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Review

Vulvar Melanoma: Clinical Features, Diagnosis, Staging, Treatment and Prognosis

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Abstract

Objective: This article presents a review of the current diagnosis and treatment of vulvar melanoma in detail to provide useful references for the diagnosis and treatment of the disease in the future. **Mechanism**: In this review, the author first specifies the topic of the article and the content covered. PubMed was searched for a series of keyword combinations related to the topic, and there was extensive reading of search engine- and database-derived literature from 1970–2022 related to the vulvar melanoma guidelines, including randomized clinical studies, observational studies, and basic research. Based on the published content, the articles were screened according to the year of publication, the number of citations, and the publishing unit. The data and content needed in each article were collected. Finally, the collected data were summarized to provide an in-depth introduction to vulvar melanoma, a rare disease, covering the aspects of clinical features, diagnosis, staging, treatment and prognosis. **Findings in Brief**: Through this review, we gain a comprehensive understanding of the current diagnosis and treatment of vulvar melanoma and the breakthrough direction of future research. **Conclusions**: At present, the main diagnostic methods in cases of vulvar melanoma include macroscopic examination, dermoscopy, microscopy, histopathology and imaging examination. The main treatment modalities for vulvar melanoma are surgery, radiotherapy, chemotherapy, immune checkpoint inhibitors, targeted therapy and immune modulators.

Keywords: vulvar melanoma; vulvar cancer; malignant melanoma; diagnosis; treatment

1. Introduction

Vulvar cancer is the fourth most frequent gynaecologic tumour, accounting for 3%–5% of malignant tumours of the female reproductive tract [1]. Approximately 2–3 out of every 100,000 women develop vulvar cancer each year, and the vast majority of patients are postmenopausal women between the ages of 50–70 [2]. The main pathological types of vulvar carcinoma include squamous cell carcinoma, adenocarcinoma, basal cell carcinoma, malignant melanoma, sarcoma and metastatic carcinoma. The incidence of vulvar melanoma is second only to squamous cell carcinoma, accounting for 5%–6% of vulvar cancers [3]. The incidence of vulvar melanoma is increasing year by year [4].

The incidence of vulvar cancer is linked to increasing age, human papillomavirus (HPV) infection (mainly HPV 16 and 18), smoking, nonneoplastic epithelial lesions such as lichen sclerosing lesions of the vulva, previous pelvic radiotherapy, and immune deficiency [5]. The aetiology of vulvar melanoma is indefinite, and it is widely recognized that vulvar melanoma arises spontaneously from the source. In other words, vulvar melanoma develops from the malignant transformation of a single orthotopic junction melanocyte [6]. A case report using a next-generation sequencing (NGS) approach found that there were multiple somatic mutations in the platelet-derived growth factor receptor alpha (PDGFRA) and *tumor protein p53* (*TP53*) genes in the primary tumour specimens of vulvar melanoma sufferers, suggesting that PDGFRA and *TP53* gene mutations may be the underlying cause of the development of vulvar melanoma [7]. In addition, female sex [8], age increase (mean age of onset 68 years) [9], family history of cutaneous melanoma [10], race (white race has a higher incidence, while black race has a higher mortality) [11] and hormonal changes [12] are also considered to be risk factors for vulvar melanoma.

Unlike ordinary skin melanoma, vulvar melanoma is usually classified as mucosal melanoma when measured at the anatomical site [13], but its pathogenesis is also different from mucosal melanoma. First, vulvar melanomas tend to be detected later and respond worse to immunotherapy [14]. Second, vulvar melanoma has three histological types, including mucosal freckle type, nodular type and superficial diffuse type, of which mucosal freckle type is the most common. The most common cutaneous melanomas were the acral freckle type (common in Asia) and superficial spread type (Caucasian) [15]. Third, gene mutations in vulvar melanoma, mucosal melanoma and skin melanoma are also different. *Kinase receptor* (*KIT*), *neurofibromin 1* (*NF1*) and *splicing factor 3b subunit 1* (*SF3B1*) gene mutations, common in mucosal melanoma, and *neuroblastoma RAS viral oncogene Homolog* (*NRAS*) and *B-Raf Proto-Oncogene* (*BRAF*) gene mutations, common in skin melanoma, were

rarely observed in vulvar melanoma. *c-KIT* and *TP53* mutations were more common in vulvar melanoma, and vulvar melanomas patients had higher programmed cell death ligand 1 (PD-L1) expression levels [16,17]. Only 7%–26% of patients with vulvar melanoma carry *BRAF* mutations [16]. Finally, the survival rate of vulvar melanoma in all stages was worse than that of cutaneous melanoma [13].

The purpose of this review is to offer a thorough and exhaustive overview of the clinical manifestations, diagnosis, prognosis, and treatment of vulvar melanoma. We will highlight the current status of the treatment of vulvar melanoma and some of the initial successful preclinical results and clinical trials.

2. Clinical Features

The labia majora is frequently observed as the primary location, followed by the labia minora and the clitoral prepuce [18]. Vulvar melanoma often presents as red "polyps" without melanin. Approximately 27% of vulvar melanomas lack melanin [19]. These vulvar melanomas are similar in appearance to vulvar squamous carcinoma *in situ* and are called pigmented malignant melanomas. In addition, vulvar melanoma may also appear as papules, macules, or nodules with asymmetrically and irregularly coloured borders [20], and advanced vulvar melanoma can also present as ulcerous. Under dermoscopy, vulvar melanoma may appear as blue, grey, or white unstructured areas [21]. However, most vulvar melanomas are found with advanced symptoms, such as lumps, bleeding, itching, pain or ulcers [22].

3. Diagnosis

3.1 Macro Inspection

Even areas not exposed to sunlight can develop melanoma, such as the vulvar region. Vulvar melanoma is common in older women, so self-examination with a hand-held mirror is important [23]. The ABCDE (asymmetry, border irregularity, colour variation, diameter, elevation/evolving) rule and the ugly duckling sign are the first steps to distinguish pigmented nevus, nevus, brown spot from melanoma [24].

3.2 ABCDE Rule

"ABCDE rule" summarizes the early clinical symptoms of melanoma [23,25,26].

A: Asymmetry. When an axis is drawn through the centre of the pigmented spot, there is asymmetry of the pigmented spot across the axis.

B: Border irregularity. The pigmented spot has rough, notched or serrated edges, lacking a smooth round or oval outline as expected in a normal nevus.

C: Colour variation. Normal pigmentation spots are usually uniform monochromatic, while malignant melanomas are cloudy black, brown black, and brown, and may have blue, pink, red or even white patches.

D: Diameter. Melanomas are usually larger than normal moles, and caution should be exercised when the pigmented spots are larger than 5 to 6 mm in diameter or increase in size significantly in the short term. Biopsy evaluation is required for pigmented patches larger than 1 cm in diameter.

E: Elevation/evolving. The size, shape, colour and elevation of pigment spots is changing, or new symptoms such as itching, bleeding and scab have appeared.

From a histological perspective, the same rule can also be understood as the ABCDE(FG) rule, which refers specifically to A (Asymmetry); B (Buckshot scatter); C (Cytological atypia); D (Deep mitosis); E (Enclosing lymphocytes); F (Fibrosis) and G (Gainsaying (=no) maturation).

3.3 Ugly Duckling Sign

Ordinary moles tend to look similar, but the skin lesions of malignant melanoma are more unusual than those of the surrounding melanocytic moles. However, this does not apply to vulvar melanoma [24].

3.4 Dermoscopy

Vulvar melanoma can be diagnosed with dermoscopy. Early lesions, characterized by irregular dots, multiple colours, blue and white veils and atypical blood vessels, can be detected by dermoscopy [21]. Keratinocyte hyperpigmentation of the vulvar base is a benign lesion that appears dermoscopically brown (100%) and black (60%) in superficial structures. Vulvar melanoma and other vulvar atypical melanocytic lesions, in addition to brown or black, can also be blue, pink, grey or white, and other benign lesions rarely appear in the colour. This is because lesions, such as melanoma, penetrate deeply into the dermis. These colours are rarely seen in benign vulvar melanoma. These colours are often the result of lesions that have deeply invaded the dermis. In addition, blue–white veils, white structures, and atypical vascular patterns (e.g., milky red areas and atypical vessels) are often observed in vulvar melanomas, even though the Breslow thickness is less than 1 mm. These features are absent in benign pigmented lesions of the vulva [27].

3.5 Microscopy

On a cytological level, melanoma cells can mainly be divided into epithelioid cells and spindle cells. An epithelioid cell is characterized by a large round cytoplasm, abundant eosinophilic granules, and a vesicular nucleus with rough, irregular chromatin. It is most commonly seen in nodular and superficial spreading melanomas [24]. Spindle melanoma cells have obvious spindle shapes, and the cells are arranged in bundles, swirls, braids or pseudoangiomatous structures. The nuclei are curled, and melanocytes are difficult to find. They are commonly seen in sarcomatoid melanomas. Mild proliferation of fibrous tissue and obvious proliferation of blood vessels are observed in the stroma of melanoma cells. Melanoma stroma can also show myxoid degeneration [28].

3.6 Histopathology

The diagnosis of vulvar melanoma depends mainly on histopathology. In tissue biopsy, it is best to completely remove the suspected pigmented lesions 0.1~0.3 cm away from the peripheral cutting edge [29]. Partial biopsy is feasible for large lesions that cannot be completely resected. For patients with large vulvar lesions, punch biopsy could also be considered. A Keyes biopsy device with a diameter of 4~6 mm has been used to completely obtain cylindrical epithelial tissue with a depth of approximately 4 mm [30]. Freezing the pathology is not recommended. Immunohistochemical (IHC) staining with melanocyte markers and proliferation markers is used for the diagnosis and differentiating melanoma. Histopathology is particularly important in the diagnosis of non-pigmented malignant melanoma.

3.7 IHC Markers

IHC is a commonly used and economical histological examination to diagnosis melanoma. The ideal marker for vulvar melanoma should be both sensitive and specific and try to pinpoint the extent of the lesion without missing tumour cells. S-100 is a highly sensitive marker in the cytoplasm and nucleus of melanoma, with a sensitivity of approximately 97%–100%. However, the specificity of S-100 is low because it is expressed on adipocytes, chondrocytes, Langerhans cells and tumour cells associated with these cells [31]. HMB-45 is an antibody specific labelling melanoma black that recognizes melanocytic antigen GP100 (also called Pmel 17). HMB-45 is expressed in the cytoplasm, and its specificity is higher than that of S-100. Related studies have shown that HMB-45 is a sensitive melanoma marker, with a sensitivity of 69% to 93%. In primary melanoma tumours, the expression level of HMB-45 is elevated [32,33]. Other melanocytic differentiation markers include tyrosinase, Melan-A/melanoma-associated antigen recognized by T cells (MART-1), microphthalmia transcription factor (MITF), and vimentin. For melanoma with reduced or even absent expression of melanocyte markers, such as spindle cell melanomas, preferentially expressed antigen in melanoma (PRAME) can be a relevant marker [34]. Compared with single marker staining, dual staining can provide a more accurate evaluation of melanocyte proliferation. For example, the combination of the cell proliferation marker Ki67 with melanocyte markers (HMB-45 or MART-1) can more accurately evaluate the proliferation of melanocytes; combining cytoplasmic markers like HMB-45 and MART-1 with markers located in the nucleus, such as PRAME, can also contribute significantly to differentiate nodal nevus from malignant melanoma [35].

3.8 The 8th ed American Joint Committee on Cancer (AJCC) Melanoma TNM (Tumour, Lymph Node, and Metastasis) Staging

Once a vulval melanoma is confirmed, it is recommended to use the AJCC cancer staging manual instead of the International Federation of Gynaecology and Obstetrics (FIGO) staging [13] because FIGO staging does not provide adjunctive treatment decisions and prognostic indicators. The 7th edition of the AJCC staging system, published in 2009, was the first to abandon the Clark classification [36]. The staging and classification of melanoma in the 8th edition of the AJCC staging system depend upon Breslow thickness to determine the depth of invasion, thus accurately assigning staging according to classical TNM scores [37].

3.8.1 Clark Classification

Based on the depth of melanoma infiltration into the dermis and subcutaneous fat, Clark proposed a system to evaluate melanoma in 1966 [38]. Clark divides the skin into histologically recognizable anatomic compartments, and as melanoma cells cross each compartment (or Clark's "level"), the theoretical risk of distant spread increases accordingly:

- Level I: melanoma cells confined to the epidermis (melanoma *in situ*);
- Level II: melanoma with single-celled or very small nests invading the dermis;
- Level III: melanoma cells fill and expand in the dermis;
- Level IV: invasion of reticular dermis;
- Level V: invasion of subcutaneous fat.

Clark believed that patients with deep skin infiltration (Level III–V) have a higher tendency to develop lymph node infiltration and indicated that lymphadenectomy should be limited to melanoma patients with lesions beyond the dermis.

3.8.2 Breslow Thickness

Breslow's classification system is also called Breslow's thickness. Under this system, melanoma is assessed directly based on how deep the melanoma cells infiltrate from the skin's surface, which avoids the problem of different thicknesses of dissection chambers at different anatomical sites [39]. Breslow divides melanoma into five stages:

- Stage I: $\leq$0.75 mm
- Stage II: 0.76–1.5 mm
- Stage III: 1.51–2.25 mm
- Stage IV: 2.26–3.0 mm
- Stage V: $>$3.0 mm

Under this system, the prognosis of patients worsens with increasing Breslow thickness. There is a lower risk of regional and distant metastases in patients with early melanoma (stages I and II), whereas prophylactic lymphadenectomy may be beneficial to patients with advanced melanoma (Breslow thickness greater than 1.5 mm) [40]. The current staging of melanoma follows the TNM staging criteria of the AJCC (Table 1).

Table 1. Melanoma TNM criteria (AJCC 8th ed).

T (Primary tumor)	Thickness	Ulceration status
TX	N/A	N/A
T0	N/A	N/A
Tis	N/A	N/A
T1	≤1 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8~1 mm	With or without ulceration
T2	>1.0~2.0 mm	Unknown or unspecified
T2a	>1.0~2.0 mm	Without ulceration
T2b	>1.0~2.0 mm	With ulceration
T3	>2.0~4.0 mm	Unknown or unspecified
T3a	>2.0~4.0 mm	Without ulceration
T3b	>2.0~4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration
N (Regional lymph node)	Number of tumor-involved regional lymph nodes and nodal metastatic burden	Presence of in-transit, satellite, and/or microsatellite metastases
NX	Regional lymph nodes cannot be assessed	No
N0	No regional lymph node metastases detected	No
N1	1 tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	1 clinically occult (i.e., detected by SLNB)	No
N1b	1 clinically detected (i.e., macroscopic)	No
N1c	No regional lymph node disease	Yes
N2	2 or 3 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	
N2a	2 or 3 clinically occult (i.e., detected by SLNB)	No
N2b	2 or 3, at least 1 of which was clinically detected (i.e., macroscopic)	No
N2c	1 clinically occult or clinically detected	Yes
N3	≥4 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with ≥2 tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	≥4 clinically occult (i.e., detected by SLNB)	No
N3b	≥4, at least 1 of which was clinically detected (i.e., macroscopic), or presence of any number of matted nodes	No
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
M (Distant metastasis)	Anatomic Site	Serum LDH levels
M0	No evidence of distant metastasis	N/A
M1	Evidence of distant metastasis	
M1a	Distant metastasis to skin, soft tissue including muscles, and/or nonregional lymph node	Not recorded or unspecified
M1a (0)		Not elevated
M1a (1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b (0)		Not elevated
M1b (1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c (0)		Not elevated
M1c (1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d (0)		Not elevated
M1d (1)		Elevated

TNM, tumour, lymph node, and metastasis; AJCC, American Joint Committee on Cancer; N/A, not applicable; SLNB, sentinel lymph node biopsy; LDH, lactate dehydrogenase; TX, primary tumor thickness cannot be assessed (e.g., diagnosis by curettage); T0, no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma); Tis, melanoma *in situ*. CNS, central nervous system.

Table 2. Treatment principles of vulvar melanoma (according to AJCC staging).

Staging	Surgery therapy	Drug therapy	
		Class I recommend	Class II recommend
Operable excision			
Stage I	WLE + SLNB	Observation	
Stage II		Observation (recommended clinical trials)	Chemotherapy; high dose IFN; PD-1 mAb
Stage III	WLE + CLND	PD-1 mAb	Chemotherapy
Stage IV	WLE + CLND + metastatic lesions excision	*BRAF/MEK* inhibitors (bring *BRAFV600E/K* mutations)	
Inoperable resection			
III, IV Stage		PD-1 mAb; PD-1 mAb + low dose ipilimumab mAb; *BRAF/MEK* inhibitors (bring *BRAFV600E/K* mutations); PD-1 mAb + axitinib(1)	*KIT* inhibitor (bring *KIT* mutation) chemotherapy ± bevacizumab or recombinant human endostatin injection; radiotherapy; IL-2; MEK inhibitor (bring *NRAS* mutation)
Relapse	WLE	PD-1 mAb; PD-1 mAb + low dose ipilimumab mAb; *BRAF/MEK* inhibitors (bring *BRAFV600E/K* mutations); PD-1 mAb + axitinib(1)	*KIT* inhibitor (bring *KIT* mutation) chemotherapy ± bevacizumab or Recombinant human endostatin injection; radiotherapy; IL-2; *MEK* inhibitor (bring *NRAS* mutation)

WLE, wide local excision; SLNB, sentinel lymph node biopsy; CLND, complete lymph node dissection; IFN, interferon; PD-1, programmed death ligand 1; mAb, monoclonal antibody; *BRAF*, recombinant Human B-Raf Proto-Oncogene; *MEK*, mitogen-activated extracellular signal-regulated kinase; *KIT*, kinase receptor; *NRAS*, neuroblastoma RAS viral oncogene homolog; IL-2, Interleukin-2. Unless otherwise noted, the above evidence is class 2A evidence; (1) This category is recommended as 2B evidence.

3.9 Imaging in Diagnosis

Vulvar melanoma has a high tendency for local or distant metastasis, so imaging examination is needed to obtain relevant information to make accurate surgical plans. Inguinal lymph node ultrasound could assist in the diagnosis of inguinal lymph node metastasis (sensitivity 86%, specificity 96%). Ultrasound combined with fine needle aspiration biopsy (FNAB) has a sensitivity of 93% and a specificity of 100% in the evaluation of positive lymph nodes. Magnetic resonance imaging (MRI) plain scan and enhanced scan can clearly show the infiltration of the lesion and its surrounding tissues. Plain and contrast-enhanced computed tomography (CT), brain contrast-enhanced MRI, and positron emission tomography-computed tomography (PET-CT) can be used to evaluate the distant metastasis of vulvar melanoma [41–43].

4. Treatment

Surgery is the main treatment for vulvar melanoma, along with radiotherapy, chemotherapy, cytokine treatment, etc. Vulvar melanoma patients have more treatment options in recent years thanks to the grow of immune checkpoint inhibitors and targeted therapies. The treatment principles are shown in Table 2.

4.1 Surgery

The role of surgery in vulvar melanoma remains unshaken. When metastasis has not occurred, surgical margins can refer to cutaneous melanoma. The negative margin distance for melanoma *in situ* is 0.5–1 cm. For invasive melanoma lesions, the negative margin distance is correlated with the Breslow thickness: when the Breslow thickness is $\leq$1 mm, the negative margin distance is 1 cm; when the Breslow thickness is 1.01–2 mm, the negative margin distance is 1–2 cm; when the Breslow thickness is $>$2 mm, the negative margin distance is 2 cm [44]. Depending on the particular location of vulvar melanoma, surgery may damage the urinary and sexual function of patients such that the postoperative quality of life of patients is greatly compromised. Last few years, an increasing number of clinical studies have proven that patients with vulvar melanoma undergoing radical vulvar resection have no significant difference in survival rate compared with patients undergoing more limited vulvar resection [19,45]. Therefore, conservative surgery, such as local extended resection (WLE), is considered a better treatment option [19]. Regardless of the depth of tumour invasion, the minimum surgical margin required for WLE is 1 cm, and the margin can extend into the subcutaneous fascia through the subcutaneous fat.

Complete lymph node dissection (CLND) is performed when lymph node metastasis is indicated by physical examination or imaging examination [43]. Complete surgical resection includes resection of the involved lymph nodes and surrounding tissues. Inguinal lymphadenectomy includes superficial and deep inguinal lymph nodes, and at least 10 lymph nodes are removed. When 3 or more inguinal lymph nodes are positive or Cloquet lymph nodes are positive, further pelvic lymph node dissection should be considered [46]. CLND is not recommended for early-stage (stage I, II) vulvar melanoma because of the high incidence of complications such as wound rupture, infection, and oedema after inguinal lymphadenectomy [47].

4.2 Sentinel Lymph Node Biopsy (SLNB)

SLNB is a minimally invasive surgical technique used to assist lymph node staging in patients with cutaneous melanoma by identifying sentinel lymph nodes (SLNs) preoperatively and predicting the status of the remainder of the draining lymph node pool based on their histopathologic status [48]. In brief, SLNs were identified by blue dye (methylene blue solution, isosulfan or patent blue) combined with radionuclide tracer (Tc-99) [49], dissected and separated, and serial sections were obtained for immunohistochemical staining. Hematoxylin-eosinstaining staining was performed, and markers such as HMB-45 antibody, S-100 antibody and melanoma-pan staining were performed. Patients with positive sentinel lymph nodes needed further inguinal lymph node dissection [50]. In patients with vulvar melanoma, SLNB is mostly carried out under the premise of clinical research. Current small-scale clinical studies show that SLNB is only suitable for patients with moderate Breslow thickness (1–4 mm). For patients with thin Breslow thickness (<1 mm), SLNB should be considered only when there are adverse factors such as high mitotic rate, ulceration, age <40 years, microsatellite lesions, vascular infiltration or Clark level IV. SLNB conducted in thick tumours (>4 mm) may increase the risk of regional metastasis. In this case, radical vulvar resection combined with bilateral inguinal lymph node dissection should be performed directly [50–52].

4.3 Radiotherapy

Vulvar melanoma is considered to be a radioresistant tumour. High-dose radiation can improve the local response, achieving a complete response rate of 20%–30%, while carbon-ion radiotherapy (C-ion RT) can achieve a 3-year survival rate of 53% [53]. Radiotherapy is only suitable for inoperable advanced patients or patients with postoperative recurrence or metastasis, and the dose is usually 40–60 Gray (Gy). Adverse reactions to radiotherapy include desquamation, ulceration, genital fistula, lymphatic fistula, rectal stenosis, and lower limb oedema [54].

4.4 Chemotherapy

Chemotherapy used to be the only systemic treatment for recurrent and metastatic melanoma. Chemotherapy is currently considered only when cutaneous melanoma is resistant to immune checkpoint inhibitors (ICIs) and targeted therapies. Given the lack of ICIs and targeted therapy in mucosal melanoma, chemotherapy is still an important treatment for vulvar melanoma. Commonly used chemotherapeutic drugs include amenimide (dacarbazine, DTIC), temozolomide, formustine, vinblamide, cisplatin, paclitaxel, and carboplatin. The effectiveness of dacarbazine alone or in combination with chemotherapy is only 10% to 20%, and the complete response rate is only 5% to 12% [55–57]. Janco *et al*. [58] reported 2 cases of vulval and vaginal melanoma treated with neoadjuvant chemotherapy. The patients were treated with neoadjuvant chemotherapy of paclitaxel and carboplatin ± bevacizumab first and then underwent surgical treatment after the lesion was reduced and then treated with paclitaxel and carboplatin plus bevacizumab after surgery. The final relapse-free survival (RFS) was 2 and 5 years, respectively. However, due to the small number of samples in clinical trials, some studies have concluded that postoperative adjuvant chemotherapy is significant for prolonging progression-free survival (PFS) and overall survival (OS), while some research results show that postoperative adjuvant chemotherapy does not affect RFS and OS [58–61]. Therefore, the actual effect of postoperative adjuvant chemotherapy is still under debate.

4.5 ICIs

Immune checkpoints are molecules expressed on immune cells that regulate the degree of immune activation. Tumour cells can inhibit the immune function of the body by activating immune checkpoints to achieve escape. ICIs can relieve immune suppression by inhibiting the corresponding immune checkpoints and enhance the antitumour ability of T cells. Melanoma is a highly immunogenic tumour. ICI-based immunotherapy has been approved by the Food and Drug Administration (FDA) as the standard of care for patients with advanced or recurrent melanoma [62]. Multiple clinical studies have shown that PD-1 (Programmed death 1) and PD-L1 are highly expressed in patients with vulvar melanoma, which provides a theoretical basis for the application of ICIs in vulvar melanoma [16,63,64].

4.5.1 Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA-4) Antibodies

CTLA-4 is an immune checkpoint molecule involved in the negative feedback of immune responses [65]. Ipilimumab, a fully human monoclonal antibody (IgG1), can block CTLA-4, thereby activating innate and adaptive immunity and enhancing antitumour effects [66–69]. Ipilimumab has shown promising antitumour effects both as a single agent and in combination with other drugs. A phase II study showed a dose-dependent effect of ipilimumab as a single agent in patients with metastatic melanoma, with the highest response rate (11.1%) in the group receiving a dose of 10 mg per kilogram of body weight. The response rates were 4.2% and 0% in the 3 mg and 0.3 mg/kg groups, respectively [70]. In another study of 676 HLA-A*0201+ patients with advanced melanoma (stage III and IV), the ipilimumab group (137 patients) had the longest median survival of 27.8 months over a follow-up of up to 55 months. This was higher than that in the gp100 group (17.2 months) and the ipilimumab+gp100 group (21 months) [71].

4.5.2 PD-1 Antibodies

In the latest double-blind phase III trial (NCT02388906) of 736 patients with surgically re-

sectable advanced melanoma, 370 patients were treated with nivolumab at 3 mg per kilogram and 366 with ipilimumab. The results showed that nivolumab was more effective than ipilimumab in both RFS and distant metastasis-free survival (DMFS) [72]. In another phase III trial involving 945 patients (NCT01844505), compared with anti-PD-1 antibody monotherapy (nivolumab) or anti-CTLA-4 monotherapy (ipilimumab), combination immunotherapy with anti-PD-1 and anti-CTLA-4 antibodies (nivolumab + ipilimumab) resulted in better response rates (RR), PFS, and OS. However, the rate of grade 3–4 treatment-related adverse events in the combination therapy group was as high as 59% [73]. Reducing the dose of ipilimumab in combination therapy or using combination therapy as second-line therapy for patients with melanoma refractory to anti-PD-1/L1 antibody can reduce the occurrence of adverse events while still providing antitumour effects [74]. In comparison with immune checkpoint inhibitor treatment in vulvar melanoma clinical trials, in a retrospective study of 7 cases of female genital tract melanoma with advanced/recurrent disease treated with immune checkpoint inhibitors (genital [n = 2], vaginal [n = 4] and cervix [n = 1]), four patients received ipilimumab treatment, while three patients received anti-PD-1 (pembrolizumab [n = 2], nivolumab [n = 1]). The response rate to immunotherapy was 28.5%. Patients who received anti-PD-1 therapy experienced better PFS and OS than those who received anti-CTLA-4 therapy [75].

4.5.3 Lymphocyte-Activation Gene 3 (LAG-3) Antibodies

LAG-3 is a negative immunomodulator expressed on activated T cells, B cells, natural killer (NK) cells and other immune cells [76]. In recent years, many clinical studies have shown that LAG3 is a potential target for next-generation immunotherapy. LAG-3 is often coexpressed with PD-1. Opdualag, a newly developed dual immunosuppressive agent targeting both PD-1 and LAG-3, was approved by the FDA as a first-line treatment for unresectable or metastatic melanoma in March 2022. Compared with nivolumab monotherapy, Opdualag more than doubled PFS in patients with advanced melanoma (4.6 months *vs*. 10.1 months) [77].

4.6 Targeted Therapy

4.6.1 Tyrosine Kinase Inhibitors (KIT Inhibitors)

KIT mutations/amplifications are common in both vulvar and vaginal melanomas [78,79]. KIT inhibitors can be used as second-line therapy for unresectable or advanced metastatic melanoma with *KIT* mutations. In two phase II trials, the combined response rate of imatinib, a KIT inhibitor, in patients with mucosal melanoma carrying a *KIT* mutation was 10/24 (42%) [80,81]. Because of the suboptimal efficacy of dasatinib (a tyrosine kinase inhibitor that targets exon 11 mutations), imatinib remains the preferred option among KIT inhibitors [82]. Avapritinib (BLU-285) is a highly potent and selective oral kinase inhibitor. In a clinical case report of a patient with exon *c-KIT* mutation, after failure of two-line therapy with surgery, ipilimumab and nivolumab combined immunotherapy, the disease continued to progress with systemic metastasis, including central nervous system involvement. The use of avapritinib is still effective in the case of high tumour burden and brain metastases and can reduce the tumour burden of each metastasis and achieve partial response [83].

4.6.2 BRAF/MEK Inhibitors

Darafenib combined with trametinib is recommended for adjuvant treatment of stage III–IV melanoma with the *BRAF V600E/K* mutation. However, *BRAF* mutations are rarely present in vulvar melanomas (3%–26% of cases) [16]. The prognosis of patients with *NRAS* mutant melanoma is poor. Mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors (such as bimetinib) may be effective in some patients with *NRAS* mutation, but the benefit is transient [43,64].

4.7 Antiangiogenic Agents

Vulvar melanoma is highly reactive to vascular endothelial growth factor (VEGF) inhibitors because of its rich blood supply [84]. Representative drugs are lenvatinib, bevacizumab and axitinib. Lenvatinib is a multireceptor tyrosine kinase inhibitor that primarily targets VEGF and fibroblast growth factor (FGF) receptors [85]. In a retrospective analysis, 12 patients with brain metastatic melanoma with extremely poor prognosis were treated with bevacizumab. All patients showed good tolerance to bevacizumab, 10 of whom received immunotherapy after bevacizumab treatment, 5 of whom survived for more than 6 months, with 1 patient remaining relapse-free 4 years after the end of treatment [86]. An animal experiment showed that lenvatinib could not only be used as a direct cytotoxic drug against tumour angiogenesis and proliferation but also achieve antitumour effects by enhancing the infiltration and activation of NK cells in the tumour microenvironment [87]. Axitinib is a potent second-generation tyrosine kinase inhibitor (TKI) that blocks signalling via vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3 (as well as platelet-derived growth factor receptor (PDGFR) and c-KIT/CD117) and has been used clinically as a monotherapy for a variety of cancers [88,89]. Axitinib also inhibits tumour progression and controls distant metastasis when used as a single agent in patients with advanced melanoma [90]. Many animal and clinical experiments have shown that the combination of PD-1 antibody and antiangiogenic drugs can further enhance the antimelanoma effect [91–93].

4.8 Immunomodulator

Imiquimod is a synthetic Toll-like receptor 7 (TLR7) agonist with antiviral and antitumour activity. Imiquimod activates TLR7 on antigen-presenting cells (APCs), thereby

inducing the secretion of proinflammatory cytokines, mainly Interferon α, Interleukin 12, and tumor necrosis factor-α. TLR7 activation also promotes the maturation and migration of dendritic cells [94]. Esther Fuchs reported a case of recurrent vulvar melanoma with urethral involvement that where the patient successfully completed imiquimote treatment and was relapse-free for 4 years after completion of treatment [95]. Lonsdale-Eccles reported successful treatment of patients with vulvar melanoma *in situ* with topical 5% imiquimot cream [96]. Sadownik published a report on the success of 5% imiquimod treatment in patients with recurrent vulval melanoma after surgical resection [97]. Lauren S Prescott reported on imiquimod 5% cream in a patient with recurrent vaginal melanoma. Pelvic examination after the completion of topical treatment showed complete remission of the tumour, and there was no recurrence 18 months after the completion of treatment [98].

5. Prognosis & Prognostic Factors

The prognosis of vulvar melanoma is poor, with a 5-year survival rate between 10% and 63% [99] and a median overall survival time of 53 months [13]. The average recurrence time was 43.5 months, and the overall recurrence rate was 50% [100].

5.1 Histological Type

Patients with superficial spreading vulvar melanoma had a relatively better prognosis, while patients with nodular vulvar melanoma had a worse prognosis [13].

5.2 Breslow Thickness

Breslow thickness is a key prognostic factor for patients with vulvar melanoma. Thicker Breslow thickness often predicts poor prognosis [13,101]. In a multicentre retrospective analysis involving 77 vulvar melanoma patients, Breslow thickness was associated with tumour recurrence [102]. In another retrospective study of 16 patients with primary vulvar melanoma, the median depth of patients without recurrence after surgery was 0.9 mm (range 0.1 to 1.75 mm), while the median depth of patients with recurrence was 4.6 mm (range 3 to 8 mm). Patients with a Breslow thickness $\leq$1.75 mm had no recurrence, while patients with a lesion depth greater than 1.75 mm had recurrence [103].

5.3 Lymph Node Metastasis

Lymph node metastasis is a related prognostic factor in vulvar melanoma. Patients with vulvar melanoma with regional or distant metastases tend to have a worse prognosis. In one study of 1917 cases of vulvar melanoma, the five-year OS of patients with localized lesions, regional metastases, and distant metastases was 55.8%, 22.2%, and 5.1%, respectively [104]. Sugiyama *et al*. [105] analysed 644 vulvar melanoma patients, of whom 179 (27.8%) underwent lymphadenectomy and 58 (9%) developed lymph node metastases. The 5-year OS rates of patients with lymph node positive scores of 0, 1, and $\geq$2 were 68.3%, 29% and 19.5%, respectively [105].

5.4 Tumour-Infiltrating Lymphocytes

According to the density and extent of tumour infiltrating lymphocytes, they were classified as none, present but inactive (focal distribution), and active (diffuse distribution). When there are fewer infiltrating lymphocytes, the prognosis of vulvar and vaginal melanoma is poor [64]. The pathological diagnosis of tumour-infiltrating lymphocytes can be made by immunohistochemical labelling of CD8+ cytotoxic T cells.

5.5 Lactate Dehydrogenase (LDH)

LDH can catalyse the conversion of pyruvate to lactate in the hypoxic tumour microenvironment. In the AJCC melanoma staging system, 8th edition, LDH can not only affect tumour staging but also be used as a clinical predictor of the prognosis of melanoma patients. Elevated LDH often indicates a poorer chance of survival [106,107].

5.6 c-KIT

c-KIT mutation is common in patients with vulvar melanoma [108], and increased c-KIT expression has been identified as a strong negative predictor of disease-free survival (DFS) and a strong positive predictor of early recurrence [99,105].

5.7 High-Risk Pathological Manifestations (Satellite Metastasis, Intermediate Metastasis, Lymphatic Vascular Space Infiltration (LVSI), Dermal Mitosis)

Satellite metastases refer to macroscopic metastases around the primary melanoma lesion (within 2 cm in diameter). Intermediate metastasis/transitional metastasis refers to macroscopic metastases located between the primary melanoma (2 cm in diameter) and the primary lymph node. LVSI means that at least one cluster of tumour cells is seen in the space surrounded by flattened endothelial cells. One study found that the presence of any of these high-risk pathological features (satellite metastasis, mid-course metastasis, LVSI, dermal mitosis) increased the risk of melanoma recurrence by five times [99].

5.8 Ki67, Phosphohistone H3 (PHH3)

Ki67 and PPH3, both proliferation markers, have been shown to provide some limited independent prognostic information for melanoma, and their use does not affect staging. Increased expression of Ki67 and PPH3 indicates that tumour cells are proliferating at a high speed and are more aggressive [99,109].

5.9 Others

The prognosis of patients with vulvar melanoma is also related to age, complications, race, economic conditions and other factors.

6. Conclusions

Vulvar melanoma is an important subclass of melanoma with unique molecular characteristics and cannot be simply classified as cutaneous or mucosal melanoma. Because of its rarity and the hidden location of the disease, patients often do not receive early diagnosis and treatment. Clinicians' lack of relevant theoretical knowledge and experience in diagnosis and treatment often delay disease diagnosis. This review provides a detailed description of the diagnosis and treatment of vulvar melanoma, a rare gynaecologic tumour, to provide a rough picture of the disease.

Vulvar melanoma is characterized by its rarity, occult onset, frequent metastasis, radiation resistance, strong immunogenicity, and unique gene mutation spectrum. Future treatment should target these characteristics. First, we need to conduct a multicentre study to obtain a larger sample size to explore its pathogenesis and to also verify the effectiveness of the existing treatment options. Second, as a highly immunogenic tumour, how to further enhance the immunogenicity and immunoreactivity of vulvar melanoma is a direction worth exploring. Finally, combination therapy is a future trend of tumour treatment. On the one hand, we need to explore new treatment modes, and on the other hand, we need to optimize and combine existing treatment modes to comprehensively inhibit tumour progression in multiple ways.

Abbreviations

NGS, next-generation sequencing; PDGFRA, platelet-derived growth factor receptor alpha; IHC, immunohistochemical; MITF, microphthalmia transcription factor; PHH3, phosphohistone H3; AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynaecology and Obstetrics; SLNB, sentinel lymph node biopsy; FNAB, fine needle aspiration biopsy; CLND, complete lymph node dissection; ICIs, immune checkpoint inhibitors; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; TLR7, Toll-like receptor 7; APCs, antigen-presenting cells; DFS, disease-free survival; LVSI, lymphatic vascular space infiltration; RFS, relapse-free survival; DMFS, distant metastasis-free survival; RR, response rates; PFS, progression-free survival; OS, overall survival.

Author Contributions

NC designed the research study. JZ performed the research and analyzed the data. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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