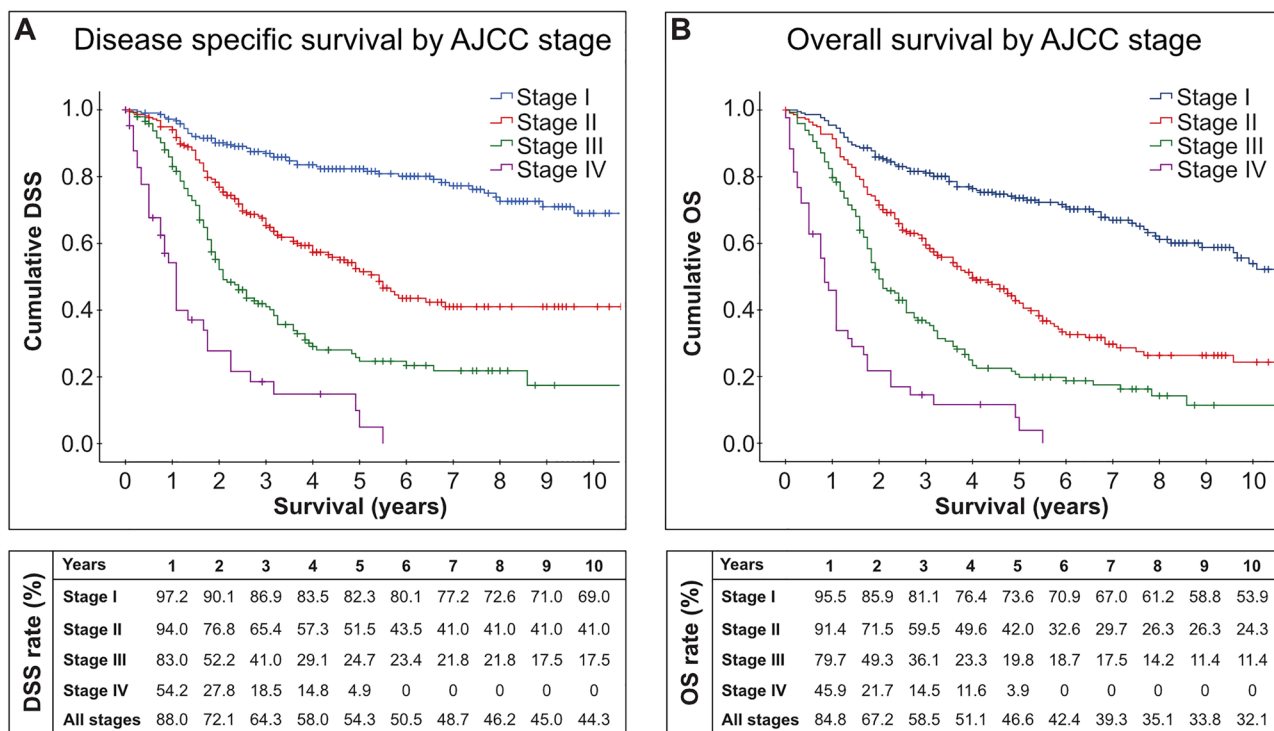
3 Prognosis

Overall, women with VM have a poor prognosis. As shown in Fig. 2, the 5-year overall survival rate is only 46.6% compared with 92% in cutaneous melanoma [1]. Previous studies suggest that age, ethnicity, stage at diagnosis, tumor thickness, lymph node status, histologic subtype, mitotic count, ulceration, lymphovascular invasion, perineural invasion, and microscopic satellitosis are predictors for outcome [2, 10, 39–44]. In multivariable logistic regression analyses, lymph node status and mitotic count appear to be the most important predictors for survival [2, 39, 40]. The latter is especially important as mitotic count is not included in the current staging system [45]. Nagarajan et al. have shown that women with a low mitotic count (0–1 mitotic figures/mm^2) have a significantly better outcome compared with women with a high (2–10 mitotic figures/mm^2) or very high (> 10 mitotic figures/mm^2) mitotic count, which we confirmed in a subsequent study, where the number of mitotic figures was independently associated with disease-specific survival (hazard ratio 1.11, 95% confidence interval [CI] 1.02–1.21) [39]. Lymph node metastasis was associated with a hazard ratio of 3.15 (95% CI 1.54–6.45) [2]. In the era of immune checkpoint inhibitors, the importance of lymph node status as a prognostic factor may even be higher, as we are now able to offer adjuvant treatment in lymph node-positive VMs (see below).

4 Diagnosis

Clinically, VMs may remain oligosymptomatic or asymptomatic flat or raised pigmented lesions during early disease stages [2, 10]. Amelanotic melanomas account for only 2% of all VMs [2]. At the time of diagnosis, the lesions present with a mean size of 3 cm (standard deviation ± 4 cm) and may be associated with pruritus, ulceration, or

A Disease specific survival by AJCC stage

DSS rate (%)	Years	1	2	3	4	5	6	7	8	9	10
	Stage I	97.2	90.1	86.9	83.5	82.3	80.1	77.2	72.6	71.0	69.0
	Stage II	94.0	76.8	65.4	57.3	51.5	43.5	41.0	41.0	41.0	41.0
	Stage III	83.0	52.2	41.0	29.1	24.7	23.4	21.8	21.8	17.5	17.5
	Stage IV	54.2	27.8	18.5	14.8	4.9	0	0	0	0	0
	All stages	88.0	72.1	64.3	58.0	54.3	50.5	48.7	46.2	45.0	44.3

B Overall survival by AJCC stage

OS rate (%)	Years	1	2	3	4	5	6	7	8	9	10
	Stage I	95.5	85.9	81.1	76.4	73.6	70.9	67.0	61.2	58.8	53.9
	Stage II	91.4	71.5	59.5	49.6	42.0	32.6	29.7	26.3	26.3	24.3
	Stage III	79.7	49.3	36.1	23.3	19.8	18.7	17.5	14.2	11.4	11.4
	Stage IV	45.9	21.7	14.5	11.6	3.9	0	0	0	0	0
	All stages	84.8	67.2	58.5	51.1	46.6	42.4	39.3	35.1	33.8	32.1

Fig. 2 Disease-specific survival (DSS) [**A**] and overall survival (OS) [**B**] of primary malignant melanoma of the vulva by American Joint Committee on Cancer (AJCC) stages derived from the Surveillance, Epidemiology and End Results-18 population between 2000 and 2017

(November 2019 submission) of the National Cancer Institute [135]. In the *lower part* of the figure, the DSS and OS rates by year are shown for AJCC stages I–IV and all stages combined

bleeding—symptoms that typically occur in advanced stages of melanoma [2, 46].

Differential diagnoses of pigmented vulvar lesions include genital nevi, vulvar melanosis, post-inflammatory hyperpigmentation, low-grade and high-grade squamous intraepithelial lesions, differentiated vulvar intraepithelial neoplasia, and pigmented seborrheic keratosis [47–49]. Differentiation of VMs from benign vulvar lesions is often challenging and sometimes impossible to make based on the clinical judgment alone. The "ABCDE" rule may aid as a simple guide for a first assessment of pigmented lesions: "A" stands for asymmetry and most melanomas are asymmetrical; "B" stands for border as melanomas typically exhibit an irregular border, while nevi typically have a smoother border. "C" stands for color. While benign moles are often unicolor brown, multiple colors including different shades of brown, black, blue, white, or red are typically a sign for malignancy. "D" stands for diameter and lesions greater than 6 mm should raise awareness. "E" stands for elevation or evolving and any change of shape, size, structure, color, or symptoms is a potential indicator for malignancy [50].

The introduction of dermoscopy as a diagnostic tool and the development of several algorithms have improved the early detection of cutaneous malignant melanoma over recent years [51]. In contrast to cutaneous melanoma, studies on the dermoscopy of VMs are limited by small case numbers. Table 2 summarizes the dermoscopy features of VMs from a total of 38 patients identified in the literature. The most common features were asymmetry of structure and color (91.7%), blue-white veil or blue-gray areas (68.4%), structureless areas (47.4%), irregular dots and globules (42.1%), atypical vessels (42.1%), irregular network or atypical patterns (34.2%), and reticular depigmentation (16.7%). The characteristic dermoscopy features in VM are shown in Fig. 3. A retrospective study by the International Dermoscopy Society evaluated the application of dermoscopy for genital lesions and suggested that the presence of a blue, gray, or white color plus the presence of a structureless zone had a sensitivity of 100% and a specificity of 82.2% to detect a melanoma [52]. Ferrari et al. proposed that a multicomponent pattern composed of irregular brown-black dots, blue-white veil, atypical vessels, and reticular depigmentation appear to be characteristic features for VMs [53]. However, there remains a significant overlap between benign and malignant lesions and a biopsy should be performed in all suspicious lesions for a definitive diagnosis. Particularly with larger or multiple lesions, meticulous mapping of the biopsy site is mandatory and the position on the clock face with distance from the midline and vaginal introitus as well as the anatomic location should be reported [46].

If VM is confirmed on biopsy, staging should be based on the American Joint Committee on Cancer (AJCC) staging system instead of the FIGO staging system used for vulvar squamous cell carcinoma, as the AJCC has been found to be a better predictor of survival in the prospective GOG-73 study and this was recently confirmed by a large population-based study [2, 42]. The AJCC staging system is currently in its eighth edition and the staging of the primary tumor (T category) is based on Breslow's thickness and the presence/absence of ulceration [45]. Histologic grading is not used in melanomas, but the lesion is classified into one of the histopathologic subtypes: superficial spreading, nodular, lentigo maligna, acral lentiginous, and desmoplastic [45]. Women with superficial spreading VM appear to have a better prognosis compared with those with nodular melanomas [2].

Because of the often advanced disease stages, pre-operative imaging is recommended [46, 54]. Magnetic resonance imaging may be useful to delineate the disease extent and for surgical planning. Computed tomography or positron emission tomography-computed tomography may be used for the evaluation of regional and/or distant metastases [46].

5 Surgical Treatment

The primary treatment modality for localized melanoma is surgical excision. In cutaneous melanoma, the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend surgical margins depending on tumor thickness (based on category I evidence): 0.5–1 cm for melanoma in situ, 1 cm for invasive melanoma with a Breslow's thickness ≤ 1 mm, 1–2 cm for Breslow 1.01–2 mm, and 2 cm for Breslow > 2 mm. Noteworthy, these are based on measured clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist [55, 56]. The same margins must apply for VM. However, in accordance with the National Comprehensive Cancer Network guidelines, margins may be modified to accommodate individual anatomic or functional considerations, which may be considered in VM in terms of preservation of continence and sexual function [46, 55]. Although urinary incontinence has been reported after surgical resection of vulvar cancer, a partial resection of 1–1.5 cm of the distal urethra, if required for a complete excision, does not appear to be associated with an increased risk for urinary incontinence [57, 58]. The GOG-73 trial, the only prospective study on VM performed to date, and retrospective data indicate that more radical vulva surgeries such as primary vulvectomy are not associated with a better oncologic outcome compared with a local excision using the margins above, but are associated with an increased complication rate [10, 15, 42, 59, 60].

Sentinel lymph node biopsy should be offered to all women with VM and clinically unsuspicious nodes if the AJCC stage is greater than IA or in the presence of ulceration [55–56]. The Multicentre Selective Lympadenectomy

Table 2 Dermoscopy features in malignant melanomas of the vulva

Study, year	VM (n)	Asymmetry of color/structure	Irregular dots/globules	Veil (blue/white, blue/grey, white)	Whitish-grey or grey areas	Irregular network/atypical pattern	Atypical vessels	Reticular depig-mentation	Structure-less areas	Milky red or red areas
Virgili (2004) [127]	1	100% (1/1)	100% (1/1)	0% (0/1)	0% (0/1)	100% (1/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)
DeGiorgi (2005) [128]	1	100% (1/1)	0% (0/1)	100% (1/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)
Lin (2009) [129]	2	100% (2/2)	0% (0/2)	100% (2/2)	0% (0/2)	100% (2/2)	100% (2/2)	0% (0/2)	0% (0/2)	0% (0/2)
Blum (2011) [52]	2	100% (2/2)	0% (0/2)	100% (2/2)	0% (0/2)	0% (0/2)	0% (0/2)	0% (0/2)	100% (2/2)	0% (0/2)
Ferrari (2011) [53]	5	100% (5/5)	60% (3/5)	100% (5/5)	0% (0/5)	0% (0/5)	40% (2/5)	80% (4/5)	0% (0/5)	0% (0/5)
Ronger-Savle (2011) [130]	5	100% (5/5)	0% (0/5)	80% (4/5)	0% (0/5)	40% (2/5)	40% (2/5)	0% (0/5)	0% (0/5)	0% (0/5)
Rogers (2016) [131]	1	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	100% (1/1)	0% (0/1)
Oakley (2016) [48]	3	100% (3/3)	0% (0/3)	33% (1/3)	67% (2/3)	33% (1/3)	67% (2/3)	0% (0/3)	33% (1/3)	0% (0/3)
Blum (2016) [132]	1	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	100% (1/1)	0% (0/1)	0% (0/1)	0% (0/1)
Resende (2018) [133]	2	100% (2/2)	50% (1/2)	50% (1/2)	0% (0/2)	50% (1/2)	50% (1/2)	0% (0/2)	100% (2/2)	50% (1/2)
Theillac (2019) [134]	1	100% (1/1)	100% (1/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)
Vaccari (2019) [47]	14	n.a.	71% (10/14)	71% (10/14)	79% (11/14)	43% (6/14)	43% (6/14)	n.a.	86% (12/14)	14% (2/14)
Studies combined	38	91.7% (22/24)	42.1% (16/38)	68.4% (26/38)	34.2% (13/38)	34.2% (13/38)	42.1% (16/38)	16.7% (4/24)	47.4% (18/38)	7.9% (3/38)

Summary of dermoscopy features of VMs from previously published studies

n number, *n.a.* not assessed, *VM* vulvar melanoma

Fig. 3 Characteristic dermoscopy features of malignant melanomas of the vulva
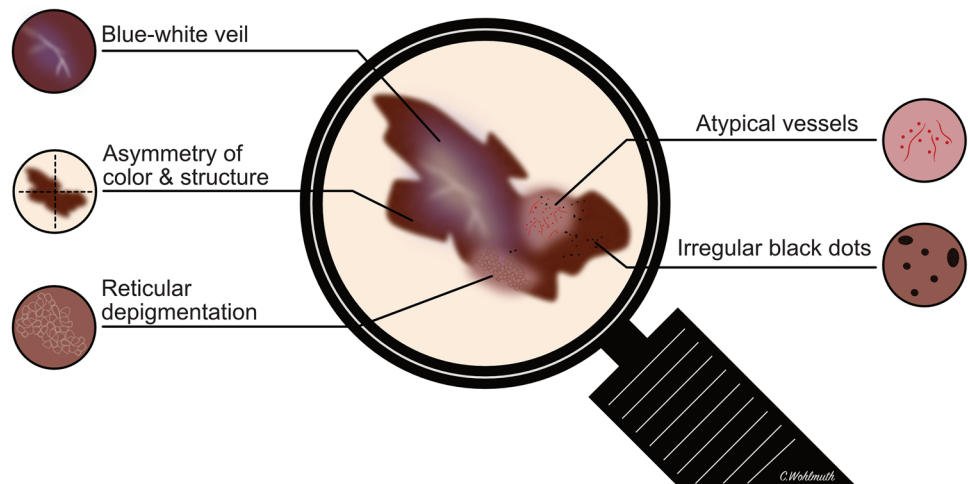
Trial I has validated the staging potential of sentinel lymph node biopsy but did not show an unequivocal survival benefit in terms of treatment-related 10-year melanoma-specific survival [61]. Noteworthy, the study enrolled patients between 1994 and 2002, in the era before adjuvant treatment with checkpoint inhibitors was offered to node-positive patients. Sentinel lymph node biopsy has been extensively studied in vulvar cancer. A meta-analysis has shown that the detection rate using blue dye in combination with radiocolloid tracer is 97.7% (95% CI 96.6–98.5) if ultra-staging and immunohistochemistry is performed [62]. A similar detection rate of 98.3% has been reported in a literature review of VMs [63].

More recently, near-infrared fluorescence imaging with indocyanine green has been implemented to visualize sentinel lymph nodes in gynecologic cancers. Prospective and retrospective studies suggest that indocyanine green is as good as radiocolloids and blue dye or may even improve the detection rate of the sentinel lymph node [64, 65]. In lateral vulvar tumors, a unilateral sentinel lymph node biopsy is usually sufficient; however, in primary tumors that are within 2 cm of, or crossing, the vulvar midline, a bilateral evaluation is warranted [66, 67]. Lymphoscintigraphy with radiocolloid tracers aids in the identification of unilateral vs bilateral sentinel nodes [68].
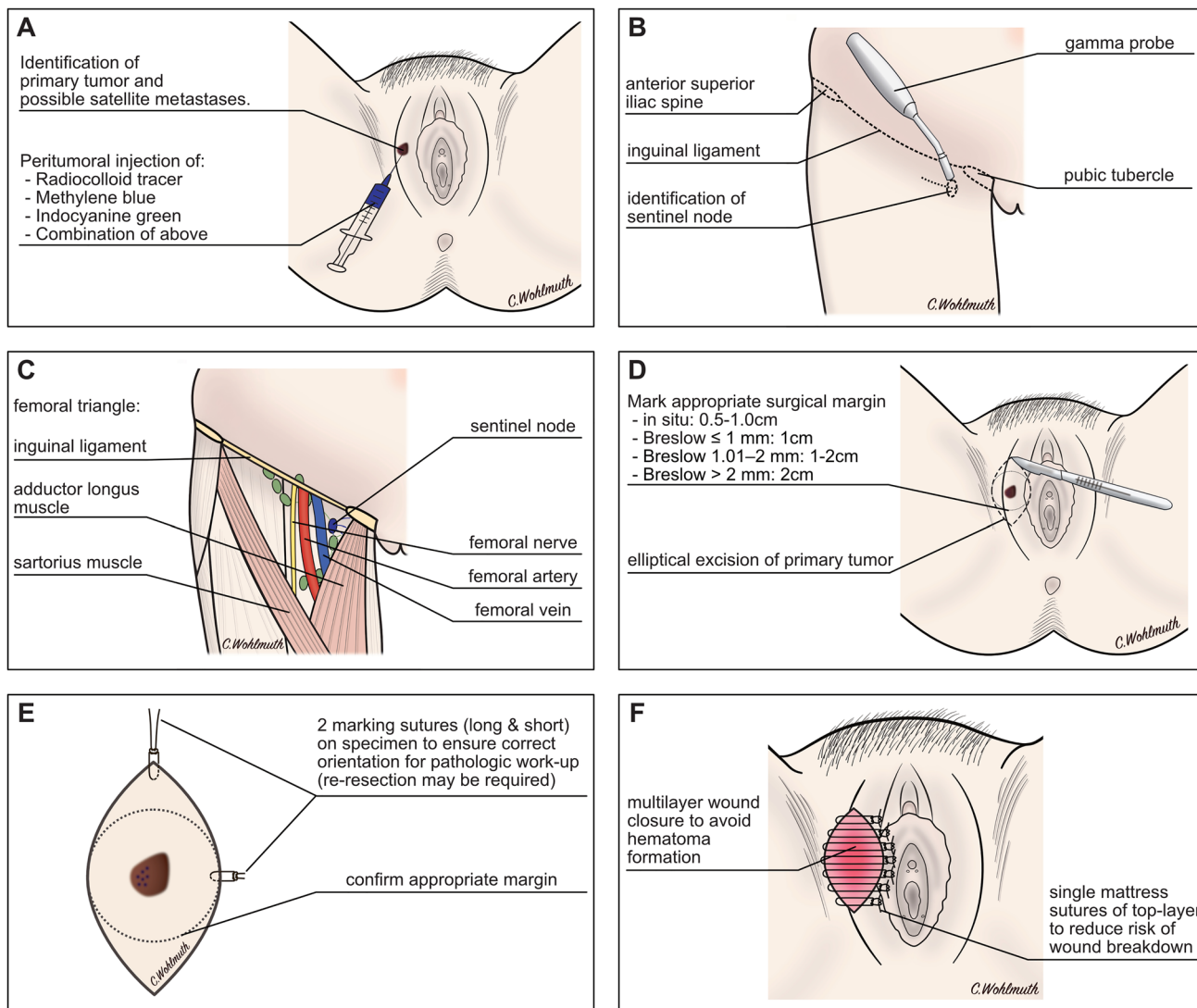
For patients with a positive sentinel node, two randomized-controlled phase III studies have shown no difference in melanoma-specific or overall survival in patients undergoing completion lymphonodectomy compared to those who underwent nodal basin ultrasound surveillance [55, 69, 70]. The Multicentre Selective Lympadenectomy Trial II trial indicated a lower rate of regional recurrence, which did not translate into a survival benefit and was associated with an almost four times higher rate of lymphedema [69]. Although these studies investigated patients with cutaneous melanomas, this likely translates into VM, where the complication rates of full inguinofemoral lymph node

dissection are high [68, 71]. In women with clinically apparent lymph node metastases, therapeutic lymph node dissection combined with local excision is indicated after excluding distant metastases [55, 56, 72]. A summary of the key surgical steps and relevant anatomical landmarks is shown in Fig. 4.

6 Medical Treatment

Before the era of immune checkpoint inhibitors and targeted therapy, women with unresectable or metastatic VM were typically offered cytotoxic chemotherapy, which was associated with response rates between 12 and 26% without improving survival [73–75]. Polychemotherapy regimens are not associated with better survival compared to single-agent chemotherapy and interferon-alpha and interleukin-2 improve progression-free survival, but not overall survival [76]. With the US Food and Drug Administration and European Medicines Agency approval of CTLA-4, PD-1, BRAF, and MEK Inhibitors, the medical treatment of melanoma has drastically changed accompanied by ground-breaking improvements of survival [46, 77–80].

Many of the landmark trials allowed the inclusion of mucosal melanomas and VMs. A pooled post-hoc analysis of six clinical trials [81–86] on the efficacy and safety of ipilimumab and nivolumab suggested a lower response rate in mucosal melanomas compared with cutaneous melanomas. The objective response rate (ORR) for ipilimumab monotherapy was 8.3% (95% CI 1.8–22.5%), for nivolumab alone 23.3% (95% CI 14.8–33.6), and for a combination therapy with ipilimumab and nivolumab 37.1% (95% CI 21.5–55.1) [87]. However, the analysis included all mucosal melanomas without separately reporting the disease sites. Similarly, a post hoc analysis on the efficacy and safety of pembrolizumab in 84 patients with mucosal melanoma

A Identification of primary tumor and possible satellite metastases.

Peritumoral injection of:
- Radiocolloid tracer
- Methylene blue
- Indocyanine green
- Combination of above

C.Wohlmuth

B anterior superior iliac spine

gamma probe

inguinal ligament

identification of sentinel node

pubic tubercle

C.Wohlmuth

C femoral triangle:

inguinal ligament

adductor longus muscle

sartorius muscle

sentinel node

femoral nerve

femoral artery

femoral vein

C.Wohlmuth

D Mark appropriate surgical margin
- in situ: 0.5-1.0cm
- Breslow ≤ 1 mm: 1cm
- Breslow 1.01–2 mm: 1-2cm
- Breslow > 2 mm: 2cm

elliptical excision of primary tumor

C.Wohlmuth

E 2 marking sutures (long & short) on specimen to ensure correct orientation for pathologic work-up (re-resection may be required)

confirm appropriate margin

C.Wohlmuth

F multilayer wound closure to avoid hematoma formation

single mattress sutures of top-layer to reduce risk of wound breakdown

C.Wohlmuth

Fig. 4 A–F Key steps in the surgical management of vulvar melanoma. The sentinel technique is now considered standard of care in the management of vulvar cancer and melanoma in women with clinically negative lymph nodes. Radiocolloid tracers, methylene blue dye, indocyanine green, or a combination of these can be used to locate the sentinel node in vulvar melanoma (**A**). Radiocolloid tracers facilitate the localization of the sentinel node using a gamma probe and a small incision is made at the region of the located sentinel node (**B**). The anatomical landmarks of the femoral triangle are the inguinal ligament, the adductor longus muscle, and the sartorius muscle. The sentinel node can be visualized if methylene blue or indocyanine green have been used and confirmed with a gamma probe if radiocolloid tracers have been injected (**C**). If possible, a local wide excision is usually preferred over more radical procedures. The suggested surgical margin depends on the depth of invasion, i.e. Breslow's thickness of the primary tumor (**D**). The specimen should be marked for further pathologic work-up in the anatomically correct orientation in case a re-resection due to R1 status is necessary (**E**). The wound should be closed in layers to reduce the risk of hematoma formation. The top layer is often closed using single mattress sutures to reduce the risk of wound breakdown (**F**).

pooled from the KEYNOTE-001, 002, and 006 trials [79, 88, 89] was performed: the ORR for pembrolizumab was 19% (95% CI 11–29) with anti-tumor activity observed in ipilimumab-naive and ipilimumab pre-treated patients [90]. Again, the disease site was not specified.

We have recently published our data on CTLA-4 and PD-1 inhibitor treatment in vulvovaginal melanomas at the Princess Margaret Cancer Centre in Toronto [11]. Women with VM treated with ipilimumab had an ORR of 12.5% (95% CI 0–35.4) and the disease control rate (DCR) was 25.0% (95% CI 0–55.0). For PD-1 inhibitors or a combination of CTLA-4 and PD-1 inhibitors, the ORR was 33.3% (95% CI 2.5–64.1) and the DCR was 66.7% (95% CI 35.9–97.5). In addition, previously published case reports and case series on immune checkpoint inhibitors in VMs were analyzed separately and showed similar ORRs [11].

The safety profile and rate of grade 3 or 4 immune-related adverse events were comparable to cutaneous melanomas with a range of 8–13% for monotherapy and up to 40% with combination treatment [11, 87, 90]. Therefore, immune checkpoint inhibitors should be offered to all women with unresectable or metastatic VMs, although the response rates may be slightly lower compared with cutaneous melanomas. Other immune checkpoints that are currently under investigation include LAG3, TIM3, and OX40 [91–93].

As shown in Table 1, *c-KIT* mutations are present in >20% of VMs. Tyrosine kinase inhibitors may therefore be considered in recurrent VM. While studies have shown that tyrosine kinase inhibitors are ineffective in unselected cases of advanced melanoma, it may be considered in those patients harboring a *c-KIT* mutation [94–96]. In three phase-II clinical trials, a total of 92 patients with melanoma with *c-KIT* mutations were given imatinib. The ORR range was 16–29% and the DCR was 36–54% [97–99]. Nilotinib, a different tyrosine kinase inhibitor that was originally approved for imatinib-resistant chronic myeloid leukemia, was also tested in a total of 135 *c-KIT*-mutated melanomas in five phase II trials. The reported ORR range was 16–26% and the DCR was 53–78%. Nilotinib was generally well tolerated with grade 3/4 toxicities observed in approximately 20%, the most common being elevated hepatic and pancreatic enzymes [100–104].

Although the sample size of the studies was limited, the authors observed that most of the responders harbored *c-KIT* mutations located on exons 11 and 13 [102, 104]. In our literature review, 85.7% of *c-KIT* mutations found in VMs were located in these exons (Fig. 1A). Other tyrosine kinase inhibitors that have been used include sunitinib [105, 106], dasatinib [107, 108], and sorafenib [109].

With *BRAF* mutations being relatively rare, targeted treatment with a combination of BRAF and MEK inhibitors plays a less important role in VMs (Table 1). The recently published American Society of Clinical Oncology guidelines on systemic therapy, however, suggest that a combination therapy with the BRAF/MEK inhibitors dabrafenib/trametinib, encorafenib/binimetinib, or vemurafenib/cobimetinib may also be offered in *BRAF*-mutant mucosal melanomas [110].

Data regarding adjuvant treatment in mucosal melanomas remain scarce. Most clinical trials on adjuvant therapy in melanoma (including the EORTC-18071 and Keynote-054 protocol) have either excluded mucosal melanoma or did not further specify melanoma subtypes [46, 111–113]. The CheckMate-238 trial included 29 patients with mucosal melanomas, of whom 16 received nivolumab, but the study was not sufficiently powered to show differences in the subgroups [114].

The American Society of Clinical Oncology guidelines suggest that patients with mucosal melanomas should be offered the same therapies recommended for cutaneous melanomas. Nivolumab or pembrolizumab should thus be offered to patients with resected stage IIIA/B/C/D *BRAF* wild-type VMs, while either of those two agents or the combination of dabrafenib and trametinib may be considered in *BRAF*-mutant disease [110]. Several clinical trials (NCT03241186, NCT04462965, NCT03178123, NCT04180995, NCT04622566) are currently ongoing that may further guide adjuvant and neoadjuvant treatment of mucosal melanomas in the near future (www.clinicaltrials.gov).

7 Conclusions

Vulvar melanomas represent an important subclass of melanomas with distinct molecular characteristics. Diagnosis is often delayed with 38% being diagnosed at advanced disease stages and the prognosis of women with VMs remains dismal. With often overlapping features between benign and malignant lesions, the threshold to biopsy suspicious lesions should be kept low. Surgery remains the primary treatment modality for localized melanoma and should include a sentinel node biopsy. Adjuvant treatment with nivolumab or pembrolizumab should be discussed with nodal involvement. Medical treatment with checkpoint inhibitors should be offered to women with unresectable or metastatic VMs and tyrosine kinase inhibitors may be considered in recurrent disease if a *c-KIT* mutation is identified.

Declarations

Conflicts of interest/Competing interests Christoph Wohlmuth and Iris Wohlmuth-Wieser have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval No ethics approval was required for the preparation of this review article.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material All data are available in this published article and are available from the corresponding author on reasonable request.

Code availability Not applicable.

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