Review

Genitourinary melanoma: An overview for the clinician

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Abstract Genitourinary (GU) melanoma is a rare presentation of melanoma accounting for approximately 0.5% of all melanomas. GU melanomas include primary melanomas of the vulva, vagina, uterine cervix, ovary, penis, scrotum, urethra, bladder, ureter, and kidney. These melanomas are often diagnosed in advanced stages and stigma is thought to contribute to delays in presentation. As the likely diagnosing provider, it is imperative that dermatologists, urologists, and gynecologists are aware of these uncommon sites of presentation. While there have been major advances in the treatment of melanomas as a whole in the last 10 years, their applications to GU melanomas have often been overlooked. GU melanomas have not been included in many of the major phase III clinical trials which brought contemporary advanced treatments to market and the prognoses for GU melanomas remain poor. Due to the rarity of GU melanomas, much of the literature provides generalized recommendations across multiple different organs affected by GU melanomas or omits certain topics, making it difficult to appreciate the fundamentals of the individual presentations. This review aimed to provide background information on the pathogenesis and epidemiology of the different sites of GU melanomas and categorize data specific to the presentation, staging, treatment, and prognosis of each type of GU melanoma to guide the clinician. It was also meant to encourage a multidisciplinary approach to the management of these patients as it spans the expertise of surgical oncologists, medical oncologists, radiation oncologist, dermatologists, urologists, and gynecologists.

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1. Introduction

Primary melanoma of the genitourinary (GU) tract is a type of melanoma that usually arises on mucosal surfaces of the female genital, male genital, and urinary tract, but can also arise on epidermal skin bearing surfaces [1,2]. All melanomas are thought to derive from neural crest cells; however, cutaneous melanomas are believed to arise from epidermal or dermal melanocytes, and mucosal melanomas are theorized to arise from melanoblasts [3,4]. Mucosal melanomas vary from cutaneous melanomas on a molecular level as well [5,6]. In cutaneous melanomas, BRAF somatic mutations are present in approximately 52%–66%, neuroblastoma RAS (NRAS) in 28%, and neurofibromin 1 (NF1) in 14%, while only 14% are wild-type for these oncogenes [7,8]. Comparatively, mucosal melanomas most frequently have mutations in KIT (up to 39%), NRAS (up to 18%), and NF1 (up to 16%), with BRAF mutations in only 0%–16% [5,6,9].

The presence of BRAF and KIT mutations in GU melanomas has been evaluated by multiple studies. In female GU melanomas, Hou et al. [10] found BRAF mutations in 26% of 51 cases of vaginal and vulvar melanomas, while they were observed in only 8.3% of 105 cases of non-GU mucosal melanomas which differs from prior findings of BRAF mutations in 4.3% of 416 pooled cases of vaginal and vulvar melanomas. Additionally, they found KIT mutations in 22% of vaginal and vulvar melanomas, compared to 8.8% in non-GU mucosal melanomas and 3% in non-GU cutaneous melanomas. NRAS mutations were found in 4% of vaginal and vulvar melanomas compared to 26% of all non-GU melanomas. Wylomanski et al. [11] also evaluated vulvo-vaginal melanomas and found BRAF mutations in 33% of the 15 cases of vulvar melanomas and none of seven cases of vaginal melanomas while KIT were present in 7% and 14%, respectively. No NRAS mutations were observed in vulvar melanomas, but they were present in 43% of primary vaginal melanomas. Saglam et al. [12] evaluated 13 female GU melanomas for mutations; BRAF mutations were observed in 23% (all vulvar primaries); KIT mutations were observed in 31% (equally divided between vulvar and vaginal primaries); and NRAS mutations were observed in 15% (all vulvar primaries). Both male and female mucosal melanomas were evaluated by Omholt et al. [13]; BRAF mutations were found in 9% of 23 cases of vulvar melanomas, none of seven cases of vaginal melanomas, and 20% of five cases of penile mucosal melanomas. KIT mutations were found in 35% of 23 cases of vulvar melanomas, none of seven cases of vaginal melanomas, and 20% of five cases of penile mucosal melanomas. NRAS mutations were found in 0%, 43%, and 20%, respectively. Penile melanomas were further evaluated by Oxley et al. [14] who did not find any BRAF or KIT mutations in 12 cases.

More recently, the expression of programmed death-ligand 1 (PD-L1) has been evaluated in melanomas. While it has been observed to be expressed in up to 76% of cutaneous melanomas, the same might not hold true for all GU melanomas [15,16]. Kaunitz et al. [17] evaluated PD-L1 expression in melanoma subtypes and found that it was expressed in 44% of 36 cases of mucosal melanomas. Hou et al. [10] specifically examined 51 vaginal and vulvar melanomas and found programmed death-1 expressed in 75% of the cases and PD-L1 expressed in 56% of the cases.

1.1. Epidemiology: distribution and determinants

Mucosal melanomas account for only approximately 1%–4% of new melanoma diagnoses, but GU melanomas represent 43%–45% of all mucosal melanomas [2,18,19]. Review of the Survival Epidemiology and End Results (SEER) database by Vyas et al. [1] revealed 817 cases of GU melanomas between 1992 and 2012. Eighty-nine percent were of the female genital tract, 6.6% were of the male genital tract, and 4.3% were of the urinary tract. Sanchez et al. [20] also reviewed the SEER database from 1973 to 2010 and found 1586 primary GU melanoma cases. In females, 75% were vulvar melanomas and 25% were vaginal melanomas. In males, 69% were penile melanomas and 31% were scrotal melanomas. Review of the North American Association of Central Cancer Registries by McLaughlin et al. [2] found 776 cases of genital tract mucosal melanomas from 1996 to 2000. The majority of the cases (723 cases) were in females; 77% were vulvar melanomas; 20% were vaginal melanomas; and 2.2% were cervical melanomas. The remaining 53 cases were in males; 66% were penile melanomas and 32% were scrotal melanomas.

GU melanomas are thought to represent 3%–7% of all cases of melanomas in females compared to less than 1% of cases in males [21,22]. McLaughlin et al. [2] found an overall age-adjusted incidence rate of 1.0 per million person-years, while it was only 0.2 per million person-years in males compared to 1.6 per million person-years in females. Similarly, Vyas et al. [1] found that both genital and urinary tract melanomas were over 10 times more common in females with an overall GU melanoma incidence rate of 1.74 per million person-years in females and 0.17 per million person-years in males. Likewise, Sanchez et al. [20] found an age-adjusted incidence of 1.80 per million person-years in females compared to 0.19 per million person-years in males. They also specifically examined urothelial melanomas and observed that the incidence was again higher in females compared to males, 0.06 versus 0.02 per million person-years, respectively.

Like cutaneous melanomas, non-Hispanic White people appear to be at highest risk for GU melanomas [1,2,20]. However, in available literature, the racial distribution of GU melanomas appears to be less skewed towards White people than in cutaneous melanomas [23,24]. A review of the SEER database from 1992 to 2005 found that the overall incidence ratio of mucosal melanomas in White to Black people was 2.30:1 and more specifically, in vulvar and vaginal melanomas, the incidence in White to Black people is 3.14:1 and 1.02:1, respectively [23]. A more expanded SEER database review from 1975 to 2016 found that in vulvar melanomas, 85.3% were White. 3.5% were African American, 7.3% were Hispanic, 2.9% were Asian or Pacific Islander, and 0.3% were American Indian or Alaska Native [24]. In vaginal melanomas, they found 71.7% were White,
9.5% were African American, 7.1% were Hispanic, 11.4% were Asian or Pacific Islander, and 0.2% were American Indian or Alaska Native.

Infection with human papillomavirus (HPV) may also contribute to the development of GU melanomas; however, the role is less clearly defined than in other GU malignancies. In a small series of six cases of vulvar melanomas and three cases of vaginal melanomas, HPV DNA was identified in 67% [25]. HPV-3, cutaneous, was identified in four of nine cases, and HPV-38, epidermodysplasia verruciformis-associated, was identified in four of nine cases; none of the cases had genital-mucosal HPV. In contrast, only one of 10 normal vulvar tissue controls tested positive for HPV DNA. This reflected similar trends seen in cutaneous melanomas in which HPV infection, especially cutaneous HPV, is associated with a higher rate of developing melanomas [26].

Age is also a risk factor with the highest incidence rate seen in those aged greater than 80 years regardless of sex [1,2]. The median ages of presentation are 66–68 years for female genital, 62 years for male genital, and 75 years for urothelial melanomas [20,21]. Unlike cutaneous melanomas, ultraviolet radiation exposure does not appear to be a risk factor for the development of mucosal melanomas [19,27]. Additionally, they appear to develop from preexisting nevi less frequently [28].

While the risk factors for GU melanomas are not entirely understood, the incidence of the disease has remained stable over several decades [20].

2. Site-specific presentation, staging, surgical treatment, and prognosis

2.1. Female genital melanomas

2.1.1. Vulvar melanomas

2.1.1.1. Presentation. Vulvar melanomas account for up to 10% of all vulvar malignancies [29]. Up to 12% of females have pigmented lesions of the vulva; however, only 4% of dermatologists check the vulva on annual examination [30,31]. Vulvar melanomas may present as papules, macules, or nodules with asymmetric borders, irregular coloration, and diameter greater than 7 mm (Fig. 1A) [32]. Up to 27% can present as amelanotic red colored papules [28]. Aside from a visible lesion, vulvar melanomas may present with a mass, pain, bleeding, pruritis, dysuria, discharge, irritation, or ulceration [33,34]. In order of frequency, it may arise on the labia majora, clitoral hood, and labia minora [34]. The majority develops on glabrous skin followed by the mucocutaneous border.

Vulvar melanomas may appear similar to cutaneous melanomas on dermoscopy, with structureless zones, atypical vascular supply, irregular globules, and with blue, gray, or white coloration or veil [35,36]. Similarly, reflectance-mode confocal microscopy may be used to identify vulvar melanomas with identifying features including loss of normal architecture of the chorion papillae and presence of atypical cells in the epithelium [37].

2.1.1.2. Evaluation and staging. Upon diagnosis of vulvar melanomas, clinical work-up should include computed tomography (CT) scan of the chest, abdomen, and pelvis (C/A/P) or whole-body positron emission tomography (PET)/CT scan with fluorodeoxyglucose (FDG) radiotracer, with or without magnetic resonance imaging (MRI) brain for all suspected Stage IIIA or higher as with non-GU cutaneous melanomas [38–40]. Fine needle aspiration (FNA) should be considered to assess any suspicious lymph nodes preoperatively [41]. Historically, vulvar melanomas were staged based on the International Federation of Gynecology and Obstetrics (FIGO) staging system for squamous cell carcinoma of the vulva, but the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for cutaneous melanomas has been found to more accurately predict recurrence- and progression-free survival [33,42,43]. Nagarajan et al. [44] proposed a modified T-category which classifies vulvar melanomas into two categories based upon tumor thickness and mitotic rate to improve prognostication of overall survival (OS) and disease-specific survival (DSS) (Table 1A). Stage T1 is classified as tumor thickness less

Figure 1 Melanoma of the left labium minus with clinically and radiographically node-negative disease undergoing modified radical left vulvectomy with lymphoscintigraphy-guided sentinel lymph node biopsy. (A) Vulvar melanoma visible only after retraction of the labia majora; (B) Margins of resection; (C) Specimen for pathology; (D) Closure of modified radical left vulvectomy (images courtesy of Mitchel S. Hoffman, M.D. and Jonathan S. Zager, M.D.).
### Table 1  Alternative staging systems applied to genitourinary melanoma.

| Alternative staging system | Description |
|----------------------------|-------------|
| **(A) Staging system proposed by Nagarajan et al. [44]** (adjunct to TNM staging in vulvar melanoma) | |
| Stage T1 | ≤2.0 with mitotic rate <2 per mm² |
| Stage T2 | >2.0 and/or mitotic rate ≥2 per mm² |
| **(B) 2018 FIGO staging for carcinoma of the cervix uteri [81]** (applied to cervical melanoma) | |
| Stage I | Carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded) |
| IA | Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion <5 mm |
| IA1 | Measured stromal invasion <3 mm in depth |
| IA2 | Measured stromal invasion ≥3 mm and <5 mm in depth |
| IB | Invasive carcinoma with deepest measured invasion ≥5 mm, lesion limited to the cervix uteri |
| IB1 | Invasive carcinoma ≥5 mm in depth of stromal invasion and <2 cm in greatest dimension |
| IB2 | Invasive carcinoma ≥2 cm and <4 cm in greatest dimension |
| IB3 | Invasive carcinoma ≥4 cm in greatest dimension |
| Stage II | Carcinoma invades beyond the uterus, but has not extended to the lower 1/3 of the vagina or to the pelvic wall |
| IIA | Involvement limited to the upper 2/3 of the vagina without parametrial involvement |
| IIA1 | Invasive carcinoma <4 cm in greatest dimension |
| IIA2 | Invasive carcinoma ≥4 cm in greatest dimension |
| IIB | Parametrial involvement not up to the pelvic wall |
| Stage III | Carcinoma involves the lower 1/3 of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or involves paraaortic lymph nodes |
| IIIA | Carcinoma involves the lower 1/3 of the vagina with no extension to the pelvic wall |
| IIIB | Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to from another cause) |
| IIIC | Involvement of pelvic and paraaortic lymph nodes, irrespective of tumor size and extent |
| IC | Tumor limited to one or both ovaries or fallopian tubes, with any of the following: |
| IC1 | Surgical spill |
| IC2 | Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface |
| IC3 | Malignant cells in the ascites or peritoneal washings |
| Stage II | Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer |
| IIA | Extension and/or implants on uterus and/or fallopian tubes and/or ovaries |
| IIB | Extension to other pelvic intraperitoneal tissue |
| Stage III | Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes |
| IIIA | Positive retroperitoneal lymph nodes only (cytologically or histologically proven): |
| IIIA1 | Metastasis up to 10 mm in greatest dimension |
| IIIA1 (i) | Metastasis more than 10 mm in greatest dimension |
| IIIA2 | Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes |
| IIIB | Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes |

(continued on next page)
than or equal to 2.0 mm and a mitotic rate less than 2 per mm², while tumors greater than 2.0 mm and/or with a mitotic rate greater than or equal to 2 per mm² are classified as Stage T2.

2.1.1.3. Surgical treatment. Vulvar melanomas are managed similarly to non-GU cutaneous melanomas with wide excision and sentinel lymph node biopsy (SLNB) as the standard of care, as shown in Fig. 1B–D [45]. More aggressive surgical management has been investigated including radical vulvectomy with bilateral inguinalfemoral lymphadenectomy; however, it has not been demonstrated to have a survival benefit and has significant morbidity [24,46–48]. Standard surgical margins applied to cutaneous melanomas have been compared to more extensive surgical resection and no difference in survival has been observed [42,48]. Therefore, the recommended resection margins are at least 1 cm deep extending to the muscular fascia and 1 cm skin margins for melanomas ≤1.00 mm, 1–2 cm skin margins for melanomas 1.01–2.00 mm thick, and 2 cm for melanomas >2.00 mm thick [24,49].

Elective lymph node dissection does not appear to have a survival benefit in vulvar melanomas compared to lymph node dissection performed only with clinical evidence of nodal involvement [46]. SLNB has identified the sentinel node in 98% of documented cases and should be considered the standard of care, absent of any radiographic or clinical nodal-involvement [39]. Trifirò et al. [50] found that in 12 patients who underwent SLNB, the biopsy accurately predicted the status of remaining lymph nodes, which was confirmed on lymph node dissection in 10 of the patients. While there is still limited evidence, SLNB is recommended for evaluation of regional disease and omission of lymphadenectomy if negative [50,51]. Given the variable drainage of the pelvis, SLNB may be facilitated by single photon emission CT integrated with CT (SPECT-CT) to localize lymph nodes compared to planar lymphoscintigraphy [52].

2.1.1.4. Radiotherapy. Radiotherapy has roles in the neoadjuvant and adjuvant setting for operative candidates as well as a primary or palliative treatment in patients who are not surgical candidates [48]. In the neoadjuvant setting, the primary benefit is to facilitate more conservative surgery by reducing tumor size [45,48]. Adjuvant radiotherapy may be considered in patients with nodal involvement. It is important to note that the role of radiotherapy in vulvar melanomas is largely extrapolated from the application of radiotherapy in other mucosal melanomas [39].

2.1.1.5. Systemic therapy. Historically, chemotherapy may have had a role in the neoadjuvant setting; Janco et al. [53] reported that carboplatin and paclitaxel with bevacizumab shrunk a vulvar melanoma preoperatively preventing the need for skin grafting. A survival benefit has not been demonstrated with the use of adjuvant chemotherapy in vulvar melanomas [39]. In advanced disease, the role of biochemotherapy (cisplatin, vinblastine, dacarbazine, and/or tamoxifen plus interferon-alpha and/or interleukin-2) has been evaluated by Harting and Kim [54] and found to have a 10-month median survival with 36% partial response. Anti-PD-1/PD-L1 antibodies should be considered if appropriate, in a neoadjuvant setting, given the high rate of PD-1/PD-L1 mutations observed in vulvovaginal melanomas [10]. The role of immune checkpoint inhibitors specifically in vulvar and vaginal melanomas was examined by Quéréux et al. [55] and a 50% partial response was observed. Wohlmut et al. [56] found that in vulvovaginal melanomas, ipilimumab had an overall response rate (ORR) of 13% while PD-1 inhibitors alone or in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors had an ORR of 33%. Shoushtari et al. [57] found

| Alternative staging system | Description |
|----------------------------|-------------|
| IIC | Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (including extension of tumor capsule of liver and spleen without parenchymal involvement) |
| Stage IV | Distant metastasis excluding peritoneal metastases |
| IVA | Pleural effusion with positive cytology |
| IVB | Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity) |
| (D) Staging system as proposed by Bracken and Diokno [101] (applied to penile melanoma) | |
| Stage I | Melanoma confined to the penis |
| Stage II | Melanoma with regional lymph node metastases |
| Stage III | Melanoma with distant metastases |
| (E) Staging system as proposed by Levine [121] (applied to urethral melanoma) | |
| Stage A | Tumor confined to submucosa |
| Stage B | Tumor infiltrating periurethral muscle in females and corpus spongiosum in males |
| Stage C | Periurethral invasion including vagina, bladder, labia or clitoris in females and extending beyond the corpus spongiosum in males |
| Stage D | Metastasis to lymph nodes |

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumor-node-metastasis.
an ORR of 23% and median OS of 12 months to anti-PD-1 therapy in 35 patients with mucosal melanomas; 40% were vulvovaginal melanomas. While KIT mutations appear to be present in more than 20% of tumors, the role of targeted therapies has not been evaluated specifically in the treatment vulvar melanomas [39,58].

2.1.1.6. Prognosis. The 5-year survival rates for all vulvar melanomas ranged from 47% to 58% [18,20,59]. For localized, regional, and distant disease, they were 76%, 39%, and 22%, respectively [29]. Tumor thickness, specifically Breslow depth is the most significant predictor of recurrence in early-stage disease [42]. Independent factors that have been shown to significantly impact survival include age at diagnosis, lymph node status, mitotic rate, ulceration, and macroscopic amelanosis [24,28,39,58]. Lymph node status in particular appears to be the most important predictor of survival [24,58]. Both lymph node status and number of nodes involved are significantly associated with survival with rates of 65%–68%, 20%–29%, and 0%–20% for 0, 1, and 2 positive lymph nodes, respectively [29,49,60].

2.1.2. Vaginal melanomas

2.1.2.1. Presentation. Vaginal melanomas account for up to 5% of all vaginal malignancies [61]. It may arise anywhere within the vaginal canal; however, it most commonly presents in the lower third and on the anterior wall of the vagina [62,63]. Vaginal melanomas frequently present with vaginal bleeding, less frequently with vaginal discharge, mass, and pain [64,65]. Vaginal melanomas are often polypoid and ulcerated in appearance and while they are usually pigmented, up to 10% are amelanotic [63,65]. At the time of presentation, up to 50% of patients have positive regional lymph nodes and 20% have distant metastases [48,62]. The most common sites of metastases are to the lungs, liver, bones, and brain [65].

2.1.2.2. Evaluation and staging. Since vaginal melanomas are often advanced at presentation, CT C/A/P or whole-body FDG-PET/CT and brain MRI should be considered to detect metastatic disease [38,40,48,66]. Suspicious lymph nodes may be assessed with FNA [41]. The AJCC TNM staging system has been found to be superior to FIGO staging in vaginal melanomas [48,67]. AJCC Stage 0–II vaginal melanomas have been shown to have a significantly improved DSS compared to Stage III [67]. However, tumor size less than 3 cm versus greater than or equal to 3 cm appears to be the only significant predictor of survival in early-stage disease [68–70]. Therefore, Piura [48] has proposed a modification to the AJCC TNM staging system in which primary tumor size less than 3 cm versus greater than or equal to 3 cm is included in the T staging.

2.1.2.3. Surgical treatment. Surgical resection with pelvic exenteration or wide excision has been found to improve OS compared to nonsurgical management [71]. A significant difference in survival between radical resection with pelvic exenteration and vaginectomy versus conservative resection with wide excision has not been demonstrated; therefore, wide excision is considered an acceptable treatment with decreased morbidity [24,48,71,72]. Recommended wide excision margins are the same as vulvar melanomas with a depth of 1 cm tumor-free margin and width of 1.00 cm for melanomas ≤1.00 mm, 1.00–2.00 cm for melanomas 1.01–2.00 mm thick, and 2.00 cm for melanomas greater than 2.00 mm thick [24,41,48]. Vaginectomy and pelvic exenteration are acceptable as well if wide excision is not anatomically possible [48,71]. It has also been suggested for any vaginal melanomas greater than 3.00 mm in depth [73].

There are limited and mixed data regarding the role of lymphadenectomy and SLNB in clinically node negative vaginal melanomas; however, it appears that SLNB may be a reasonable approach to the evaluation of regional disease and should be considered standard of care [15,48,74]. The vaginal mucosa has variable drainage but, in general, the upper third drains to the external iliac nodes, the middle third drains to the common and external iliac nodes, and the lower third drains to the superficial inguinal and perirectal nodes [66]. As a result, SPECT-CT should be considered to aid sentinel lymph node localization [51,52].

2.1.2.4. Radiotherapy. Radiotherapy may be used in the neoadjuvant setting to reduce tumor size and facilitate more conservative surgery [48]. In the adjuvant setting—particularly in the presence of positive margins, tumors greater than 3 cm, or nodal disease—radiotherapy has been shown to reduce the risk of local recurrence [48,61,68,71]. Radiotherapy has also been shown to provide local control in patients with surgically unresectable disease [72]. The lymph node basins targeted by radiotherapy will vary based upon the location of the primary tumor within the vagina [48,66].

2.1.2.5. Systemic therapy. There are very limited data, but there may be a role for chemotherapy in the neoadjuvant and adjuvant setting, as well as in those with recurrent disease or those who are not operative candidates [45,53,71,75]. The use of adjuvant immunotherapy (interleukin-2, interferon-alpha, bacillus Calmette-Guerin, dendritic cells, lymphokine-activated killer cells, or measles vaccine) demonstrated a survival benefit compared to surgery alone, chemotherapy alone, or chemotherapy combined with immunotherapy [76]. Given the high rate of PD-1/PD-L1 mutations observed in vulvovaginal melanomas, treatment with these inhibitors should be considered [10]. As previously discussed, Wohlmuth et al. [56] found that in vulvovaginal melanomas, ipilimumab had an ORR of 13% while PD-1 inhibitors alone or in combination with CTLA-4 inhibitors had an ORR of 33%. Shoushtari et al. [57] found an ORR of 23% and median OS of 12 months to anti-PD-1 therapy in 35 patients with mucosal melanomas; 40% were vulvovaginal melanomas. The role of targeted therapies in vaginal melanomas is not well understood, but should be considered in those with targetable mutations [45].

2.1.2.6. Prognosis. The 5-year survival rates for vaginal melanomas are very poor and estimated at 5%–27%.
As previously mentioned, tumor size (< 3 cm) is the greatest predictor of survival in early stage disease [68–70]. Nodal involvement is significantly associated with decreased survival [71]. Tumor thickness, ulceration status, and pathologic clearance of margins have been shown to predict DFS [67]. In addition, mitotic rate was found to predict DFS.

### 2.1.3. Uterine cervix melanomas

#### 2.1.3.1. Presentation

Cervical melanomas may account for up to 9% of all malignancies of the uterine cervix [77].

Diagnostic criteria for primary cervical melanomas include presence of melanin in the cervical epithelium, absence of melanomas outside the cervix, junctional activity in the cervical epithelium adjacent to the lesion, and if present, metastatic spread consistent with the pattern of cervical malignancy [48,78,79]. It most commonly presents with abnormal bleeding including postcoital spotting and increased menstrual bleeding; however, 13% of diagnoses are made on routine gynecologic examination [78]. The lesion is often exophytic, polypoid, and varies in color with up to 45% of cervical melanomas presenting as amelanotic lesions [45,78].

#### 2.1.3.2. Evaluation and staging

Once a patient is diagnosed with cervical melanoma using the above criteria, full body imaging is recommended to evaluate the extent of the primary tumor and if there is any metastatic spread [40,80,81]. The FIGO system for cervical carcinoma (Table 1B) is applied to cervical melanomas due similarities in presentation and pattern of spread [48,81]. In both FIGO and AJCC TNM systems, staging is affected by tumor depth, lymph node involvement, and distant metastases; however, FIGO is also based largely upon local anatomic involvement as well.

#### 2.1.3.3. Surgical treatment

At this time, radical surgery, often radical hysterectomy with partial vaginectomy, is favored for the treatment of early-stage cervical melanomas [45,48,78,80]. Pelvic lymphadenectomy is advised for prognostication and planning of adjuvant treatment; however, the survival benefit of lymphadenectomy and the role of SLNB have not been evaluated [48,78].

#### 2.1.3.4. Radiotherapy

Pelvic radiotherapy is recommended for palliation in late-stage cervical melanomas when surgical resection is not possible [45,48,78]. There may also be a role for adjuvant radiotherapy if the tumor is greater than 4 cm, and/or if there is regional nodal disease, positive surgical margins, and/or involvement of the corpus uteri or parametrium.

#### 2.1.3.5. Systemic therapy

Single-agent dacarbazine is the most commonly used and only proven effective agent in recurrent or advanced cervical melanomas with up to 20% response rate [70]. The benefit of immunotherapy in cervical melanomas has not been demonstrated [82]. The role of targeted therapy specifically in cervical melanomas is not yet understood; however, it should be considered in patients with targetable mutations [83].

#### 2.1.3.6. Prognosis

The 5-year survival for cervical melanomas is 10% with up to 88% passing within 3 years of diagnosis [45]. The most significant predictor of survival is FIGO stage [45,82,84]. However, even though most patients are diagnosed with early-stage disease, the prognosis remains poor [41,82]. The 5-year survival rates by stage are 19%, 11%, and 0% for Stages I, II, and III–IV respectively [82]. Tumor thickness, nodal status, lymphovascular invasion, and neovascularization have also been found to have prognostic value in cervical melanomas [45,84].

### 2.1.4. Ovarian melanomas

#### 2.1.4.1. Presentation

Primary ovarian melanomas account for less than 1% of all female GU melanomas [1]. It occurs only in the presence of mature cystic teratomas as it is a malignant transformation of melanocytes in the ectoderm [48]. It presents at a younger age than other GU melanomas, with a median age of 47 years [85]. Since it is so obscure, the diagnosis of primary melanomas of the ovary is dependent upon criteria established by Cronje and Woodruff [86]. There must not be an extraovarian primary melanoma; there must be a unilateral ovarian tumor with teratoid element; and the patient's age and symptoms must correlate with other reported cases. The fourth criterion is that the tumor must have melanocytic junctional activity; however, this is only present in 50% of reported cases and not necessary for diagnosis [86,87]. Symptoms include lower abdominal pain, abdominal distension, palpable lower abdominal mass, dysuria, and dyschezia [87,88]. Diagnosis of ovarian melanomas is often made at the time of surgery as it is rarely suspected [87,89]. Ovarian melanomas spread in a nature similar to epithelial ovarian cancer with the addition of lymphatic and hematogenous routes, commonly involving the lymph nodes, lung, liver, and bone [88].

#### 2.1.4.2. Evaluation and staging

The FIGO staging system for ovarian epithelial carcinoma (Table 1C) is commonly applied to ovarian melanomas [48,90]. Stage I is confined to the ovaries; Stage II extends below the pelvic brim; Stage III has cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes; and Stage IV has distant metastases beyond peritoneal metastases [90]. However, some have suggested that the use of a depth-based staging system as is used in cutaneous melanomas may better estimate prognosis as it has been argued that FIGO staging does not provide valuable prognostication [87,89,91].

#### 2.1.4.3. Surgical treatment

Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy is the procedure of choice in those who do not wish to preserve fertility [48,87,88]. In those with Stage IA to unilateral IC disease who wish to preserve fertility,
unilateral salpingo-oophorectomy is a less radical option [48]. Pelvic and para-aortic lymphadenectomy is typically performed in the surgical management of ovarian melanomas, though there is no evidence supporting its benefit [48,88].

2.1.4.4. Radiotherapy. There is no evidence that radiotherapy improves prognosis in ovarian melanomas [87].

2.1.4.5. Systemic therapy. Cisplatin- and dacarbazine-based combination regimens have most commonly been used as adjuvant therapy for ovarian melanomas [48,88]. In a series of seven patients who received postoperative adjuvant chemotherapy (primarily cisplatin-based combination regimens), four had no evidence of disease at 12 months and three had passed within 9 months [85]. A single case of metastatic ovarian melanoma was successfully treated with adjuvant dacarbazine, vinblastine, and cisplatin after pneumonectomy with no evidence of disease at 18 months [88]. An important consideration for those that underwent ovary-sparing surgery is that chemotherapy should also be selected to preserve ovarian function; cisplatin-based regimens are often employed [48]. Immunotherapy with adjuvant interferon-alpha was attempted in a single case; however, the patient developed metastatic disease 12 months after surgery and was subsequently treated with dacarbazine, cisplatin, and vinblastine and passed away 17 months after initial diagnosis [89]. To our knowledge, the role of checkpoint inhibitors and targeted therapies has not been evaluated in ovarian melanomas, but there is at least one case of KIT mutations identified in an ovarian melanoma making it a potential therapeutic target [92].

2.1.4.6. Prognosis. In a series of 25 patients, 44% were alive without evidence of disease at median 18 months while the other 56% passed away at a median 8 months from diagnosis [85]. Of 25 patients in another series, 60% presented as Stage IA, 12% as Stage IC, 8% as Stage IIB, 16% as Stage III, and one had an unknown stage [93]. While most of these patients presented at early stages, only 21% were alive at 2 years. Similarly, Hyun and Mun [89] found that of 36 cases, 15 were deceased within 2 years and eight of those who passed away were Stage IA at diagnosis. This may be in part due to the aggressive nature of the disease, but also due to the poor prognostic value of the FIGO staging system for ovarian melanomas [87].

2.2. Male genital melanomas

2.2.1. Penile melanomas

2.2.1.1. Presentation. Penile melanomas account for less than 2% of all primary penile malignancies and less than 0.2% of all melanomas [94,95]. It most often presents as a nodular brown or blue-black lesion (Fig. 2A and B) that is frequently ulcerated [95]. It may be red and amelanotic in rare instances [96]. Patients are typically asymptomatic at presentation, but dysuria, hematuria, urethral discharge, obstructive symptoms, and even urinary fistula may be present in advanced disease [97]. At the time of presentation, over half of patients with penile melanomas had palpable inguinal lymphadenopathy in one series [20]. In order of frequency, penile melanomas may present at the glans penis, prepuce, penile shaft, or urethral meatus [98]. Penile melanomas are less likely to involve mucosa when compared to vulvar melanomas as there is theorized to be a lower concentration of melanocytes at the mucocutaneous border [99].

2.2.1.2. Evaluation and staging. Since disease is often advanced at the time of presentation, completion of CT C/A/Por whole body FDG-PET/CT with or without brain MRI is recommended [20,38,40,100]. FNA should be considered to evaluate clinically positive lymphadenopathy [41]. A simple staging system developed by Bracken and Diokno [101] is often used in penile melanomas (Table 1D). Stage I disease is localized to the penis; Stage II involves regional lymph nodes; and Stage III is disseminated disease. AJCC TNM staging for cutaneous melanomas may also be applied to penile melanomas, though its prognostic ability is not well defined [22,38,40].

2.2.1.3. Surgical treatment. Aggressive surgical resection with total penectomy, perineal urethrostomy, and radical inguinal, iliac, and obturator lymphadenectomy was the preferred treatment in the past [102]. Recent recommendations favor more conservative management with wide excision or partial penectomy when possible to achieve standard margins applied to cutaneous melanomas, as seen in Fig. 2C–F [22,95,96,103–105]. There is a high recurrence rate regardless of surgical procedure; when comparing organ-sparing to amputative surgery in cutaneous penile melanomas, Bittar et al. [106] found recurrence rates of 19% and 13%, respectively. Cutaneous guidelines for lymphadenectomy and SLNB have also been extrapolated to penile melanomas [22,100]. Lymphoscintigraphy has been found to facilitate mapping of lymph node drainage in penile carcinomas and is recommended in SLNB for penile melanomas [96,107].

2.2.1.4. Radiotherapy. Adjuvant or palliative radiotherapy can be used but does not appear to have significant benefit in the treatment of penile melanomas [22,100,105].

2.2.1.5. Systemic therapy. Systemic therapy may be applied in the adjuvant or palliative setting [105]. At this time, there are not enough data to draw conclusions specifically for penile melanomas; however, there are single cases of success with adjuvant combined thymosin, bleomycin, vincristine, and cisplatin as well as with interferon [96,108]. Evaluation for targetable mutations is recommended since KIT mutations are present in up to 20% of penile melanomas and targeted therapies have shown promise in anal mucosal melanomas [13,100]. Despite lack of robust data, we feel that consideration should be given to use newer immunotherapy agents such as anti-PD-1 as a
monotherapy or in combination with anti-CTLA-4 in a neoadjuvant setting when penile melanomas are advanced and/or associated with regional nodal disease.

2.2.1.6. Prognosis. The 5-year survival rates for all penile melanomas range from 20% to 69% [14,20,109]. When examining penile melanomas of only mucosal origin, van Geel et al. [109] found a 5-year survival of 31%; however, this was comparable to 5-year survival for cutaneous melanomas of similar depth. All patients with mucosal penile melanomas with regional nodal involvement or distant metastases passed away within 2 years of diagnosis even with surgical intervention. Poor prognostic factors include Breslow depth greater than or equal to 3.5 mm, tumor diameter greater than 15 mm, presence of ulceration, and microsatellitosis.

2.2.2. Scrotal melanomas

2.2.2.1. Presentation. Scrotal melanomas are exceedingly rare with less than 50 documented cases [20,110]. Like other cutaneous melanomas, they most commonly present as a pigmented macule or papule; however, there are rare cases of it presenting as an exophytic, ulcerated mass [22,111]. In one series, 19% of scrotal melanomas presented as AJCC TNM Stage I or II; 56% presented as Stage III; and 25% presented as Stage IV [110]. In another series, at presentation, tumor thickness was greater than 2 mm in 76% and 44% had regional or distant disease [106].

2.2.2.2. Evaluation and staging. Given that scrotal melanomas often present at late stages, imaging with CT C/A/P or whole-body FDG-PET/CT with or without MRI brain should be considered [38,106,110]. Palpable lymphadenopathy may benefit from sampling with FNA [41]. Scrotal melanomas are staged using the AJCC TNM staging system [22,111].

2.2.2.3. Surgical treatment. Bittar et al. [106] observed that local recurrence rate was 18% in 18 patients who underwent organ-sparing surgery while the two patients that underwent amputation did not recur. Sanchez-Ortiz et al. [22] found that all six patients in their series who underwent wide local excision had 0% local recurrence and 33% DSS at median follow-up of 36 months. It appears that the greater risk is for regional recurrence, which patients remain high-risk for even if they undergo scrotectomy [22,110]. Therefore, conservative management with wide local excision is recommended for local control [22]. Historically, elective lymphadenectomy was recommended in cases with Breslow depth greater than 1 mm, ulceration, or Clark Level IV or V involvement [22]. While the role of SLNB has not been described in scrotal melanomas to our knowledge, it is the standard of care in cutaneous melanomas and should be considered standard of care in scrotal melanomas, not elective lymph node dissection [38].

2.2.2.4. Radiotherapy. Radiotherapy in combination with systemic therapy has been applied in the metastatic setting; however, it is not a well described treatment of scrotal melanomas [112].

2.2.2.5. Systemic therapy. Adjuvant chemotherapy and immunotherapy in combination with radiotherapy as well as adjuvant chemotherapy alone in regional and distant metastatic disease have been described [22,112,113]. However, there does not appear to be a clear benefit. There is one
case report of BRAF mutation targeted therapy in scrotal melanomas that is ongoing [114].

2.2.2.6. Prognosis. The 5-year survival for scrotal melanomas is up to 69% [20]. Stage of disease is the most significant predictor of outcome. Presence of distant metastases appears uniformly fatal [110].

2.3. Urinary tract melanomas

2.3.1. Urethral melanomas

2.3.1.1. Presentation. The urethra is the most common site for primary melanomas of the urinary tract; however, urethral melanomas comprise only 4% of all urethral malignancies [48]. Urethral melanomas are more likely to occur in females (60%) and at an older age in females compared to males (67 years vs. 62 years) [115]. Time from onset of symptoms to diagnosis is nearly double in males (28 weeks vs. 15 weeks). Urethral cancer may present with a mass, dysuria, bleeding, hematuria, decreased urinary flow, incontinence, discharge, pain, weight loss, or may be asymptomatic [115–117]. In order of frequency, tumors present at the urethral meatus, distal urethra, fossa navicularis, and proximal urethra [115]. Urethral melanomas can be amelanotic in up to 20% of cases and have been mistaken for urethral caruncles [116,118]. The vast majority of patients present with late stage disease; El-Safadi et al. [115] found that 11% cases present as AJCC Stage I; 8% as Stage II; 37% as Stage III; and 44% as Stage IV.

2.3.1.2. Evaluation and staging. Evaluation with urethrocytoscopcy and MRI pelvis can assist with surgical planning and evaluate the extent of soft tissue invasion [119]. CT C/A/P or whole-body FDG-PET/CT is recommended to evaluate for spread of disease [100,120]. The Levine staging system for urethral carcinoma (Table 1E) has been applied to urethral melanomas [121]. Tumor is confined to the submucosa in Stage A, infiltrates the periurethral muscle in females or corpus spongiosum in males in Stage B, invades beyond the periurethral muscle in females or beyond the corpus spongiosum in males in Stage C, and is metastatic to lymph nodes in Stage D. AJCC TNM staging for cutaneous melanomas has also been applied to urethral melanomas [22,38] and El-Safadi et al. [115] found that the T stage, a marker of depth of invasion, correlates significantly with survival.

2.3.1.3. Surgical treatment. Surgical treatment varies based upon the location of the urethral melanomas as well as between males and females [115,119]. In females, surgical resection may include total urethrectomy, partial urethrectomy, cystectomy, and vulvectomy [115]. In males, surgical treatment may include total peneectomy, partial peneectomy, prostatectomy, and cystectomy. Complete urethrectomy in early-stage disease may reduce the risk of local recurrence [63,117,120]. Margins of at least 2 cm are recommended [120]. A more radical surgical approach is recommended if there is evidence of local invasion [119]. Pelvic exenteration has been suggested for women with urethral melanomas greater than 3 mm in depth [73]. Lymph node dissection has not been shown to improve recurrence or DSS [117]. SLNB may be considered in patients without evidence of regional or distant disease [100,120].

2.3.1.4. Radiotherapy. Treatment of recurrence (using radiotherapy, chemotherapy, or immunotherapy) has been shown to improve survival, though the role of radiotherapy has not been examined specifically [115]. However, a benefit to using radiotherapy in particular has not been observed [100,120].

2.3.1.5. Systemic therapy. Adjuvant therapy with dacarbazine and interferon-beta (nimustine and vincristine held after one cycle) has achieved complete response in a patient with metastatic disease to the liver [118]. However, in another case, DAV-Feron (adjuvant dacarbazine, nimustine, vincristine, and interferon-beta) after radical surgery and lymphadenectomy in a patient with local disease at presentation did not appear to improve survival [122]. Adjuvant interferon-alpha may improve prognosis and should be combined with chemotherapy for synergistic effect [100,116,123]. Pembrolizumab has been used in the metastatic setting, but a survival benefit was not observed [119]. In a systematic review, the role of chemotherapy and immunotherapy was not examined individually, but treatment of recurrence with radiotherapy, chemotherapy, or immunotherapy was found to improve survival [115]. Targeted therapy, especially in those who have KIT mutations, should be considered [120].

2.3.1.6. Prognosis. The median survival of urethral melanomas is 26 months, without significant difference between males and females [115]. In a series of females, an OS of 27% was seen at 3 years [117]. Papes and Altarac [120] reported a median survival of 16 months and 5-year survival of 10% in female urethral melanomas. Papes et al. [100] also reported a 5-year survival of 10% in male urethral melanomas. Depth of invasion on T-stage, recurrent disease, pulmonary metastases, and nodal involvement have been associated with survival while tumor diameter has not been associated with prognosis [20,115]. In a smaller study, Oliva et al. [116] found that mucosal location and presence of nodular growth were more predictive of outcome than depth of invasion or tumor stage. The recurrence rate is approximately 60% in 1 year or up to 71% at a median 13 months [115,117]. Sites of recurrence include local recurrence (55%), inguinal lymph nodes (28%), distant metastases primarily to the lungs (38%), central nervous system (10%), and bones (6%) [115]. Treatment of recurrence with radiotherapy, chemotherapy, or immunotherapy has been shown to improve survival.

2.3.2. Bladder melanomas

2.3.2.1. Presentation. Bladder melanomas are very rare with roughly 30 cases reported and is slightly more common in males [124]. Presenting symptoms include hematuria, dysuria, pelvic pain, and pelvic mass; however, these are
usually signs of locally advanced disease [125,126]. Since melanomas of the bladder much more commonly present as metastatic disease (up to 18% of metastatic melanomas metastasize to the bladder), a series of criteria have been established for diagnosis of primary bladder melanomas [48,125]. Patients must not have a history of prior cutaneous melanomas, must not have evidence of regressed cutaneous melanomas, must not have evidence of other visceral primary melanomas, must have a pattern of recurrence consistent with the primary visceral melanomas, and must have atypical melanocytes at the margins of the bladder lesion consistent with those seen in primary mucosal melanomas.

2.3.2.2. Evaluation and staging. Cystoscopy with transurethral biopsy is performed at diagnosis [48,126]. Additionally, intravenous pyelography and MRI pelvis are recommended to assess local involvement. CT C/A/P or whole-body FDG-PET/CT should be performed in addition to comprehensive dermatological, ophthalmological, and otorhinolaryngological exam to assess for regional or distant disease and rule out alternative primary melanomas. A staging system has not been applied to bladder melanomas in the literature; however, a distinction is made between tumors confined to the epithelium and those extending beyond the epithelium [126,127].

2.3.2.3. Surgical treatment. Transurethral resection of bladder tumor (TURBT) is recommended for bladder melanomas confined to the epithelium [126]. Bacillus Calmette-Guerin may be used as an adjunct to TURBT [124]. More aggressive surgery with partial cystectomy, or radical cystectomy is favored for localized disease extending beyond the epithelium [40,128]. The role of pelvic lymphadenectomy and SLNB in bladder cancer is not defined in the literature [48].

2.3.2.4. Radiotherapy. Radiotherapy has been used, but there are few data to support its value [40,48,129]. However, a single case of remission after combined radiotherapy and interferon-alpha in a patient who was not a surgical candidate has been reported [130].

2.3.2.5. Systemic therapy. The use of platinum-based chemotherapy has been proposed, but its effect is not documented [124]. Immunotherapy with interferon-alpha in combination with radiotherapy induced remission in single patient who was not an operative candidate [130]. However, a case of adjuvant interferon with dacarbazine was not as promising [131]. Adjuvant nivolumab following cystectomy in a case of metastatic bladder melanoma yielded clinical remission at 15 months, suggesting that checkpoint inhibitors may be beneficial especially in late-stage disease [124]. Tumors with BRAF, NRAS, or KIT mutations should be considered for targeted therapies [124].

2.3.2.6. Prognosis. In a systematic review, Barillaro et al. [124] found median survival of 21 months. In patients who underwent radical cystectomy, survival was 60% at median follow-up of 16 months while in patients who underwent conservative management, including TURBT, survival was 29% at median follow-up of 14 months. Size, depth of invasion, and presence of metastases are associated with a worse prognosis [127]. Survival beyond 3 years has not been observed in locally advanced disease [40,128].

2.3.3. Upper urinary tract melanomas
To our knowledge, only three cases of primary melanomas of the ureter have been reported [132]. The first two cases presented in the 1960s [132–134]. Recently, a single case of melanoma of the ureter presented in a patient who underwent nephrectomy for papillary renal cell carcinoma 7 years prior to presentation and was found on follow-up imaging to have a new, contralateral mass of the proximal ureter consistent with primary melanoma on biopsy [132]. The patient had metastatic disease to the lungs and scapular bone and received immunotherapy with progression of disease and ultimately passed away 16 months from diagnosis.

Primary renal melanomas are more commonly of metastatic origin, similar to bladder melanomas [135]. Thus, it has been proposed that criteria established by Ainsworth et al. [125] for primary bladder melanomas be applied to the diagnosis of primary renal melanomas [135]. To meet these criteria, the patient must not have history of prior cutaneous melanomas or evidence of regressed cutaneous melanomas, must not have evidence of other visceral melanomas, must have a pattern of recurrence consistent with the primary lesions, and atypical melanocytes or in situ melanomas should be present in the urothelium in the vicinity of the melanomas. There are only five reported cases of primary renal melanomas in the literature that meet these criteria [135]. Presenting symptoms included flank and lumbar pain, hematuria, and polyuria [135]. All patients underwent nephrectomy—three radical and two simple—as well as ureterectomy in one case, paracaval and interaortocaval lymph node dissection in one case, and liver biopsy in another case. All patients received adjuvant treatment, three received interferon-alpha—one with the addition of fotemustine, one received Bacillus Calmette-Guerin with a melanoma cell vaccine, and one received chemotherapy. Of the four with known follow-up, two were alive with no evidence of disease at 22 months and 27 months and two developed distant metastatic disease within 1 year of diagnosis.

Due to the limited number of cases, there are no guidelines on the management of upper urinary tract melanomas; however, Gakis et al. [136] have extrapolated data from the treatment of other advanced melanomas to establish recommendations. When resectable, treatment should include primary nephroureterectomy with regional lymphadenectomy. Adjuvant dacarbazine-based chemotherapy regimen is recommended when the primary tumor depth is greater than 1.5 mm, there are positive surgical margins, or there are positive lymph nodes. Unresectable disease should be treated with local radiation and dacarbazine-based chemotherapy. Palliative stenting of the upper urinary tract may be performed, but they advise that...
tumor manipulation with ureteroscopy or double-J stent placement may lead to distribution of melanoma cells throughout the ureter. Palliation with endoscopic resection of ureteral masses can also be considered [137]. Of note, these recommendations are for the management of melanomas metastatic to the upper urinary tract but may be applied to primary ureteral and renal melanomas in lieu of more relevant guidelines.

3. Conclusion

The presentation, diagnosis, staging, treatment, and prognosis are variable with regards to GU melanomas. This variability in addition to the rare nature of the diseases makes them difficult to study and establish definitive staging and treatment guidelines. There have been significant advances in the treatment of melanomas in the last 10 years, particularly in systemic therapy for late-stage disease and even consideration of neoadjuvant strategies [138]. While many of the trials that led to the approval of these drugs included cutaneous and mucosal GU melanomas, the generalizability of these data to GU melanomas is not well defined [139]. Unfortunately, even studies attempting to specifically examine these novel therapies in mucosal melanomas do not discuss the primary location or have very few GU-specific melanomas, the majority of which are vulvar or vaginal primaries [57,140–143]. Additionally, these publications lag years behind updates to standard of care. To our knowledge, there is only one active clinical trial dedicated to the treatment of GU melanomas: a single-center, open-label study evaluating the safety and efficacy of anti-PD-1 antibody, camrelizumab, in the treatment of malignant melanoma of the female genital tract (NCT04593485). This paucity of treatment information in addition to the tendency for GU melanomas to present in advanced stages likely contributes to the poor prognosis associated with the disease [144]. Outcomes may be improved by increasing clinician awareness of the current literature and may benefit from future trials focusing specifically on the management of GU melanomas, particularly in advanced stages.

Author contributions

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Conflicts of interest

Jonathan S. Zager has advisory board relationships with Merck, Novartis, Philogen and Castle Biosciences, speaker’s bureau for Castle Biosciences, Pfizer, and Sun Pharma. He also receives research funding from Amgen, Delcath Systems, Philogen, Proventus, and Novartis. He serves on the medical advisory board for Delcath Systems. Philippe E. Speiss serves as the vice chair for the National Comprehensive Cancer Network Panel for bladder and penile cancer. He also serves as an author for UpToDate.com. The remaining authors have no relevant conflicts of interest to disclose.

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References

[1] Vyas R, Thompson CL, Zargar H, Selph J, Gerstenblith MR. Epidemiology of genitourinary melanoma in the United States: 1992 through 2012. J Am Acad Dermatol 2016;75:144–50.
[2] McLaughlin CC, Wu XC, Jemal A, Martin HJ, Roche LM, Chen VW. Incidence of noncutaneous melanomas in the U.S. Cancer 2005;103:1000–7.
[3] Hussein MR. Extracutaneous malignant melanomas. Cancer Invest 2008;26:516–34.
[4] Dupin E, Le Douarin NM. Development of melanocyte precursors from the vertebral neural crest. Oncogene 2003;22:3016–23.
[5] Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24:4340–6.
[6] Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353:2135–47.
[7] Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell 2015;161:1681–96.
[8] Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949–54.
[9] Newell F, Kong Y, Wilmott JS, Johansson PA, Ferguson PM, et al. Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets. Nat Commun 2019;10:3163. https://doi.org/10.1038/s41467-019-11107-x.
[10] Hou JY, Baptiste C, Hombalegowda RB, Tergas AI, Feldman R, Jones NL, et al. Vulvar and vaginal melanoma: a unique subclass of mucosal melanoma based on a comprehensive molecular analysis of 51 cases compared with 2253 cases of nongynecologic melanoma. Cancer 2017;123:1333–44.
[11] Wylomanski S, Denis MG, Theóleyre S, Bouquin R, Vallée A, Knol AC, et al. BRAF mutations might be more common than supposed in vulvar melanomas. Exp Dermatol 2018;27:210–3.
[12] Saglam O, Naqvi SMH, Zhang Y, Mesa T, Teer JK, Yoder S, et al. Female genitourinary tract melanoma: mutation analysis with clinicopathologic correlation: a single-institution experience. Melanoma Res 2018;28:586–91.
[13] Omholt K, Graffstrom E, Kanter-Lewensohn L, Hansson J, Ragnarsson-Olding BK. KIT pathway alterations in mucosal melanomas of the vulva and other sites. Clin Cancer Res 2011;17:3933–42.
[14] Oxley JD, Corbishley C, Down L, Watkin N, Dickerson D, Wong NA. Clinicopathological and molecular study of penile melanoma. J Clin Pathol 2012;65:228–31.
[15] Daud AI, Wolchok JD, Robert C, Hwu WJ, Weber JS, Ribas A, et al. Programmed death-ligand 1 expression and response to
the anti-programmed death 1 antibody pembrolizumab in melanoma. J Clin Oncol 2016;34:4102–9.

[16] Madore J, Vilain RE, Menzies AM, Kakavand H, Wilmott JS, Hyman J, et al. PD-L1 expression in melanoma shows marked heterogeneity within and between patients: implications for anti-PD-1/PD-L1 clinical trials. Pigment Cell Melanoma Res 2015;28:245–53.

[17] Kaunitz GJ, Cottrell TR, Lilo M, Muthapappan V, Esandrio J, Berry S, et al. Melanoma subtypes demonstrate distinct PD-L1 expression profiles. Lab Invest 2017;97:1063–71.

[18] Bishop KD, Olzewska AJ. Epidemiology and survival outcomes of ocular and mucosal melanomas: a population-based analysis. Int J Cancer 2014;134:2961–71.

[19] Taconstacas JD, Bray J, Cohen YK, Arbesman J, Kim J, Koon HB, et al. Update on primary mucosal melanoma. J Am Acad Dermatol 2014;71:366–75.

[20] Sanchez A, Rodriguez D, Allard CB, Bechis SK, Sullivan RJ, Boeke CE, et al. Primary genitourinary melanoma: epidemiology and disease-specific survival in a large population-based cohort. Urol Oncol 2016;34:166.e7–14. https://doi.org/10.1016/j.urolonc.2015.11.009.

[21] Mert I, Semaan A, Winer I, Morris RT, All-Fehmi R. Vulvar/vaginal melanoma: an updated surveillance epidemiology and End results database review, comparison with cutaneous melanoma and significance of racial disparities. Int J Gynecol Cancer 2013;23:1118–25.

[22] Sanchez-Ortiz R, Huang SF, Tamboli P, Prieto VG, Hester G, Pettaway CA. Melanoma of the penis, scrotum and male urethra: a 40-year single institution experience. J Urol 2005;173:1958–65.

[23] Hu D-N, Yu G-P, McCormick SA. Population-based incidence of vulvar and vaginal melanoma in various races and ethnic groups with comparisons to other site-specific melanomas. Melanoma Res 2010;20:153–8.

[24] Wohlmuth C, Wohlmuth-Wieser I, May T, Vicus D, Braun R, Cabo H, Eichhorn A, et al. Dermoscopy of pigmented lesions of the mucosa and the mucocutaneous junction: results of a multicenter study by the International Dermoscopy Society (IDS). Arch Dermatol 2011;147:1181–7.

[25] Cinotti E, Perrot JL, Labelle B, Adegbidi H, Cambazard F. Reflectance confocal microscopy for the diagnosis of vulvar melanoma and melanosis: preliminary results. Dermatol Surg 2012;38:1962–7.

[26] Swetter SM, Thompson JA, Albertini MR, Barker CA, Baumgartner J, Boland G, et al. NCCN clinical practice guidelines in oncology: cutaneous melanoma. Version 1.2022 https://nccn.org. [Accessed 13 December 2021].

[27] Boer FL, Ten Eikelder MLG, Kapiteijn EH, Creutzberg CL, Galaal K, van Poelgeest MIE. Vulvar malignant melanoma: pathogenesis, clinical behaviour and management: review of the literature. Cancer Treat Rev 2019;73:91–103.

[28] Rambhia PH, Scott JF, Vyas R, Gerstenblith MR. Genitourinary melanoma. In: Scott JF, Gerstenblith MR, editors. Noncutaneous melanoma. Brisbane: Codon Publications; 2018. p. 61–81.

[29] Carr MJ, Sun J, Spiess PE, Zager JS. Advances in the management of genitourinary melanomas. AME Med J 2019:4–41.

[30] Moxley KM, Fader AN, Rose PG, Case AS, Mutch DG, Berry E, et al. Malignant melanoma of the vulva: an extension of cutaneous melanoma? Gynecol Oncol 2011;122:612–7.

[31] Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Fleming ID, et al. American Joint Committee on Cancer: the 8th edition of the AJCC cancer staging manual. New York: Springer International Publishing; 2017.

[32] Nagarajan P, Curry JL, Ning J, Piao J, Torres-Cabala CA, Aung PP, et al. Tumor thickness and mitotic rate robustly predict melanoma-specific survival in patients with primary vulvar melanoma: a retrospective review of 100 cases. Clin Cancer Res 2017;23:2093–104.

[33] Verschraegen CF, Benjakapibul M, Supakarapongkul W, Levy LB, Ross M, Atkinson EN, et al. Vulvar melanoma at the M. D. Anderson cancer center: 25 years later. Int J Gynecol Cancer 2001;11:359–64.

[34] Ragnarsson-Olding BK. Primary malignant melanoma of the vulv—agressive tumor for modeling the genetics of Non-UV light-associated melanomas. Acta Oncol 2004;43:421–35.

[35] Ronger-Savle S, Julien V, Duru G, Raudrant D, Dalie S, Thomas L. Features of pigmented vulval lesions on dermcopy. Br J Dermatol 2011;164:54–61.

[36] Blum A, Simionescu O, Argenziano G, Braun R, Cabo H, Eichhorn A, et al. Dermoscopy of pigmented lesions of the mucosa and the mucocutaneous junction: results of a multicenter study by the International Dermoscopy Society (IDS). Arch Dermatol 2011;147:1181–7.

[37] Verschraegen CF, Benjakapibul M, Supakarapongkul W, Levy LB, Ross M, Atkinson EN, et al. Vulvar melanoma at the M. D. Anderson cancer center: 25 years later. Int J Gynecol Cancer 2001;11:359–64.
[51] Abramova L, Parekh J, Irvin Jr WP, Rice LW, Taylor Jr PT, Anderson WA, et al. Sentinel node biopsy in vulvar and vaginal melanoma: presentation of six cases and a literature review. Ann Surg Oncol 2002;9:840–6.

[52] Kobayashi K, Ramirez PT, Kim EE, Levenback CF, Rohren EM, Frumovitz M, et al. Sentinel node mapping in vulvovaginal melanoma using SPECT/CT lymphoscintigraphy. Clin Nucl Med 2009;34:859–61.

[53] Vuko J, Markovic SN, Weaver AL, Ciby WA. Vulvar and vaginal melanoma: case series and review of current management options including neoadjuvant chemotherapy. Gynecol Oncol 2013;129:533–7.

[54] Harting MS, Kim KB. Biochemistry in patients with advanced vulvovaginal mucosal melanoma. Melanoma Res 2004;14:517–20.

[55] Queréux G, Wylomanski S, Bouquín R, Saint-Jean M, Janco JMT, Markovic SN, Weaver AL, Cliby WA. Vulvar and vaginal melanoma: presentation of six cases and a literature review. Gynecol Oncol 2013;129:533–7.

[56] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–30.

[57] Shoushtari AN, Munhoz RR, Kuk D, Ott PA, Johnson DB, Wohlmuth C, Wohlmuth-Wieser I. Vulvar melanoma: molecular characteristics, diagnosis, surgical management, and medical treatment. Am J Clin Dermatol 2021;22:639–51.

[58] Siegel RL, Miller KD, Limberg B, et al. Are checkpoint inhibitors a valuable option for metastatic or unresectable vulvar and vaginal melanomas? J Eur Acad Dermatol Venereol 2018;32:e39–40. https://doi.org/10.1111/jdv.14486.

[59] Frumovitz M, Etchepareborda M, Sun CC, Soliman PT, Efler PJ, Levenback CF, et al. Primary malignant melanoma of the vagina. Obstet Gynecol 2010;116:1358–65.

[60] Miner TJ. Primary vaginal melanoma: a critical analysis of therapy. Ann Surg Oncol 2003;11:34–9.

[61] Geisler JP, Look KY, Moore DA, Sutton GP. Pelvic exenteration for malignant melanomas of the vagina or urethra with over 3 mm of invasion. Gynecol Oncol 1995;59:338–41.

[62] Nakagawa S, Koga K, Kuguro T, Tsutsui O, Taketani Y. The evaluation of the sentinel node successfully conducted in a case of malignant melanoma of the vagina. Gynecol Oncol 2002;86:387–8.

[63] Takehara K, Nakamura H, Mizuno T, Nogawa T. Primary malignant melanoma of the vagina with a survival of longer than 5 years after recurrence: case report and review of the literature. Gynecol Obstet Sci 2013;2013:1–4.

[64] Huang Q, Huang H, Wan T, Deng T, Liu J. Clinical outcome of 31 patients with primary malignant melanoma of the vagina. J Gynecol Oncol 2013;24:330–5.

[65] Landis SH, Murray T, Bolden S, Wing PA. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8–30.

[66] Santuaria G, Angioli R, Nahmias J, Estape R, Penalver M. Primary malignant melanoma of the uterine cervix: case report and review of the literature. Gynecol Oncol 1999;7:170–4.

[67] Gupta R, Singh S, Mandal A. Primary malignant melanoma of cervix—a case report. Indian J Cancer 2005;42:201–4.

[68] Lee JH, Yun J, Seo JW, Bae GE, Lee JW, Kim SW. Primary malignant melanoma of cervix and vagina. Obstet Gynecol Sci 2016;59:415–20.

[69] Bhattacharjee A, Sharma D, Sarker AN, Sarker SK. Cervical cancer in the cervix uteri: 2021 update. Int J Gynecol Obstet 2021;215:28–44.

[70] Pusceddu S, Bajetta E, Carcangiu ML, Formisano B, Ducceschi M, Buzzone R. A literature overview of primary cervical malignant melanoma: an exceedingly rare cancer. Crit Rev Oncol Hematol 2012;81:185–95.

[71] Middleton MR, Hoeller C, Michielin O, Robert C, Caramella C, Ohring K, et al. Intratumoral immunotherapies for unresectable and metastatic melanoma: current status and future perspectives. Br J Cancer 2020;123:885–97.

[72] Sun H, Chen Y, Chen Y, Liu D, Yan Z, Meng B, et al. Primary malignant melanoma of the cervix: 14 cases and literature overview. Melanoma Res 2018;28:578–85.

[73] McNeillage L, Morgan J, Constable J, Jobling T. Metastatic malignant melanoma arising in a mature ovarian cystic teratoma: a case report and literature review. Int J Gynecol Cancer 2005;15:1148–52.

[74] Cronje HS, Woodruff JD. Primary ovarian malignant melanoma arising in cystic teratoma. Gynecol Oncol 1981;12:379–83.

[75] Choi WK, Lee DH, Cho DH, Jang KY, Kim KM. Primary malignant melanoma arising from ruptured ovarian mature cystic teratoma with elevated serum CA 19-9: a case report and review of literature. BMC Womens Health 2019;19:149. https://doi.org/10.1186/s12905-019-0853-8.
Lejtte JA, Kroon BK, Valde ´s Olmos RA, Nieweg OE, Bittar JM, Bittar PG, Wan MT, Kovell RC, Guzzo TJ, Shin TM, Bechara GR, Schwindt AB, Ornellas AA, Silva DE, Lott FM, Creagh TA, Murphy DM. Malignant melanoma of the penis. Fenn NJ, Johnson RC, Sharma AK, Attanoos RL, Horgan K. van Geel AN, den Bakker MA, Kirkels W, Horenblas S, Myskow MW, Going JJ, McLaren KM, Inglis JA. Malignant Pape Hyun HS, Mun ST. Primary malignant melanoma arising in a Berek JS, Renz M, Keohoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. Int J Gynecoblast et al. Systematic review of surgical treatment and outcomes and loss of heterozygosity of the PTEN region in a primary malignant melanoma arising from a mature cystic teratoma of the ovary. Cancer Genet Cytogenet 2009;190:15–20. Tare TA, Gajewski J, van der Zee E, de Waard N, van der Graaf LM, ten Hoor FA, et al. Immunohistochemical analysis of the tumor microenvironment in patients with primary melanoma of the urinary tract. Clin Genet 2006;70:13–20. Oldbring J, Mikulowski P. Malignant melanoma of the penis and male urethra. Report of nine cases and review of the literature. Cancer 1987;59:581–7. Taileraman A. Malignant melanoma of the penis. Urol Int 1972; 27:66–80. Batsakis JG, Suarez P. Mucosal melanomas: a review of the literature. Adv Cancer Res 1983;37:1–54. Maruyama Y, Sadahira T, Mitsui Y, Wada K, Tanimoto R, Batsakis JG, Suarez P. Mucosal melanomas: a review. Adv Clin Oncol 2018;9:449–52. Moehrle M, Fischbach H, Nüßle B, Rassner G. Primary malignant melanoma arising in a mature cystic teratoma (dermoid cyst). Report of two cases and literature analysis. Int J Gynecol Obstet 1996;55:356–62. Tate G, Tajiri T, Suzuki T, Mitsuya T. Mutations of the KIT gene and loss of heterozygosity of the KIT gene in malignant melanoma. J Urol 1998;160:724–8. Maruyama Y, Sadahira T, Mitsui Y, Wada K, Tanimoto R, Kobayashi Y, et al. Red nodular melanoma of the penis: a case report and literature review. Mol Clin Oncol 2018;9:449–52.

Oldbring J, Mikulowski P. Malignant melanoma of the penis and male urethra. Report of nine cases and review of the literature. Cancer 1987;59:581–7.

Taileraman A. Malignant melanoma of the penis. Urol Int 1972; 27:66–80.

Batsakis JG, Suarez P. Mucosal melanomas: a review. Adv Anat Pathol 2000;7:167–80.

Pape DS, Altarac S, Arslani N, Rajković Z, Antabak A, Čačić M. Melanoma of the glans penis and urethra. Urology 2014;83: 6–11.

Bracken RB, DiNko AC. Melanoma of the penis and the urethra: 2 case reports and review of the literature. J Urol 1974;111:198–200.

Myskow MW, Going JJ, McLaren KM, Inglis JA. Malignant melanoma of the penis. J Urol 1988;139:817–8.

Fenn NJ, Johnson RC, Sharma AK, Attanoos RL, Horgan K. Malignant melanoma of the penis. Eur J Surg Oncol 1996;22:548–9.

Creagh TA, Murphy DM. Malignant melanoma of the penis. Aust N Z J Surg 1993;63:820–1.

Bechara GR, Schwindt AB, Ornellas AA, Silva DE, Lott FM, Campos FS. Penile primary melanoma: analysis of 6 patients treated at Brazilian National Cancer Institute in the last eight years. Int Braz J Urol 2013;39:823–41.

Bittar JM, Bittar PG, Wan MT, Kovell RC, Guzzo TJ, Shin TM, et al. Systematic review of surgical treatment and outcomes after local surgery of primary cutaneous melanomas of the penis and scrotum. Dermatol Surg 2018;44:1159–69.

Leijtte JA, Kroon BK, Valdés Olmos RA, Nieweg OW, Horenblas S. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. Eur Urol 2007;52:170–7.

Li Y, Yuan H, Wang A, Zhang Z, Wu J, Wei Q. Malignant melanoma of the penis and urethra: one case report. World J Surg Oncol 2014;12:340. https://doi.org/10.1186/1477-7819- 12-340.

van Geel AN, den Bakker MA, Kikels W, Horenblas S, Kroon BBR, de Wilt JHW, et al. Prognosis of primary mucinous penile melanoma: a series of 19 Dutch patients and 47 patients from the literature. Urology 2007;70:143–7.
molecular review of a case series. Pathol Res Pract 2020;216:153095. https://doi.org/10.1016/j.prp.2020.153095.

[133] Judd RL. Melanoma of the ureter: a case report. J Urol 1962;87:805–7.

[134] Garcia AE, Monserrat JM, Gonzalez Martin G. [Melanoma of the ureter]. Rev Argent Urol Nefrol 1969;38:58–61. [Article in Spanish].

[135] Liapis G, Sarlanis H, Poulaki E, Stravodimos K, Riccioni O, Lazaris AC. Primary malignant melanoma of renal pelvis with extensive clear cell change. Cureus 2016;8:e583. https://doi.org/10.7759/cureus.583.

[136] Gakis G, Merseburger AS, Sotlar K, Kuczyk MA, Sievert KD, Stenzl A. Metastasis of malignant melanoma in the ureter: possible algorithms for a therapeutic approach. Int J Urol 2009;16:407–9.

[137] Macneil J, Hossack T. A case of metastatic melanoma in the ureter. Case Rep Urol 2016;2016:1853015. https://doi.org/10.1155/2016/1853015.

[138] Khair DO, Bax HJ, Mele S, Crescioli S, Pellizzari G, Khiabany A, et al. Combining immune checkpoint inhibitors: established and emerging targets and strategies to improve outcomes in melanoma. Front Immunol 2019;10:453. https://doi.org/10.3389/fimmu.2019.00453.

[139] Wohlmuth C, Wohlmuth-Wieser I. Vulvar malignancies: an interdisciplinary perspective. J Dtsch Dermatol Ges 2019;17:1257–76.

[140] Kliemen ND, Wang M, Rubinstein JC, Olino K, Clune J, Ariyan S, et al. Survival after checkpoint inhibitors for metastatic acral, mucosal and uveal melanoma. J Immunother Cancer 2020;8:e000341. https://doi.org/10.1136/jitc-2019-000341.

[141] D’Angelo SP, Larkin J, Sosman JA, Lebbé C, Brady B, Neyns B, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 2017;35:226–35.

[142] Hamid O, Robert C, Ribas A, Stephen Hodi F, Walpole E, Daud A, et al. Antitumour activity of pembrolizumab in advanced mucosal melanoma: a post-hoc analysis of KEYNOTE-001, 002, 006. Br J Cancer 2018;119:670–4.

[143] Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman R-A, Teitcher J, et al. KIT as a therapeutic target in metastatic melanoma. JAMA 2011;305:2327–34.

[144] Zikry J, Chapman LW, Korda DZ, Smith J. Genital melanoma: are we adequately screening our patients? Dermatol Online J 2017;23:13030/qt7zk476vn. https://doi.org/10.5070/D3233034283.