

## Review Article

# Primary malignant melanomas of the female lower genital tract: clinicopathological characteristics and management

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**Abstract:** The female lower genital tract melanomas mainly include vulvar, vaginal and cervical melanoma. There is little clinical data on the melanomas thus making them highly lethal with their prognosis being worse than for cutaneous melanoma and other gynecological malignancies. Surgery is still the primary treatment for gynecological melanomas with wide local resection (WLE) of tumors with adequate margins being preferred for early-stage vulvar melanoma while complete resection of the primary tumor is the standard treatment for early-stage cervical and vaginal melanoma. Sentinel lymph node biopsy seems to avoid unnecessary complete regional lymphadenectomy. However, it should be chosen cautiously. Recently discovered molecular changes have provided new hopes for effective systemic treatment of female genital tract melanomas. In this review, we summarize the pathogenesis and clinicopathological characteristics of these rare melanomas with particular emphasis on new therapies and clinical management methods that may affect prognosis. The review aims to provide a viable direction for clinicians to diagnose and treat female lower genital tract melanomas.

**Keywords:** Vulva, vagina, cervix, malignant melanoma, diagnosis, prognosis, target therapy

## Introduction

Malignant melanomas (MM), mainly derived from the basal layer of melanocytes, occur in the eyes, skin, and mucosal membranes (e.g., respiratory, gastrointestinal, and genitourinary mucosa). The tumorigenesis of cutaneous and mucosal melanocytes may involve different molecular mechanisms or signaling pathways [1, 2]. In recent years, the incidence of primary gynecologic melanomas has increased [3]. Due to lack of early and specific signs and symptoms, gynecologic melanomas have a poor prognosis and high mortality. Currently, there is no perfect solution for staging and treatment of female genital tract melanomas (GTMM) because only little knowledge of its pathogenesis and risk factors exists. In addition, amelanotic malignant melanoma (colorless lesions) occur in 0.4 to 27.5% of the cases [4]. GTMM clinical symptoms are similar to other histological types of lower genital tract cancer thus posing a challenge for its diagnosis [5]. In a study

on cancer survival rate, the five-year survival rate of most mucosal melanomas was 34% in total (range 3-69%) which was significantly worse than for cutaneous melanoma having 89% survival rate [6].

The main treatment for localized cutaneous melanomas involves surgical resection in proportion to the tumor stage of the primary lesion. Use of sentinel-lymph-node biopsy (SLNB) should be considered for the assessment of occult metastases in the regional lymph nodes, potentially identifying patients who may benefit from adjuvant treatment [7, 8].

In an international trial study, melanoma patients with sentinel-node metastases were randomly assigned to prompt completion lymph-node dissection (dissection group) or nodal observation with ultrasonography (observation group). The results indicated no significant difference on the survival rates of the two groups. However, the 3-year rate of disease control in

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regional lymph nodes was higher in the dissection group (92±1.0% vs 77±1.5%). In addition, non-sentinel lymph node metastases which are an independent prognostic factor for recurrence was found in 11.5% of patients in the dissection group (hazard ratio 1.78; P=0.005) [9].

According to the standard management of cutaneous melanoma, WLE and SLNB are the preferred therapies for vulvar melanoma (derived from the skin in pathology). Complete resection of the primary tumor is the first consideration for cervical and vaginal melanoma because patients with complete resection of the primary tumor are less likely to have local relapse and distant metastasis than patients with R1/2 tumor resection (P<0.001) [10]. Reports have shown that targeted therapy and chemotherapy are effective in some patients. Though controversial, postoperative radiation therapy may be useful for patients with advanced melanomas [11]. Carbon ion radiotherapy is a potentially effective treatment for gynecological melanomas exhibiting lymph node metastasis in the groin and pelvic regions with studies indicating the 2-year local control, overall survival (OS), and progression-free survival (PFS) rates at 71%, 53%, and 29% respectively [12, 13].

This review outlines the pathogenesis, clinicopathological characteristics, and different prognostic factors of gynecological malignant melanoma. We further discuss the different staging systems and available therapies to help clinicians diagnose and treat these rare and invasive tumors.

### Gynecological melanomas

#### *Epidemiology*

The overall incidence of gynecological melanoma was 1.74 per million women [14]. Accounting for 3.4-10% of all vulvar neoplasms, vulvar melanoma is the second most common vulvar malignancy after vulvar squamous cell carcinoma [15]; Primary vaginal and cervical malignant melanomas are sporadic with vaginal melanoma accounting for 1-5% of all vaginal malignancies [16] while cervical melanoma accounts for 3-9% of all cervical malignancies [17]. The peak incidence of patients with GTMM was between 50 and 60 years, 54 to 85 years for vulvar melanoma [18, 19], 57 to 68 years for vaginal mel-

anoma [20, 21], and 35 to 81 years for cervical melanoma [22, 23].

Analysis of 324 vulvar melanomas and 125 vaginal melanomas was done in various ethnic groups. Results indicated a low racial difference in vulvar and vaginal melanomas with age-adjusted incidence rates (per million female population) being 0.87 in Blacks, 0.75 in American-Indian, 1.03 in Asians and Pacific Islanders, 1.22 in Hispanics, and 1.90 in non-Hispanic Whites [24]. Most experts believe that melanoma originates from melanocytes in the basal layer of the epithelium growing from the stroma or the malignant transformation of borderline nevi [25].

#### *Pathogenesis*

The pathogenesis for most vulvar melanomas is similar to cutaneous melanomas in sun-protected sites like the volar aspects of the hands and feet subungual locations. On the other hand, the pathogenesis of vaginal, cervical, and a few vulvar mucosal melanomas is similar to other mucosal melanomas. Unfortunately, the pathogenesis of all these subtypes of melanoma is poorly understood. A study evaluating genetic aberrations in 284 patients with mucosal melanoma found that GNAQ/11 mutation occurred in 9.5% of patients with the overall survival of patients with GNAQ/11 mutation being significantly shorter than that of wild-type GNAQ/11 patients [26]. More recently, the whole-genome landscape analysis of 67 mucosal melanomas revealed that the significantly mutated genes are NRAS (17.9%), BRAF (16.4%), NF1 (16.4%), KIT (14.9%), SF3B1 (11.9%), TP53 (9.0%), and SPRED1 (7.5%), ATRX (6.0%), HLA-A (6.0%), and CHD8 (4.5%). The load of structural chromosomal variants was greater, including repeated structural rearrangements of 5p, 11p, and 12p, which resulted in the amplification of oncogenes such as TERT, MDM2, CCND1, and CDK4 [27].

Recently, there is increasing evidence that high-risk HPV (HR-HPV) infection and ultraviolet (UV) radiation play a critical role in the pathogenesis of non-melanoma skin cancer (NMSC) [28]. HPV-DNA was detected in 6 of 9 genital tract melanomas (six vulvar and three vaginal melanomas) suggesting that HPV may also be involved in the pathogenesis or progression of both cutaneous and mucosal melanoma. However, its role in pathogenesis is unclear

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**Table 1.** BRAF, NRAS and KIT mutations in the female genital tract melanomas

References	Anatomic location of the melanoma	Number of cases	BRAF	NRAS	C-KIT
[30]	Vulva and vagina	20	7.6%	27.6%	27.6%
[33]	Vulva	23	9%	0%	35%
[32]	Vagina	7	0%	43%	0%
[34]	Vulva	50	0%	10%	24%
[35]	Vagina	15	0%	13%	13%
[36]	Vulva and vagina	51	26%	-	22%
[37]	Vulva, vagina and cervix	19	0%	21%	5.2%
	Vulva	123	3.2%	8.1%	17.9%
	Vagina and cervix	67	1.4%	14.9%	7.5%
	Vagina and cervix	159	12.5%	-	8.0%

[29]. Heinzelmann *et al.* reviewed the clinicopathological characteristics of vulvar melanomas (n=33) in situ and concluded that 9.1% (n=3) had lichen sclerosis associated with melanoma, although no lichen sclerosis was found in the areas of invasive melanoma [30]. Molecular characterization of cutaneous melanomas was done by the Cancer Genome Atlas (TCGA) Network with results identifying four major genomic subtypes: BRAF mutant, NRAS mutant, NF-1 mutant and triple wild-type [31]. All subtypes are similar to female genital tract melanomas (**Table 1**). The tumorigenesis of vulvar and vaginal melanoma involves different molecular alterations with BRAF mutations being absent in both while NRAS mutations and C-KIT amplifications occur in both sites. Targeting the molecular alterations of different individuals may develop new treatment strategies for vulvar and vaginal melanomas [32].

### Clinical presentation

Vulvar melanoma may present as papules or macules, asymmetric borders and nodules of irregular coloration [19]. As a result of melanosis, vulvar nevi and melanoma have a similar clinical presentation thereby posing a challenge for the diagnosis of vulvar melanoma. Pigmented vulvar lesions can be differentiated by combining dermatoscopy with vulvar biopsy [19, 38]. Under dermoscopy, melanoma presents as blue, grey, or white structure-less zones [39]. The most common clinical presentation is the amelanotic red "polyps" with approximately 27% of vulvar melanomas being amelanotic [38]. During diagnosis, any lesion with suspicious dermoscopic or clinical features should

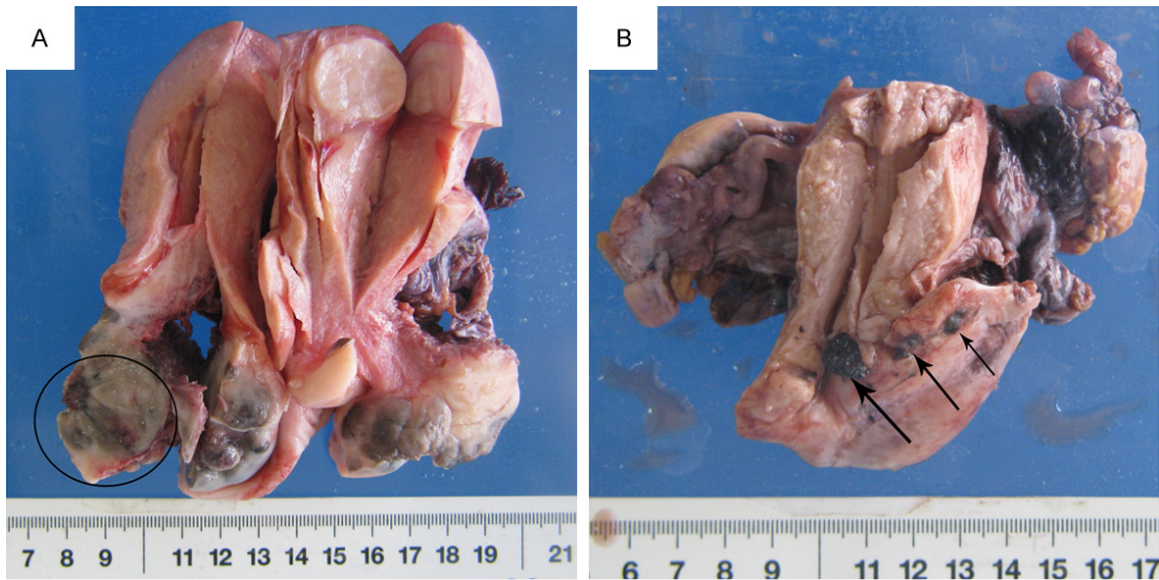
be biopsied. Other nonspecific symptoms include vulvar bleeding, itching, discharge and pain [40]. The most common origin of vulvar melanoma is the labia majora, followed by clitoral hood and the labia minora. In a large epidemiological study conducted in Sweden, the origin of melanoma was investigated in 291 patients with vulvar melanoma. In 12% of the patients, it appeared in hairy skin, in 46% it emerged in glabrous skin while in 35% it extended to both areas. However, vulvar melanoma can be multifocal [38].

Vaginal melanoma mostly occurs in the lower third and usually presents as inconstantly pigmented plaques, ulcerated or polypoid masses in the anterior wall of the vagina [37, 41]. The most common symptom of vaginal melanoma is bleeding, which is manifested by irregular vaginal bleeding or increased vaginal discharge. Other symptoms include vaginal wall mass, increased discharge, and dyspareunia [16, 34]. It is worth noting that cervical melanoma usually involves the vaginal, so when symptoms are observed it is necessary to distinguish whether it is a primary vaginal malignant melanoma or not (**Figure 1**).

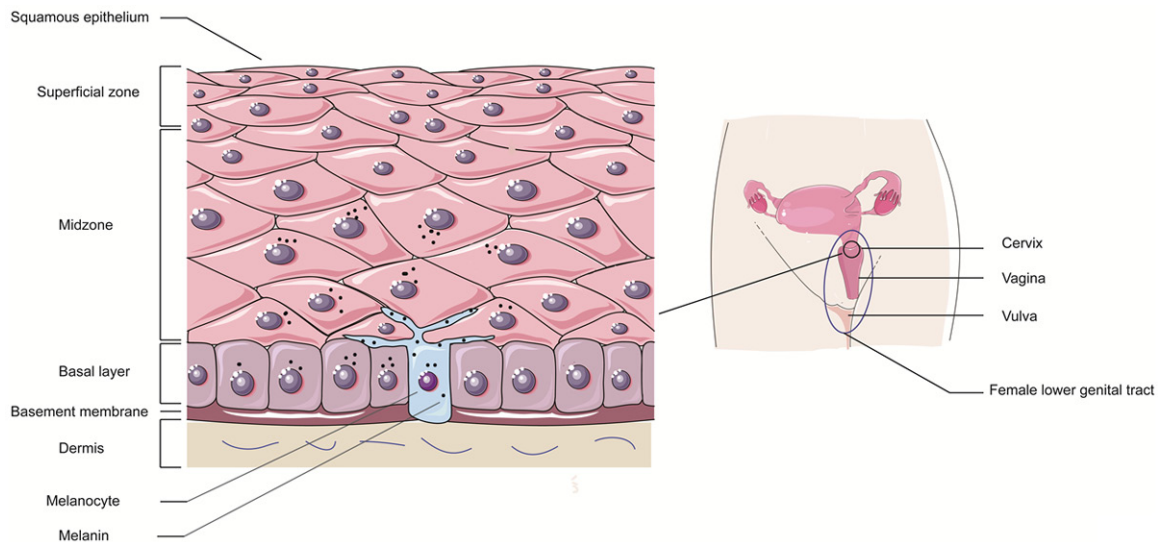
Cervical melanoma is brown or black in color, has an irregular mass shape, is polypoidal, leads to corpora mammillaria, and has a cauliflower-like look. In the early stages of cervical melanoma, the clinical symptoms are similar to other histological types of cervical cancer thus making it hard to diagnose [5]. The Cervical melanoma may present as irregular vaginal bleeding, postmenopausal vaginal bleeding, or increased vaginal discharge, while cervical squamous cell carcinoma involves contact vaginal bleeding [42-44]. These clinical symptoms are not expressed in some patients with diagnosis being done during a routine gynecological examination. During diagnosis, colposcopy can be used to observe cervical pigmentation. However, amelanotic malignant melanomas which are colorless lesions occur in 35 to 45% of the cases [25, 45].

The diagnosis of cervical and vaginal melanoma is mainly based on gynecological examinations, colposcopy, and biopsy [36, 41]. All sus-

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**Figure 1.** Two digital pictures of the gross specimens of cervical melanoma. The first patient was a 54-year-old postmenopausal woman, and the lesions had infiltrated the full thickness of the cervix and vagina. Because vaginal malignant melanoma often occurs in the anterior wall of the distal end of the vagina, this patient was diagnosed with primary malignant melanoma of the cervix infiltrating the vagina (A). The second patient was 75 years old, and a cauliflower-like mass could be seen on the cervix, approximately 2 cm in size. Also, there is a small black mass at the external cervix (B).



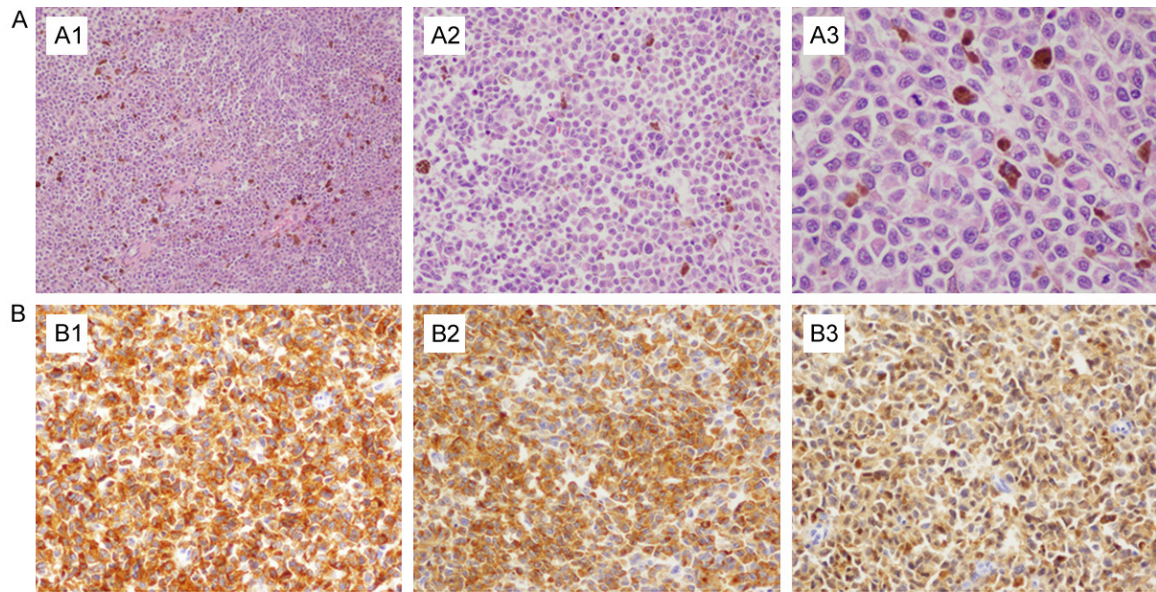
**Figure 2.** Schematic representation of normal female lower genital tract and mucosal melanoma tissue structure. The drawing shows the normal anatomy of the female genital tract, including the vulva, vagina, and cervix. The pullout shows a close-up view of the squamous cell and basal cell layers of the cervix. Melanocytes can be seen in the normal squamous cells which form the origin of melanoma. The basement membrane is between the epidermis and dermis. Melanin is shown in the cells.

pected cervical and vaginal lesions should be biopsied. Description of the normal female lower genital tract and cervical malignant melanoma tissue structure is shown in **Figure 2**.

### *Pathological characteristics*

Melanocytes originate from the neural crest cells and migrate to the basal epidermis and

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**Figure 3.** Pathological characteristics of cervical malignant melanoma. (A) Spindle tumor cells and melanin granules are visible in the cytoplasm (A1, H&E staining, 100×). The tumor cell morphology is irregular and mainly polygonal. The nucleoli are enlarged, with abundant acidophil cytoplasm. Melanin granules are visible in some cytoplasm (A2 & A3, H&E staining, 200× & 400×). (B) The tumor cells were positive for S-100 (B1, 200×), Melan-A (B2, 200×) and HMB 45 (B3, 200×).

mucosal surfaces with mutations in the melanocytes causing malignant melanoma [46]. Most melanocytes are found at the epidermal-dermal junction of the skin arising from cutaneous sites with a few being in the mucosal membranes [47]. Atypical and genetically mutated melanocytes give rise to malignant melanoma [48]. In addition, most vulvar melanomas have the same histological manifestations as cutaneous melanomas. They are superficial spreading type with the intra-epidermal proliferation of individual melanocytes being limited to the epidermal basal layer (dermal-epidermal junction) and skin appendages [49]. Cervical and vaginal malignant melanoma have similar histopathologic characteristics as mucosal melanomas where the tumor cells are round or fusiform, and the cytoplasm contains different amounts of melanin granules observed after hematoxylin-eosin (HE) staining (**Figure 3A**) [43]. Malignant melanoma cells show bidirectional differentiation in carcinoma and sarcoma.

However, it is difficult to distinguish the lesion from poorly differentiated carcinoma or sarcoma if the tumor cells have fewer melanin granules after HE staining. Therefore, immunohistochemistry is an essential means for auxiliary examination where human melanoma black-45

(HMB45), s-100, and Melan-A proteins are usually positive [22]. Almost all primary and metastatic malignant melanomas show positive expression of s-100 protein thus making it a standard marker for malignant melanoma [50]. HMB-45 has a higher specificity for malignant melanoma but its sensitivity is only 60% to 80%, while Melan-A protein has a higher sensitivity (**Figure 3B**) [51].

Histological features related to pathological staging are important prognostic indicators in female genital tract melanomas. They include histological type, tumor size, invasion depth, ulceration, margins (peripheral and deep), mitotic rate, lymph vascular space involvement (LVSI), and tumor-infiltrating lymphocytes (TILs) [52, 53].

### *Neoplasm staging*

Detection of a female genital tract melanoma is followed by the exclusion of metastatic lesions from other parts such as skin, mucosa, and the eyes [54]. The staging approved by the International Federation of Gynecology and Obstetrics (FIGO) might not be appropriate for vulvar melanomas because it cannot provide adjuvant treatment decisions and prognostic indicators. Therefore, cutaneous mela-

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**Table 2A.** Clark classification (Level of Invasion of cutaneous melanoma)

Level of Invasion	Description
Level I	Lesions involving only the epidermis (in situ melanoma); not an invasive lesion.
Level II	Invasion of the papillary dermis; does not reach the papillary-reticular dermal interface.
Level III	Invasion fills and expands the papillary dermis but does not penetrate the reticular dermis.
Level IV	Invasion into the reticular dermis but not into the subcutaneous tissue.
Level V	Invasion through the reticular dermis into the subcutaneous tissue.

**Table 2B.** Chung's modified classification (Level of Invasion of mucosal melanoma)

Level of Invasion	Description
Level I	Tumor confined to the epithelium (i.e., Clark's level I)
Level II	Tumor penetrates basement membrane and invades depth of $\leq 1$ mm
Level III	Tumor invades depth of 1-2 mm
Level IV	Tumor invades depth of $> 2$ mm, but not subcutaneous fat
Level V	Tumor penetrates subcutaneous fat (i.e., Clark's level V)

noma micro-staging systems have been recommended for vulvar melanoma [38, 40]. The first staging systems to be used provided results on the vertical thickness of the lesion in millimeters (Breslow classification) [55] and the level of invasive anatomy (Clark classification) [56] (**Table 2A**). A modified Clark system (Chung classification) has been specifically used for the micro-staging of vulvar melanoma [57] (**Table 2B**). However, Clark classification is not used in the 8th Edition AJCC staging system though it should be recorded as a primary tumor characteristic. Tumor thickness (Breslow classification) is more reproducible and more accurate in predicting the prognosis of early-stage malignant melanoma [40]. A clinicopathological study of vulvar melanoma suggests that the American Joint Committee on Cancer (AJCC) staging system for cutaneous malignant melanoma is the only independent prognostic factor for vulvar melanoma [40]. Eventually, new prognostic factors that are more important for predicting the prognosis of melanoma were added to the AJCC system when it was revised in 2017 [58] (**Tables 3A, 3B**).

Presently, no standardized staging of mucosal melanoma tumors has been used unlike in cutaneous melanoma which has a well-defined stage [59]. Several studies have shown that tumor size ( $\geq 3$  cm or  $< 3$  cm) is an independent risk factor for early-stage vaginal melanoma [60, 61]. The 8th Edition of the AJCC staging clearly states that there is no available AJCC staging system for vaginal mucosal melanoma.

However, the “vaginal cancer” section of the FIGO cancer report 2018 does not indicate that mucosal melanoma should be excluded. In addition, FIGO staging incorporates tumor size and regional lymph nodes status. Therefore, FIGO 2009 vaginal cancer staging may be applicable to vaginal melanoma [62, 63]. TNM AJCC staging for cutaneous melanoma was significantly associated with prognosis [10, 54]. Challenges posed by tumor staging for mucosal melanoma can be solved by having a thorough understanding of the prognostic factors of mucosal melanoma which would help in establishing a valid staging system. The general staging system can be divided into three stages: Stage I, clinically localized disease, no regional lymph node involvement; Stage II, regional lymph node involvement; Stage III, distant metastatic disease.

In summary, clinical manifestations of primary cervical melanoma are similar to other histological cervical cancers. The “cervix uteri” of the FIGO cancer report 2018 does not exclude mucosal melanoma. Therefore, FIGO 2018 cervical cancer staging system is applicable to cervical melanoma.

### Treatment

As mentioned above, the clinical management for most vulvar melanoma is mainly based on cutaneous melanoma. The preferred treatment for primary tumors being SLNB and WLE with different safety margins [64]. Cutaneous mel-

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**Table 3A.** Revised American Joint Committee on Cancer 2017 tumor-node-metastasis (TNM) melanoma staging

	Description
Primary tumor (T)	
TX	Primary tumor thickness cannot be assessed (i.e., diagnosis by curettage)
T0	No evidence of primary tumor (i.e., axillary metastases without known primary tumor)
Tis	Intraepithelial (i.e., melanoma in situ)
T1	Tumor ≤1.0 mm thick, without or with ulceration:
T1a	≤0.8 mm thick and Clark's level II or III, without ulceration
T1b	<0.8 mm thick and Clark's level IV or V, or with ulceration 0.8-1.0 mm thick and Clark's level IV or V, with or without ulceration
T2	Tumor 1.01-2.0 mm thick, without (T2a) or with ulceration (T2b)
T3	Tumor 2.01-4.0 mm thick, without (T3a) or with ulceration (T3b)
T4	Tumor >4.0 mm thick without (T4a) or with (T4b) ulceration
Regional lymph node (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to one lymph node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N1a	clinically occult (i.e., detected by SLN biopsy)
N1b	clinically apparent (i.e., macroscopic)
N1c	in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N2	Metastasis to two or three regional lymph nodes, or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N2a	clinically occult (i.e., detected by SLN biopsy)
N2b	clinically apparent (i.e., macroscopic)
N2c	in-transit, satellite, and/or microsatellite metastases combine with one clinically occult or apparent
N3	Metastasis to four or more regional lymph nodes; matted lymph nodes; or combination of in-transit metastasis or satellite(s) and metastatic regional lymph node(s)
N3a	clinically occult (i.e., detected by SLN biopsy)
N3b	clinically apparent (i.e., macroscopic), or presence of matted nodes
N3c	in-transit, satellite, and/or microsatellite metastases combine with two or more clinically occult or clinically detected and/or presence of matted nodes
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis, lactic dehydrogenase (LDH) status (designated as "0" for "not elevated" and "I" for "elevated" level, no suffix is used if LDH is not recorded or is unspecified)
M1a	distant skin, subcutaneous, or lymph node
M1b	lung
M1c	all other non-central nervous system (CNS) visceral sites
M1d	CNS

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**Table 3B.** American Joint Committee on Cancer 2017 prognostic stage group for cutaneous melanoma

Stage	T	N	M
0	Tis	NO	M0
IA	T1a	NO	M0
IB	T1b, T2a	NO	M0
IIA	T2b, T3a	NO	M0
IIB	T3b, T4a	NO	M0
IIC	T4b	NO	M0
IIIA	T1a/b-T2a	N1, N2a	M0
IIIB	T0	N1b, N1c	M0
	T1a/b-T2a	N1b/c, N2b	M0
	T2b/T3a	N1a-N2b	M0
IIIC	T0	N2b/c, N3b/c	M0
	T1a-T3a	N2c, N3	M0
	T3b/T4a	Any N $\geq$ N1	M0
	T4b	N1a-N2c	M0
IIID	T4b	N3	M0
IV	Any T, Tis	Any N	M1

noma treatment has been revolutionized by the approval of immune checkpoint inhibitors (nivolumab and pembrolizumab), BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib and cobimetinib). All these inhibitors have been shown to have a significant impact on the prognosis of melanoma patients [64-66]. Alternatively, chemotherapy is considered as second-line treatment for melanoma of the vagina, cervix and a few vulvar melanomas belonging to the mucosal melanoma subtypes. However, the treatment of mucosal melanoma is based on retrospective case series which poses challenges to the development of clinical guidelines. A study has reported that mucosal melanomas with different primary anatomy have similar natural history and molecular characteristics [37]. Complete resection of the primary tumor followed by adjuvant radiotherapy is the preferred treatment because it is favorable for local control [10, 67]. Postoperative adjuvant chemotherapy has a positive impact on survival after resection of mucosal melanomas. However, other benefits of adjuvant chemotherapy for mucosal melanoma have not yet been determined. One study compared 189 patients with resected mucosal melanoma and interferon or observed patients with results indicating that chemotherapy based on temozolomide plus cisplatin significantly improved relapse-free survival (RFS) and

OS [68]. Details on the differences between the two subtypes of female lower genital melanoma are described in **Table 4**.

### *Vulvar melanoma*

Radical vulvectomy has been the recommended therapy for vulvar melanoma which is similar to vulvar squamous cell carcinomas treatment [72]. However, there was no significant difference in the survival rate when patients who underwent radical vulvectomy were compared to patients who underwent more limited resection [38, 73]. Consequently, conservative surgery such as wide local excision (WLE) has been accepted as a better treatment [38]. Treatment of localized vulvar melanoma should be a WLE with adequate tumor-free surgical margins where tumors with less than 1 mm require 1 cm tumor-free lateral margins while 1 to 4 mm thick tumors require 2 cm tumor-free lateral margins [73]. The least surgical margin required for a WLE regardless of the thickness of the tumor is 1 cm. The margin may extend to the subcutaneous fascia through subcutaneous fat [74].

In cutaneous melanoma, selective regional lymphadenectomy may improve survival rates since tumor thickness is related to the incidence of positive regional lymph nodes [75]. However, in a prospective clinicopathological study involving 71 patients with primary vulvar melanoma, the role of groin node dissection was inconclusive [76]. Therefore, SLNB should be routinely considered before the WLE of primary melanoma. In cases where metastatic melanoma is detected, a complete groin node lymphadenectomy can be performed [77]. Dhar *et al.*, reviewed the literature of 26 patients with vulvar melanoma after SLNB was done. The study reported that subsequent complete groin node lymphadenectomy detection rate of SLN was 100% with the false-negative rate being approximately 15% [78], which is lower than the 0-2% false-negative rate of cutaneous melanoma [79]. Therefore, the decision to abandon complete regional lymphadenectomy should be made with caution when a negative SLN is present for vulvar melanoma.

Radiotherapy is another option for the treatment of vulvar melanoma. Preoperative neoadjuvant radiotherapy of the vulva or groin is first done to reduce tumor size and achieve more



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**Table 4.** The differences between the two subtypes of female lower genital tract melanoma

	Sun-protected cutaneous melanoma (most vulvar melanoma)	Mucosal melanoma (vaginal, cervical, and a few vulvar melanoma)
Molecular alteration [69-71]	BRAF, NRAS, TERT, CDKN2A, PTEN	c-KIT, NRAS, BRAF, NF1, CDKN2A, TERT, PTEN
Metastatic pattern	First evident in local lymph nodes, distant metastases (lung, brain) arise later	More likely to distant metastases (lung, liver, brain)
Surgical modality	WLE with adequate excision margins	Complete resection of the primary tumor
Lymph nodes assessment	SLNB, resection of regional lymph nodes if necessary	SLNB and routine resection of regional lymph nodes is not recommended
Systemic therapy [64]		
Chemotherapy	Interferon, Dacarbazine, Paclitaxel	Cisplatin, Vinblastine, Dacarbazine, Interferon
Radiotherapy	Optional, preoperative neoadjuvant and postoperative adjuvant radiotherapy	Optional, palliate local or metastatic disease
Targeted therapy	BRAF and MEK inhibitors	BRAF and c-KIT inhibitors
Immunotherapy	PD-1 and CTLA-4 checkpoint inhibitors	PD-1 and CTLA-4 checkpoint inhibitors
Palliative therapy	Palliative surgery or radiotherapy	Palliative surgery or radiotherapy
Prognosis factors	AJCC staging, Breslow thickness, LDH status, distant metastases, and lymph nodal status	Breslow thickness, LDH status, distant metastases, lymph nodal status and the depth of invasion

Abbreviation: WLE, wide local resection; SLNB, sentinel-lymph-node biopsy; CTLA-4: Cytotoxic T lymphocyte antigen 4; PD-1: Programmed cell death protein 1.

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conservative surgery. Postoperative adjuvant radiotherapy can then be done based on the number of positive lymph nodes, lateral (unilateral or bilateral), and metastatic type (micro metastases or macro metastases) for patients with positive groin or pelvic lymph nodes [54].

A study on 36 patients with primary or recurrent vulvar melanoma who underwent surgery reported that adjuvant treatment failed to improve the PFS and OS for the ten patients who underwent different postoperative adjuvant chemotherapy or immunotherapy. This may be due to the positive lymph nodes or depth of invasion during surgery. However, preoperative chemotherapy with carboplatin and paclitaxel improved the outcome in two patients where PFS was two years and five years for both cases [80]. Carbon ion radiotherapy is an alternative treatment for malignant melanoma [12] and used it to treat GTMM for 23 patients (6 cases of the vulva, 14 cases of vagina, and 3 cases of cervix) with results indicating that lymph node metastasis remained in the groin and pelvic regions. The 3-year local control rate was 49.9% while the 3-year OS rate was 53.0%. Similar results were published in 2019 showing that after 37 patients with gynecological melanoma (12 cases of vulva, 22 cases of vagina, and 3 cases of cervix) received this treatment, 81% (n=30) patients achieved complete tumor disappearance [13]. Management guidelines for the treatment of vulvar melanoma by combining the revised AJCC 2002 melanoma staging system with the SLN assessment are shown in **Figure 4**.

### *Vaginal melanoma*

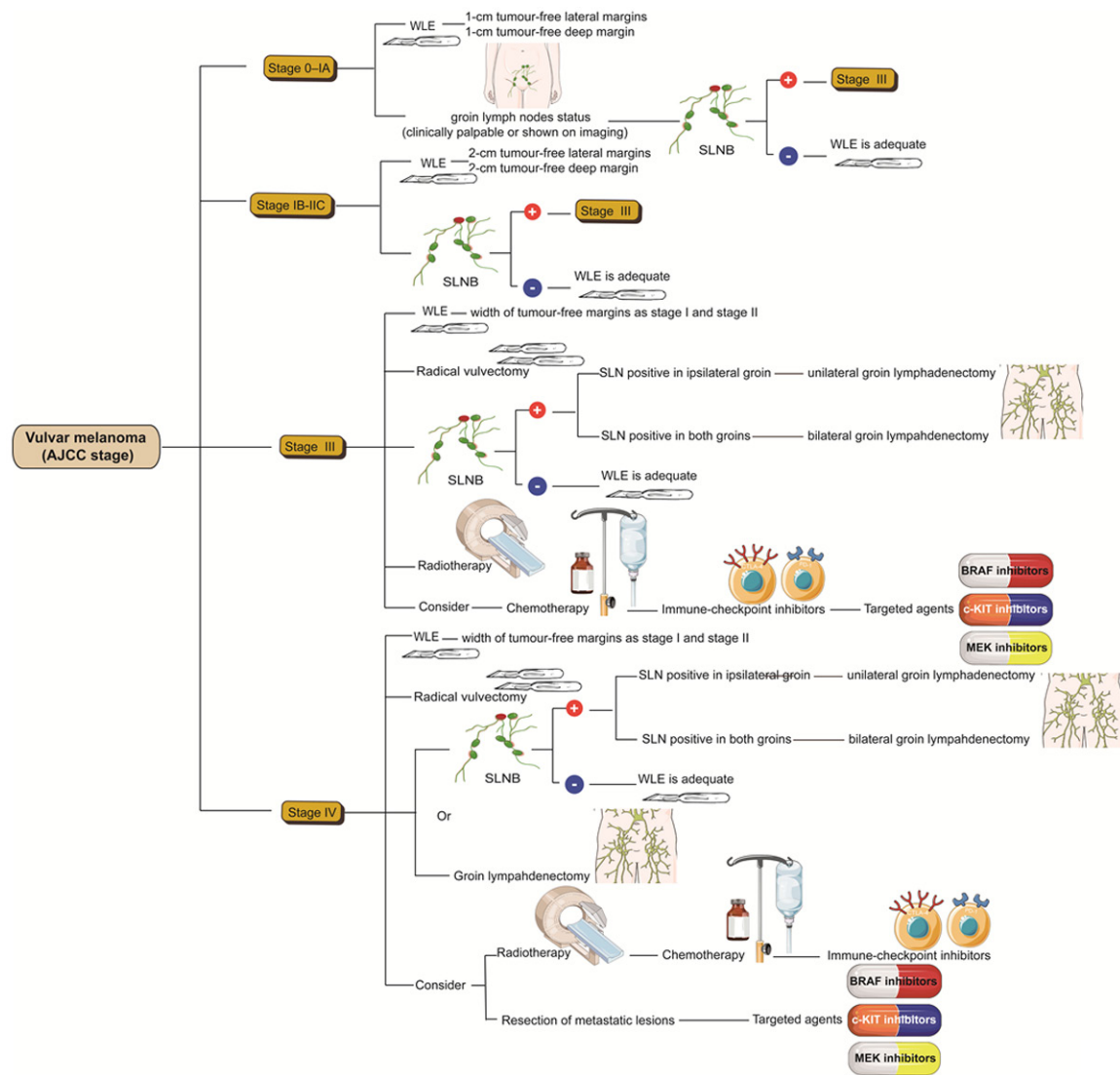
Surgery remains the preferred treatment for vaginal melanoma with studies showing that vaginal melanoma patients who underwent surgery had significantly longer OS [21, 42, 81]. There is no significant difference in the clinical outcome when radical surgery (from vaginectomy to pelvic exenteration) is compared with conservative surgery. Therefore, local resection with an adequate surgical margin (1 cm or 2 cm according to Breslow thickness) is the primary treatment for vaginal melanoma. If local excision is not possible or the extent of the tumor is difficult to determine, more aggressive approaches can be wisely considered. In a case involving close or positive margins, radical surgery is a viable option alone or in combination

with adjuvant radiotherapy [20, 60, 82]. In a retrospective study involving 37 women with stage I vaginal melanoma, 25 patients underwent WLE, eight patients underwent pelvic exenteration, and four patients received radiotherapy and/or chemotherapy. Recurrence occurred in 89% (n=33) of the patients with only 22% (n=7) of patients having local recurrence. Most recurrences were still distant or multifocal indicating that recurrence does not mainly depend on inadequate surgical resection. Interestingly, adjuvant radiotherapy done after extensive local resection reduced the local recurrence rate [81]. Results from the study indicate that extensive local resection followed by radiotherapy is a viable treatment for vulvar melanoma. Available data do not support the use of SLNB in the treatment of vaginal melanoma [83, 84]. Many researchers do not recommend groin and/or pelvic lymphadenectomy for patients without evidence of positive lymph node by clinical and radiologic evaluation because of the low rate of regional lymph node metastasis. However, resection of the groin and/or pelvic lymph nodes in patients with clinically positive lymph nodes can improve regional control and reduce the risk of recurrence [80, 82].

Radiotherapy can be used as preoperative neo-adjuvant radiotherapy to reduce tumor size and make WLE possible. It can also be used as a postoperative adjuvant therapy for patients with high-risk factors such as tumor size being greater than 3 cm, positive or unclear surgical margins and positive groin and/or pelvic lymph nodes [16, 72, 82, 85]. WLE followed by high-dose radiotherapy is an effective treatment for vaginal melanoma because it provides excellent loco-regional control [61]. However, the radiotherapy field to be used should be selected according to the location of the vaginal melanoma where tumors in the lower vagina should include the groin lymph nodes while tumors in the middle and upper vagina should involve pelvic lymph nodes [54].

In another retrospective study involving 31 cases of vaginal melanoma (surgery, n=22; immunotherapy, n=19), patients who underwent surgery followed by immunotherapy attained the most prolonged OS on average with a five-year OS of 47%, which was higher than 29% of patients who underwent surgery alone [20]. The role of chemotherapy or biotherapy has not

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**Figure 4.** Schematic diagram of vulvar melanoma management. The revised AJCC 2017 melanoma staging system based on the current information on vulvar cancer and standard treatment of cutaneous melanoma is recommended for vulvar melanoma. WLE = wide local excision. SLNB = sentinel lymph node biopsy.

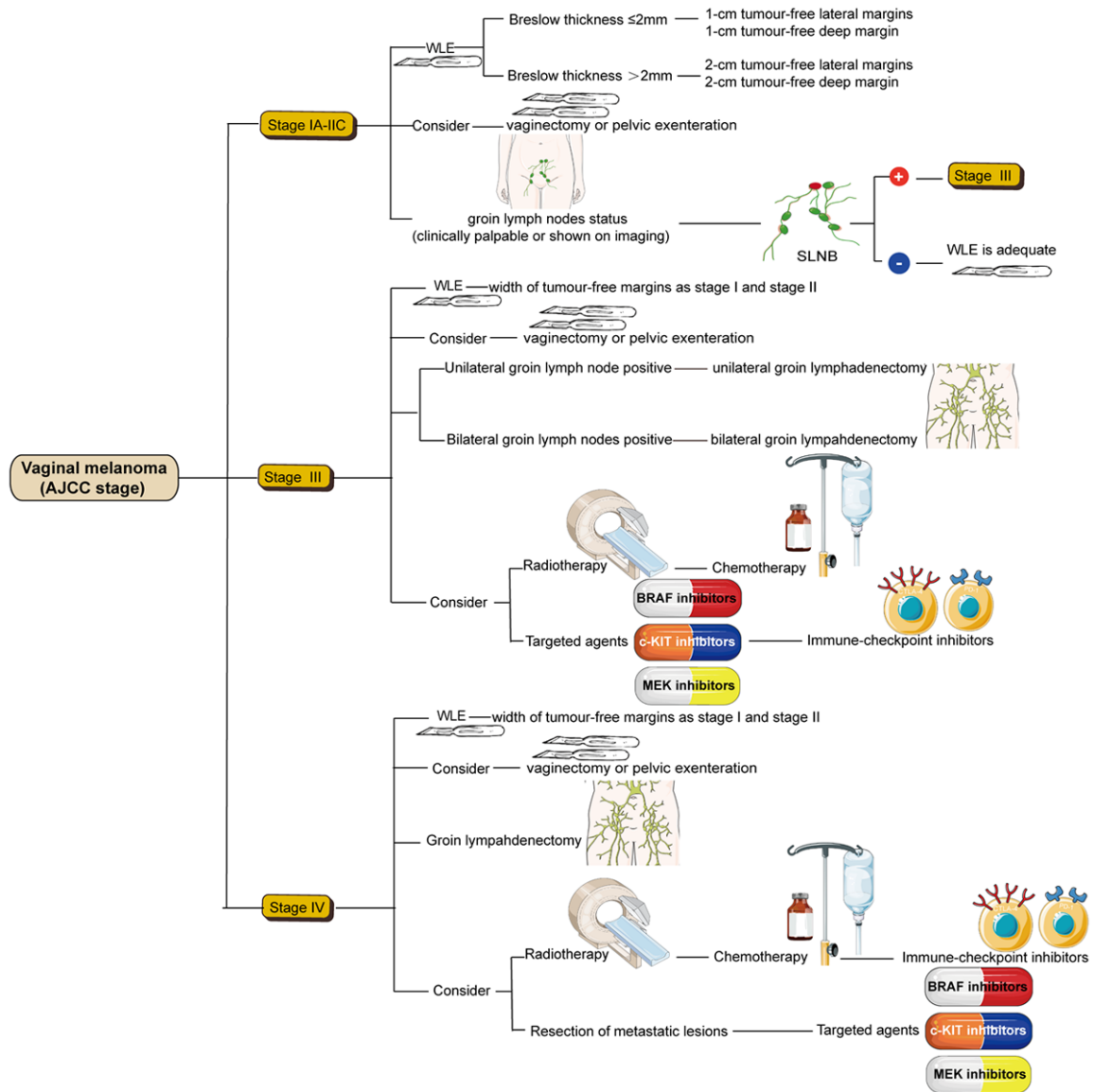
been determined due to the rarity of vaginal melanoma. Management guidelines for the treatment of vaginal melanoma are shown in **Figure 5**.

### *Cervical melanoma*

Treatment of cervical melanoma is mainly based on other histological types of cervical cancer. Radical hysterectomy and pelvic lymphadenectomy are often chosen for early-stage tumors with para-aortic lymphadenectomy being optional. Primary surgery with a free surgical margin of at least 2 cm is recommended for

early-stage tumors while primary pelvic radiotherapy is usually selected for advanced-stage tumors [43, 54]. Some studies advocate for adjuvant pelvic radiotherapy in cases where the patient has one or more of the following risk factors: positive surgical margins, positive regional lymph nodes, corpus uteri and/or parametrial metastasis and tumor size greater than 4 cm [22, 23]. Dacarbazine (DTIC) is an active chemotherapeutic agent for treating malignant melanoma with a single drug with the effective rate of temozolomide (the oral preparation of DTIC) being 12-20% [86, 87]. However, there are no chemotherapy regimens

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**Figure 5.** Schematic diagram showing the management strategies for vaginal melanoma. The revised AJCC 2017 melanoma staging system is based on the current information on vaginal cancer and standard treatment of mucosal melanoma. WLE = wide local excision. SLNB = sentinel lymph node biopsy.

that significantly reduce relapse. Management guidelines for the treatment of cervical melanoma are shown in **Figure 6**.

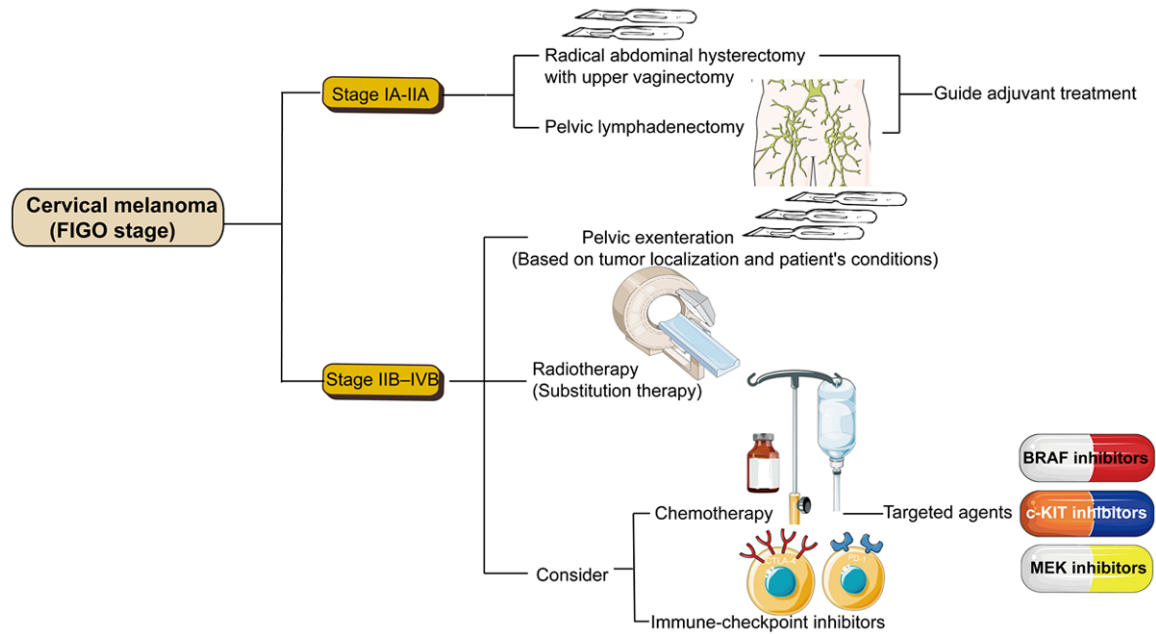
### *Immunotherapy and targeted therapy in genital tract melanomas*

Distant metastasis and poor prognosis have been the most challenging factors to resolving advanced melanoma for many years. Recently, a better understanding of the regulatory mechanism between tumors and the immune micro-environment has led to the development of immune checkpoint inhibitors [88, 89]. A study comparing the use of a combination of pro-

grammed death-1 (PD-1) checkpoint inhibitors and cytotoxic T-lymphocyte antigen-4 (CTLA-4) checkpoint inhibitors with the use of either agent alone has shown clinically significant improvements in PFS and objective remission rate (ORR) [90]. In another study, however, PD-L1 was not expressed in 63 advanced malignant melanomas and was not associated with OS [91]. Therefore, the role of PD-L1 expression as prognostic and predictive biomarkers is still controversial in malignant melanoma.

In a trial involving patients with advanced melanoma, the five-year OS rate of the nivolumab-

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**Figure 6.** Schematic diagram of cervical melanoma management. The FIGO staging system is recommended for cervical melanoma, based on the current information on cervical cancer. WLE = wide local excision. SLNB = sentinel lymph node biopsy.

plus-ipilimumab group was 52%, 44% for the nivolumab group, and 26% for the ipilimumab group [92]. In a French multicenter retrospective study, 229 patients with metastatic mucosal melanoma underwent immunotherapy (anti-CTLA-4 or anti-PD-1 monoclonal antibodies,  $n=151$ ) or chemotherapy ( $n=78$ ). Immunotherapy had better response rates at 11.9% with OS being longer than that of the chemotherapy group. The median OS for immunotherapy was 15.97 months with that of chemotherapy being 8.82 months. The study concluded that immunotherapy can significantly increase OS in patients with metastatic mucosal melanoma [93]. Similar to observations in mucosal melanomas, approximately 35% of cutaneous melanomas express PD-L1 [88]. However, the clinical response rate of immune checkpoint inhibitors in genital tract melanomas has not yet been reported.

As mentioned above, c-KIT, NRAS, and BRAF mutations are frequently detected in GTMM indicating that selective inhibitors targeting these mutations may be effective treatment avenues. An example is vemurafenib which is an inhibitor of mutated BRAF kinase in patients with metastatic melanoma. In a phase III trial comparing vemurafenib with dacarbazine, vemurafenib reduced the risk of death by

63% and disease progression by 74% ( $P<0.001$ ) [94]. And in East Asian patients with advanced BRAF V600-mutant cutaneous melanoma, vemurafenib had an overall response rate of 52.2%-61% and a median PFS of 7.9 months, with tolerable adverse events [95, 96]. On the other hand, Imatinib is a KIT-directed tyrosine kinase inhibitor. Treatment with imatinib of patients with advanced melanoma having KIT mutations resulted in significant clinical response [97]. MEK inhibitors are expected to become an effective treatment strategy for targeted therapies in patients with NRAS-mutant melanoma [65]. In a multicenter phase III trial, 402 patients with advanced NRAS-mutant melanoma were enrolled and randomly assigned to binimetinib (MEK inhibitor) or dacarbazine treatment. The median of progression-free survival (PFS) in the binimetinib group was 2.8 months while that of the dacarbazine group was 1.8 months (one-sided  $P<0.001$ ) with the side effects of binimetinib being tolerable. In summary, binimetinib offers a new treatment for patients with NRAS-mutant melanoma [98]. In addition, patients with BRAF V600E or V600K mutations in metastatic melanoma have prolonged PFS and OS when treated with a combination of BRAF and MEK inhibitors with the 5-year PFS and OS being 19% and 34% respectively [99].

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Immunotherapy combined with angiogenesis targeted therapy for advanced mucosal melanoma has been approved by the Food and Drug Administration (FDA). In East Asian patients with chemotherapy-naïve metastatic mucosal melanoma, Toripalimab (anti-PD-1 monoclonal antibody) plus Axitinib (vascular endothelial growth factor receptor inhibitor) had an ORR of 48.3% (14/29) and a median PFS of 7.5 months [100].

### Prognosis

#### *Vulvar melanoma*

The main factors that affect the prognosis of vulvar melanoma are AJCC staging, Breslow thickness, LDH status, distant metastases, and lymph nodal status [15, 30, 34, 40, 76]. Notably, serum lactic dehydrogenase (LDH) status is included in the M1 category of the eighth edition of the AJCC tumor-node-metastasis (TNM) staging (**Tables 3A, 3B**). In clinical trials where patients with advanced melanoma received a combination of BRAF and MEK inhibitors, the 5-year OS of patients with normal baseline LDH versus those with elevated LDH was 43% versus 16% [66, 99]. In other clinical trials of immunotherapy, baseline serum LDH was independently associated with overall survival of ipilimumab [101] and anti-PD-1 treatment [102].

Several other factors, such as tumor ulceration, age, and c-KIT expression have been reported to be prognostic factors for vulvar melanoma [15, 30]. A retrospective study in the Netherlands enrolled 489 patients with vulvar basal cell carcinoma and 350 patients with vulvar melanoma between 1989 and 2012. The 5-year OS of vulvar melanoma patients was 37% (95% CI 28-47%), while that of vulvar basal cell carcinoma was 100%. Referring to the AJCC staging system, the 5-year OS of cutaneous melanoma patients and matched vulvar melanoma patients was 50% (95% CI 40.5-59.1%) ( $p=0.002$ ). Interestingly, the 5-year OS of vulvar melanoma patients increased from 37% in 1989-1999 to 45% (95% CI: 37-54%) in 2000-2012, suggesting better clinical management employed since 2000 [103].

AJCC staging is a strong independent prognostic factor for vulvar melanoma [40, 76, 104]. A study conducted in M. D. Anderson Cancer

Center covering 51 vulvar melanoma patients revealed that the median survival time of all patients was 41 months. More specifically, the 5-year survival rate was 91% in patients with stage I, and 31% with stage  $\geq$  IIA ( $P=0.0002$ ) [40]. A retrospective analysis of 85 cases of primary vulvar or vaginal melanoma in Australia showed that the 5-year OS of patients with AJCC stage 0-II (63.6%,  $n=59$ ) was higher than for those with stage III (0%,  $n=12$ ,  $P<0.001$ ).

In addition to AJCC staging, Breslow thickness has been found to be an independent prognostic factor of vulvar melanoma [76]. A multicenter retrospective study enrolling 77 patients with vulvar melanoma showed that Breslow thickness was associated with recurrence ( $P=0.002$ ) [104]. In a retrospective study on 16 patients with primary vulvar melanoma who underwent surgery at Indiana University Hospital, the median depth was 0.9 mm (range, 0.1-1.75 mm) in those who did not experience a recurrence and 4.6 mm (range, 3-8 mm) in those who relapsed ( $P<0.01$ ). Patients with Breslow depth  $\leq 1.75$  mm had no recurrence, whereas all patients with a lesion deeper than 1.75 mm had a recurrence ( $P=0.0004$ ) [105].

It has been reported that lymph node metastasis is an interrelated prognostic factor of vulvar melanoma, Sugiyama et al. analyzed 644 patients with vulvar melanoma, of which 179 (27.8%) underwent lymphadenectomy, and 58 (9%) had lymph node metastasis. The 5-year OS of patients with positive lymph node scores of 0, 1, 2, or more was 68.3%, 29%, and 19.5%, respectively ( $P<0.001$ ) [15]. Similarly, in patients with vulvar melanoma who underwent SLNB or groin lymph node dissection at the Mayo Clinic, lymph node metastasis was significantly associated with OS ( $P=0.02$ ) and DFS ( $P=0.007$ ) [80]. A prospective study of vulvar melanoma showed that capillary lymphatic space involvement ( $P=0.0001$ ) was independently associated with central primary tumor location ( $P=0.003$ ) and groin node status [76].

#### *Vaginal melanoma*

Studies evaluating 5-year survival of vaginal melanoma have reported rates ranging from 13% to 32.3% [20, 82, 106, 107]. AJCC stage [108], lymph node status [81, 106], tumor size [60], and primary treatment [81, 82] are the major prognostic predictors of vaginal melano-

ma. Specifically, lymph node involvement was associated with worse overall survival (hazard ratio, 1.98;  $P=0.02$ ) [106]. In another study, patients with negative lymph nodes exhibited a significantly higher median OS than those with positive lymph nodes (30 months vs 7.8 months) [81]. The 5-year OS of patients with AJCC stage 0-II (63.6%,  $n=59$ ) was significantly higher than that of patients with stage III (0%,  $n=12$ ,  $P<0.001$ ) [108]. Patients with tumor size  $<3$  cm showed a median OS of 41 months versus 12 months for those with larger tumors ( $n=67$ ,  $P<0.0024$ ) [60].

### *Cervical melanoma*

Generally, the clinical outcome of cervical melanoma is poor. It has been observed that the 5-year OS of patients with this cancer is approximately 10%, with many patients dying within three years of diagnosis (87.5%). The main prognostic factor of cervical melanoma is the FIGO stage at the time of diagnosis [5, 22, 109, 110]. Compared with other histological types, cervical melanoma is mostly diagnosed at an early stage (FIGO stage I and II), possibly because it is a rare malignant tumor. Of all cases reported in the literature, FIGO stage I accounted for 41%, stage II for 34.4%, while stages III and IV accounted for 18.0% and 6.5%, respectively [22]. Sun et al. analyzed 25 patients who underwent FIGO stage assessment. Among them, 56% were in stage I ( $n=14$ ), 28% in stage II ( $n=7$ ), and 8% in stage III and IV ( $n=2$ ) [110]. Although about 75% of patients are diagnosed as early-stage (FIGO I and II), only a minority of patients live beyond five years. Specifically, the five-year survival rates observed in these patients evaluated accounted for 18.8% in stage I, 11.1% in stage II, and 0% in stage III-IV, respectively [22, 110]. Other prognostic variables, including lymph vascular space involvement, tumor thickness, nodal status, and neovascularization, have also been reported to correlate with clinical outcomes of cervical melanoma [25, 110, 111].

As mentioned above, cervical and vaginal melanoma belongs to a subtype of mucosal melanoma. Mucosal melanoma is usually aggressive and has a poor prognosis, even in patients with presumed early-stage disease. Although the primary site for mucosal melanoma is different, the natural history and prognostic profile are similar [10, 37, 112]. Moreover, there is

no significant difference in the incidence of metastatic disease at different primary sites. The 1-, 2- and 5-year OS rates for gynecological and urological melanoma were 86%, 61%, and 20%, respectively [37]. The prognostic factors of mucosal melanoma differ from those of cutaneous melanoma. The main prognostic factors of mucosal melanoma are Breslow thickness, LDH status, distant metastases, lymph nodal status [10, 113] and the depth of invasion [37, 112].

### **Conclusions and perspectives**

The female lower genital tract melanomas are clinically uncommon malignancies. Notably, such melanomas have a worse prognosis than gynecological cancers and cutaneous melanoma. The revised AJCC 2017 staging system is currently used to diagnose vulvar melanoma, while the FIGO 2018 staging system is recommended for cervical melanoma, but there is no available staging system for vaginal mucosal melanoma.

WLE with adequate margins is the mainstay treatment for early-stage vulvar melanoma while complete resection of the primary tumor is the standard treatment for early-stage vaginal melanoma. SLNB is the major treatment for vulvar melanoma, but its efficacy in vaginal melanoma remains to be defined. Groin lymphadenectomy should be considered if positive lymph nodes are suspected symptomatically or radiologically (e.g., ultrasonography, CT, MRI, or PET). The standard treatment for early-stage cervical melanoma is radical hysterectomy and pelvic lymphadenectomy, and SLNB is also an alternative treatment for patients with clinically positive pelvic lymph nodes.

Besides, immunotherapy and biotherapy are recommended as part of the procedure, even if the response rate is low for female genital tract melanomas, there are exceptions where patients may benefit from long-term remission.

Radiotherapy may be useful for patients with advanced tumors or as adjuvant therapy for positive margins or histologically positive lymph nodes. Postoperative adjuvant chemotherapy has shown survival benefits for resectable mucosal melanoma, and it has been clinically demonstrated as an adjuvant treatment. Although targeted therapies such as immune

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checkpoint inhibitors and molecularly targeted drugs have been successful, large-scale studies are required to confirm their effectiveness in female genital tract melanomas.

In conclusion, with an understanding of the biology of different melanoma subtypes and their interaction with the immune system, as well as a multidisciplinary approach to melanoma treatment, benefits for melanoma patients will be greatly improved. Besides, the application of various immune checkpoint inhibitors has reactivated the immune response against cancer, and more patients have significantly higher survival rates. However, melanomas of the female lower genital tract must be investigated in more detail as they may be different from other subtypes of melanoma. At the same time, new predictive and prognostic markers need to be identified for further treatment guidance. Finally, the development of individualized treatment plans for patients who do not respond to standardized treatments will be the key to increasing the number of long-term survivors.

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## Disclosure of conflict of interest

None.

## Abbreviations

GTMM, Genital tract melanoma; MM, Malignant melanoma; SLNB, Sentinel-lymph-node biopsy; HPV, Human papillomavirus; TCGA, The Cancer Genome Atlas; FIGO, International Federation of Gynecology and Obstetrics; DTIC, Dacarbazine; CTLA-4, Cytotoxic T lymphocyte antigen 4; PD-1, Programmed cell death protein 1.

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