5 Genitourinary Melanoma

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Abstract: Primary melanoma of the genitourinary (GU) tract is an extremely rare and clinically aggressive entity that comprises 0.2–1% of all melanoma cases, and includes tumors arising from the female GU tract, male GU tract, and urinary tract. Unlike cutaneous melanoma, etiological risk factors and epidemiological trends are not well established due to the rarity of GU melanoma. Little is known about the clinical course of GU melanoma subtypes, and the relative lack of documented cases has made it challenging to establish guidelines for clinical management of these neoplasms. Since a uniform staging system for these diseases has not yet been established, a number of different staging systems have been adopted and modified. Approaches to treatment are similarly heterogeneous, ranging from radical surgical excision to immunotherapies. Recent advancements in drug development and genetic analysis of tumors have led to promising new treatment modalities that warrant further investigation in clinical trials. Much of what is known about GU tract melanomas is documented in case studies and case series. It is possible that the establishment of centralized reporting databases could facilitate greater advancements in the understanding of GU tract melanomas and approaches to treatment. This chapter reviews the current literature on GU melanoma, highlighting key distinctions from cutaneous melanoma, with a focus on epidemiology,

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molecular and genetic alterations, diagnostic workup, clinical staging criteria, treatments, and future perspectives on the landscape of GU melanoma.

Key words: B-raf proto-oncogene serine/threonine kinase; Genitourinary melanoma; Mitogen-activated protein kinase; Sentinel lymph node biopsy; Urinary tract melanoma

INTRODUCTION

Mucosal melanoma is a rare subtype of melanoma, comprising 4% of all melanoma cases (1). Mucosal melanoma differs significantly from cutaneous melanoma with regard to risk factors, tumor biology, clinical manifestations, and management. Diagnosis is typically made late due to a lack of early or specific signs and symptoms, as well as the location of lesions in areas that are difficult to visualize on physical examination (1, 2). Whereas cutaneous melanomas are thought to arise from the malignant transformation of melanocytes in the skin, noncutaneous melanomas are hypothesized to arise from melanoblasts migrating to noncutaneous sites after neural crest cells undergo an epithelial-mesenchymal transition (1). Mucosal melanoma may arise from the mucosal surfaces of the head and neck (55%), female genital organs (18%), anorectal region (24%), and urinary tract (3%) (3).

Genitourinary (GU) melanoma comprises almost half (44.8%) of all mucosal melanomas, and includes: (i) female GU melanoma (vulvar, vaginal, and cervical melanomas); (ii) male GU melanoma (penile and scrotal melanomas); and (iii) urinary tract melanoma (urethral and bladder melanomas) (4). While the majority of GU melanomas arise on mucosal surfaces, some arise on cutaneous GU surfaces including the labia majora, penile shaft, and scrotum, and more infrequently, non-mucosal GU surfaces such as the ovaries or kidneys (4). Vyas et al. evaluated a total of 817 primary GU melanoma cases from the Surveillance, Epidemiology, and End Results (SEER) database diagnosed from 1992 to 2012, and found the female GU tract to be the most commonly reported site (89.4%), followed by the male GU tract (6.6%), and urinary tract (4.3%). Moreover, the vast majority of GU melanomas occurred in women (91%), with highest age-specific-incidence rates in patients aged 85 years and older for both women and men (4). Similarly, Bishop and Olszewski reported that the median age of diagnosis was higher for GU melanoma than for cutaneous melanoma (5). The reasons for this age difference are unclear, although difficulty in visualizing lesions due to anatomic location may factor into the later age at diagnosis in women. GU melanomas are usually more aggressive than other types of cutaneous melanomas.

EPIDEMIOLOGY OF GU MELANOMA

Female GU melanoma

Female GU tract melanomas are rare, accounting for less than 5% of all vaginal malignancies and between 0.2 and 0.8% of all melanomas, and most arise from the vulva (76%) and vagina (19%) (6). When compared with cutaneous

melanoma and other types of gynecologic cancers, the clinical outcome for female GU melanoma is poor with a 5-year overall survival (OS) of 27% for vaginal melanoma, and between 8 and 58% for vulvar melanoma (7, 8). Mucosal melanomas arising from the GU tract are more prevalent and have worse outcomes in women compared with men, and their pattern of growth resembles that of aggressive cutaneous melanoma (4). It is also reported that up to 50% of women with vulvar and vaginal melanoma present with regional lymph node or distant metastatic disease, likely due to the richly innervated lymphatic system that facilitates nodal spreading (9). A late stage at diagnosis, in conjunction with high rates of drug resistance with advanced tumors, results in poor outcomes (7). Historically, mortality approached 90% with recurrence largely due to the lack of curative options available in addition to the aggressive nature of female GU melanoma.

Male GU melanoma

Male GU melanomas are also rare neoplasms of either cutaneous GU origin (penile or scrotal) or mucosal GU origin (glans penis, meatus, and inner blade of the prepuce). It is estimated that primary penile melanomas account for less than 1.4% of all primary penile carcinomas (10). Penile melanoma normally manifests as a pigmented papule, macule, or ulceration with an irregular border, and classically affects men in the seventh and eighth decades of life (11). More than half of the penile melanomas arise from the glans penis (55%), followed by the foreskin (28%), penile shaft (9%), and urethral meatus (8%) (11, 12). The prognosis of male GU melanoma is also poor, particularly in patients presenting with ulceration, Breslow depth of 3.5 mm or greater, or a diameter greater than 15 mm, resulting in a 5-year OS between 18 and 20% (1, 3, 13). Interestingly, however, Van Geel et al. reported that the prognosis of primary penile melanoma was no worse than cutaneous melanoma with a comparable Breslow depth (3).

Primary melanoma of the scrotum appears to have a similar prognosis as penile melanoma (14, 15). Similar to penile melanoma, stage is the most important prognostic factor impacting disease-specific survival (DSS) for scrotal melanoma (14). Generally, epididymis, and seminal and testicular melanomas are metastatic tumors originating from distinctive primary melanomas, and have no symptoms until they reach a critical size that can be detected during physical examinations. Consequently, they are most often detected during autopsies (1).

Urinary tract melanoma

Primary melanoma of the urethra accounts for less than 1% of all cases of melanoma, and 4% of all cases of urethral cancers (16). Urethral melanoma is more common in older adults, usually over the age of 60 years (17). Safadi et al. reported a significantly earlier age at presentation for men compared to women, with an average age at presentation of 62.9 years compared to 66.7 years, respectively ($P = 0.008$) (18). Urethral melanomas also have a three-fold higher incidence in women than men, likely due to the higher number of melanocytes in the vulvar mucosa (6, 18). In women, metastatic spread occurs early in urethral melanomas, either through the superficial lymphatics to the vulva and vagina, through the deep lymphatics to the inguinal lymph nodes, or occasionally to distant body sites via the hematogenous spread (18). Distant metastases, palpable tumor masses,

and palpable lymph nodes indicate advanced disease and portend an unfavorable prognosis, with stage and lymph node involvement being the most important factors affecting DSS (14). Late detection is also associated with the poor prognosis of urethral melanoma due to the difficulty in diagnosis (14).

Primary melanoma of the bladder is exceedingly rare, even more so than the aforementioned GU melanoma subtypes (19). More commonly, bladder melanoma occurs as a secondary, metastatic lesion from a cutaneous primary, with up to 18% of metastatic melanomas presenting with bladder metastases (19, 20). Consequently, when bladder melanoma is detected, it is imperative to attempt to identify a primary site in order to exclude metastatic disease (19, 21). In fact, criteria for the diagnosis of primary bladder melanoma have been established to ensure the exclusion of secondary metastatic disease (22, 23). These criteria include no prior history of a primary cutaneous melanoma, no evidence of a regressed cutaneous melanoma, a recurrence pattern consistent with the diagnosis of an initial primary visceral melanoma, and atypical melanocytes observed at the margin of the specimen during histologic evaluation (20, 22).

Risk factors and prognosis of GU melanoma

The etiological risk factors for GU melanoma are poorly characterized compared with cutaneous melanoma. In particular, the GU tract is not readily exposed to ultraviolet radiation, a strong risk factor for the development of cutaneous melanoma. Chronic inflammatory diseases, viral infections, and chemical irritants have all been suggested as risk factors for GU melanoma in women (14). Similar to cutaneous melanoma, vulvar and vaginal melanoma are rare in patients of African ancestry compared to Caucasians, although urethral melanoma in women is not associated with racial or ethnic background (24). In terms of outcomes, African ancestry is associated with a poorer prognosis in GU melanoma (4). Compared to cutaneous melanomas, GU melanoma carries a poor prognosis with a 5-year relative survival of 15% for a vaginal location, 18% for a urinary tract location, 53% for a female external genital location, and 69% for male external genital location (5). Twelve-month OS was 76.9%, with a 5-year OS of 36.3%, with women having worse OS than men (34.9% vs. 55.6%), respectively, at the 5-year mark (4). Interestingly, in a systematic review of urethral melanoma specifically, there were no significant differences in mean tumor diameter at presentation between men and women (17). Regardless of GU melanoma subtype, survival is diminished with advanced stage of disease, and is particularly poor in those patients with distant metastatic disease discovered at the time of diagnosis (4, 25).

GENETIC AND MOLECULAR ALTERATIONS IN GU MELANOMA

Melanoma initiation and progression are the result of distinct genetic modifications in driver genes that control processes, including cellular senescence, DNA repair, apoptosis, proliferation, and angiogenesis, among others (26). The molecular profile of melanoma varies considerably across its different subtypes.

In particular, a number of studies have demonstrated distinct molecular signatures and patterns of chromosomal aberrations in mucosal melanoma compared to cutaneous melanoma (1, 7, 27). Activating mutations in *BRAF* result in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, which leads to uncontrolled cell growth and proliferation. Mutations in the B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene, are prevalent in cutaneous melanomas without signs of chronic sun damage, occurring in approximately 59% of cases; however, they are quite rare in mucosal melanoma, occurring in between 0 and 10% of cases (7, 27, 28). Omholt et al. reported a case series of five penile melanomas, one of which was found to have a BRAF mutation (29). In an evaluation of 12 cases of penile melanomas, Oxley et al. did not identify any BRAF mutations at the V600E loci (13). More recently, Hou et al. compared the molecular profile of 51 vulvar and vaginal melanomas to over 2000 nongenital melanomas (cutaneous, mucosal, and acral) (7). *BRAF* mutations were found in 26% of female GU melanomas, compared to only 8.3% of mucosal nongenital melanomas, contrary to previously described studies. The most frequently mutated loci (BRAF V600), however, was more common in nongenital melanomas (82.1%) compared to female GU tract melanomas (50%). Overall, the prevalence of BRAF mutations in GU melanomas have been described with variable frequency, though the majority of studies point to lower prevalence, compared to cutaneous melanoma.

PD-l, the programmed cell death receptor, and its ligand PD-L1 have also been of interest recently in GU melanoma, and more so in metastatic melanoma treatment. PD-1 signaling has been shown to induce T-cell tolerance via inhibition of TCR signaling pathway, ultimately dampening anti-tumor adaptive immune responses (30). Thus, its blockade via immune checkpoint inhibitors has been crucial in tumor eradication, and as such PD-1 inhibitors have changed the face of metastatic melanoma treatment. Hou et al. recently found PD-1 and PD-L1 to be highly expressed markers in both vulvar and vaginal melanoma (7). Kaunitz et al. similarly found PD-L1 expression on tumor cells that were most closely associated with CD8+ T-cells, illustrating an adaptive immune-response mechanism of expression (31). In this study of mucosal melanoma, that included 33 primary mucosal melanomas (7 vulvovaginal, 2 anorectal, 24 sinonasal), 44% of mucosal melanomas expressed PD-L1, which was no different from cutaneous disease ($P = 0.38$) (31). Immune checkpoint inhibitors directed against the programmed cell death (PD)-1 receptor have improved outcomes for cutaneous melanoma patients, thus these early studies illustrate a role for the PD-1-specific immunotherapies in treatment of GU melanoma.

Mucosal melanomas have been described to frequently possess activating mutations in the c-KIT proto-oncogene receptor tyrosine kinase gene (*KIT*), which codes for a transmembrane tyrosine kinase (7, 32). Interestingly, *KIT* mutations are also commonly found in acral melanomas and melanomas arising from chronically sun-exposed skin. Downstream targets of KIT include the RAF/MEK/extracellular signal-regulated kinase (ERK) and PI3K/AKT pathways, both of which are heavily involved in proliferation, apoptosis, and survival of melanocytes (29). Various studies have reported that the frequency of *KIT* amplifications in mucosal melanoma varies greatly depending on anatomical site. For example, Omholt et al. reported the highest prevalence of *KIT* mutations in vulvar melanomas (35%), compared to penile (20%) and vaginal (0%) melanoma (29). Still, the

presence of a KIT mutation was not associated with any significant impact on prognosis or OS in this study (29). Hou et al. found that *KIT* mutations were also significantly more prevalent in vulvar and vaginal melanomas (22%), compared to other mucosal melanomas (8.8%) and cutaneous melanomas (3.0%) (7). Udager et al. similarly found an enrichment for *KIT* mutations, specifically in exon 11, present in vaginal, vulvar, and cervical melanomas (33). Beadling et al. also reported a higher frequency of *KIT* mutations in GU melanomas (including anorectum, vulvar, vaginal) compared to mucosal melanoma of the head and neck (44.0% vs. 8.3%, respectively) (34). Contrary to other studies, Oxley et al.'s study of 12 cases of penile melanomas showed no KIT mutations (13). Omholt et al. did not find an association between the presence of *KIT* mutations and a worse prognosis (29). From these data, it is difficult to extrapolate whether KIT mutational prevalence is truly noted in female GU melanomas compared to male GU melanomas due to low sample size, thus necessitating further studies. In sum, studies indicate that GU melanomas, particularly vulvovaginal melanomas, generally have a higher rate of KIT mutations compared to other forms of melanoma.

Finally, activating mutations in the N-ras proto-oncogene (*NRAS*) have been implicated in roughly 20% of cutaneous melanomas, and some mucosal melanomas, which results in increased MAPK and PI3K/AKT signaling (35). With regard to GU melanoma specifically, Van Engen-van Grunsven et al. reported *NRAS* mutations in 21% of vaginal melanomas and 20% of urethral melanomas, and Aulmann et al. detected *NRAS* mutations in 12% of vulvar melanomas and 13% of vaginal melanomas (35, 36). Consistent with these studies, Hou et al. found that *NRAS* mutations were less prevalent in vulvar and vaginal melanomas (4%) compared to cutaneous melanomas (25.9%, P = 0.009) and acral melanomas (40.6%, P = 0.002) (7, 35, 36). These findings were in contrast to those of Omholt et al. which found NRAS mutations in 43% (3 of 7) of vaginal melanomas included in their study and were associated with worse survival outcomes in univariate analysis (29). Taken altogether, these studies demonstrate that NRAS mutations are present in a significant but nonmajority amount of GU melanomas.

Additional investigation is required to fully elucidate the genetic profiles of various subtypes of GU melanoma. The rarity of GU melanoma makes it unclear whether results from these genetic and molecular studies are due to a distinct biology of GU melanoma, or the result of poorly powered studies with heterogeneous cohorts. Moreover, few studies have examined tumor specimens for oncogenic mutations. It remains unclear how these mutations correlate to prognosis of GU melanoma. Larger studies examining the genetic landscape of GU melanomas are needed to more conclusively establish the molecular signature of these tumors. An improved understanding of the mutational burden of these tumors will also be useful for guiding targeted therapies for patients.

DIAGNOSTIC WORK-UP OF GU MELANOMA

Clinical presentation

Female GU melanoma typically presents with pain, vaginal discharge, a vulvar mass, dyspareunia, vaginal bleeding, and pruritus, as well as occasional dysuria and voiding dysfunction if there is urethral involvement (1, 37). The labia minora,

followed by the labia majora and clitoris, are the most common sites for involvement, followed by the urethra and cervix (25). The most common histologic types of vulvar melanoma include lentiginous, superficial spreading, and nodular melanoma. Furthermore, up to 25% of vulvar melanomas can present as amelanotic lesions, which adds significant difficulty to the clinical diagnosis (8).

Male GU melanoma typically presents as a pigmented macule, papule, plaque, or an irregularly demarcated, ulcerated lesion on the glans penis. Patients are typically asymptomatic when presenting at an early stage; however, in advanced stages, patients may note obstructive symptoms, hematuria, urethral discharge, and rarely a urinary fistula (11). The most common presentation is a crusted nodular lesion, which is typically nontender and blue–black in color (10). Histologically, these tumors are identical to mucosal melanomas and cutaneous melanomas arising at other sites (38). Sanchez et al. noted that over half (57.5%) of their 77 penile melanoma cases presented with palpable inguinal lymph nodes (14). The aggressiveness of these tumors is likely related to the vertical, nodular growth pattern of penile melanomas, which occurs in between 70 and 100% of cases (39).

Urinary tract melanoma typically presents with hematuria, complaints of a protruding mass, and obstructive urinary symptoms, including a weak urinary stream (40). The incidence of a protruding mass in urethral melanoma is often attributed to the common involvement of the distal urethra, including the urethral meatus and navicular fossa, as compared to proximal urethra (18, 40, 41). Additional presenting signs and symptoms of urinary tract melanoma include urethral discharge, flank pain, and hydronephrosis. Complaints related to the lower urinary system can sometimes disguise mass-related symptoms, particularly in men.

Diagnostic work-up

Algorithmic approaches to the work-up of new GU melanomas do not currently exist. Typically, patients present late in their disease course, and the prognosis is extremely poor. The primary diagnostic approach includes a meticulous physical exam. In women, this involves a thorough pelvic examination, including visual inspection of the vulva, vagina, cervix, and distal urethra, as well as palpation for inguinal lymphadenopathy (42). In men, this involves visual inspection of the prepuce, glans, scrotum, frenulum, and penile shaft for any pigmented lesions with ulceration, overlying crust, and irregularity (1). Like cutaneous melanoma, excisional biopsy confirms the histologic diagnosis of GU melanoma. Finally, PET/CT, MRI, and/or chest radiography are generally obtained for newly diagnosed patients to rule out occult distant metastases.

Regarding urinary tract melanoma, Safadi et al. conducted a systematic review and reported the presence of a urethral mass to be the most common presenting symptom, followed by dysuria, localized bleeding, hematuria, incontinence, vaginal bleeding, nonspecific perineal pain, vaginal discharge, and weight loss (18). Visual detection of primary tumors in women is typically easier and more straightforward due to the comparatively shorter length of the female urethra compared to males. Moreover, given the site predilection for distal portions of the urethra, larger portions of a urethral melanoma may be more easily detected in women.

Very little data exist for bladder melanoma, as only approximately 30 cases have been reported in the literature to date (43). Bladder melanoma typically presents with clinical features similar to urethral melanoma, including pelvic pain, obstructive symptoms from a pelvic mass, dysuria, and hematuria (42). Diagnosis is generally made with cystoscopy and tumor biopsy (44).

Differential diagnosis

Primary GU melanoma can be difficult to distinguish from other pigmented lesions (Table 1). Specifically, penile melanomas are often mistaken for other pigmented lesions, including squamous cell carcinoma, melanosis, melanocytic nevi, pigmented penile macules, and seborrheic keratosis (25). Melanosis, also known as genital lentiginosis, describes benign lesions that often share clinical features of melanoma, including lesion asymmetry, poorly demarcated and irregular borders, and variable pigmentation patterns (11). Pigmentation patterns range from brown–black to blue, including areas of hyperpigmentation and hypopigmentation, often with mottling and skip lesions (45). Melanosis is most common in women, and typically localizes to the periphery of the labia minora and vulvar trigone, although any aspect of the perineum can be affected (45). In males, melanosis most commonly affects the glans penis. Due to the overlapping clinical features of melanosis and GU melanoma, biopsy is often necessary to establish the diagnosis. Biopsy of melanosis reveals a benign histology, demonstrating predominantly basilar hyperpigmentation and mild epidermal hyperplasia without atypical features (45). Genital lichen sclerosus has also been described in conjunction with melanocytic lesions, including nevi, penile lentigines, penile melanoma, and vulvar melanoma (46, 47). Sollena et al. reported a case of penile lichen sclerosus that presented with post-inflammatory hyperpigmentation that both clinically and dermoscopically mimicked penile melanoma (48).

In men, symptoms of urethral melanoma can mimic chronic prostatitis or mild prostatic hyperplasia, due to urethral discharge and obstructive urinary symptoms (40). Unfortunately, these patients may only be diagnosed with urethral melanoma after several medical treatment failures for mimicking conditions (40, 49). In women, urethral melanoma can be clinically indistinguishable from a

TABLE 1 Differential diagnosis of GU melanoma

Differential diagnosis	
Female GU tract	Benign lentigo, squamous cell carcinoma, melanosis, melanocytic nevi, atypical seborrheic keratosis, genital lichen sclerosis
Male GU tract	Benign lentigo, squamous cell carcinoma, melanosis, melanocytic nevi, pigmented macules of the penis, atypical seborrheic keratosis, genital lichen sclerosis
Urinary tract	Urethral caruncle, urethral polyp, mucosal prolapse, chancre, and other urethral malignancies (transitional cell carcinomas and sarcomas)

urethral caruncle, the most common lesion of the female urethra, which occurs predominantly in postmenopausal women. Urethral caruncles typically appear as soft pink or red polypoid nodules that extend beyond the urethral meatus, which is also the most common location for urethral melanomas and which can mimic amelanotic and polypoid urethral melanomas (17). They may also appear as purple to black pigmented lesions, which can closely resemble urethral melanomas. Additional lesions that clinically mimic female urethral melanoma include urethral polyps, mucosal prolapse, and other urethral malignancies, including transitional cell carcinomas and sarcomas (17).

Finally, diagnostic aids such as dermoscopy may be highly useful in the diagnosis of GU melanoma. However, biopsy and histopathologic evaluation is confirmatory for the diagnosis as many of these pigmented genital lesions may resemble other entities, as described above. Histologic demonstration of increased activity of atypical melanocytes within the epidermis, as well as detachment and necrosis of melanocytes in the dermis, are important for the diagnosis of melanoma. Immunohistochemistry may also be performed in more difficult cases; it specifically analyses for expression of melan-A (MART-1), HMB 45, and S-100 protein within the atypical cell population (11). With highly pleomorphic tumors, however, it may be difficult to conclusively distinguish between primary penile melanoma and penile metastatic melanoma (50).

CLASSIFICATION AND STAGING OF GU MELANOMA

Staging of female GU melanoma

There are currently no consensus guidelines for the staging of vulvar and vaginal GU melanomas. A number of studies have demonstrated that vulvar melanoma may be viewed as an extension of cutaneous melanoma due to similarities in prognostic factors and biological behavior (51, 52). The American Joint Commission of Cancer (AJCC) tumor, node, metastasis (TNM) staging system for cutaneous melanoma has been shown to be the greatest predictor of recurrence-free survival in women with vulvar melanoma (8). As such, vulvar and vaginal melanoma are currently staged according to these guidelines (53). Seifried et al. examined 85 patients with primary vaginal and vulvar melanoma and found that patients with AJCC TNM stage 0–II disease had significantly better 5-year DSS (63.6%) compared to patients with stage III disease (63.6% vs. 0%, respectively) (54). Prognostic factors associated with DSS included tumor thickness, tumor mitotic rate, ulceration status, and surgical margins (54). Additional features generally associated with a poorer prognosis include epithelioid cell type, the presence of microsatellitosis, regression, angiolymphatic involvement, high mitotic rate, amelanosis, and tumors associated with a pre-existing nevus (55). In contrast, Tcheung et al. reported that while increasing Breslow depth was associated with worse survival outcomes, other histopathologic features, including ulceration, high mitotic rate, and atypical melanocytic hyperplasia, were not associated with a significant difference in survival (55). Moxley et al. reported that Breslow depth was the most important predictor of recurrence in early-stage patients (8). This corroborates findings by Irvin et al., who also noted Breslow depth to be the single most important prognostic factor in vulvar melanoma (56). Finally, Moxley et al.

also noted that the AJCC TNM staging was not a significant predictor for recurrence, although a trend for increased recurrence was observed with increasing stage (8).

Recently, Nagarajan et al. identified 100 women with vulvar melanoma and found that the AJCC tumor (T) category (Table 2) was predictive of patient outcomes for tumors >2 mm in thickness (T3 and T4 tumors) (53). Tumors <2 mm in thickness were less predictive of patient outcomes (53). As such, Nagarajan et al. proposed a refined T-category with T1 defined as a tumor thickness <2 mm and dermal mitotic rate <2/mm^2, and T2 as a tumor thickness >2 mm and/or dermal mitotic rate ≥2/mm^2 (53). This refinement was based on univariate analyses demonstrating that only tumor thickness and dermal mitotic rate above 2/mm^2 were independently predictive of reduced melanoma-specific survival (53). Reclassification of tumors according to this staging modification exhibited better prediction of OS and DSS (53). Adoption of this novel T-category staging system by other groups will provide additional insight into its prognostic utility.

Currently, the staging of vaginal melanoma is not standardized, and no staging systems exist that provide prognostic utility. Previous staging systems, including FIGO (International Federation of Gynecology and Obstetrics), and Clark's levels are not suitable for vaginal melanoma, as they fail to incorporate tumor size and regional lymph node involvement, and also do not account for the lack of papillary and reticular dermal and subcutaneous fat landmarks that are useful for staging (42). Breslow depth does have prognostic utility for early-stage vaginal melanoma, however, as tumors <3 cm have significantly better survival outcomes than tumors ≥3 cm (42). Further studies are necessary to assess the prognostic utility of the AJCC TNM staging for vaginal melanoma (42).

In addition, lymph node involvement has been correlated with worse survival rates in female GU melanoma. One study on vulvar melanoma demonstrated a 5-year DSS of 24.0% with positive lymph nodes compared to 68.3% with negative lymph nodes (52). The 5-year DSS varied inversely with increasing number of positive lymph nodes (68.3, 29, and 19.5% for one, two, and three positive lymph nodes, respectively) (51). Despite the prognostic importance of detecting occult lymph node disease in cutaneous melanoma, the utility of sentinel lymph node biopsy (SLNB) for female GU melanoma is controversial. Only a few studies have specifically examined the role of SLNB in vulvar melanoma. Interestingly, there is no significant difference in DSS between patients with a negative and positive SLNB (52). It does appear that SLNB may aid in the assessment of occult regional lymph node disease in vulvar melanoma with a reasonable predictive value (52, 57, 58). Dhar et al. reviewed the use of SLNB in 26 patients with vulvar melanoma undergoing completion inguinal lymph node dissection, and reported a negative predictive value of approximately 85% for SLNB (57). Trifiro et al. examined 12 patients with vulvar melanoma and similarly found two patients with a negative SLNB to also have a negative complete inguinofemoral node dissection. These two patients remained disease-free at 75 and 87 months. Abramova et al. advocated for SLNB primarily due to its lower morbidity compared to prophylactic lymphadenectomy (9, 58).

Given the intricate and often unpredictable lymphatic drainage patterns of female pelvic organs, single-photon emission computed tomography integrated

with computed tomography (SPECT-CT) has been advocated as a better method of mapping sentinel nodes in GU melanoma, compared to classic lymphoscintigraphy (59). Additional studies with longer follow-up are required to further assess the role of SLNB in patients with female GU melanoma. The currently available literature does advocate for the use of SLNB to avoid the morbidity and complications associated with a complete inguinofemoral lymph node dissection, including wound breakdown, infection, and edema (52, 57).

Staging of male GU melanoma

There are also no standardized consensus guidelines for the staging of male GU melanoma (60), (39). A three-stage system is generally employed for the staging of penile melanomas, including local disease confined to the penis (stage I), disease present in the regional lymph nodes (stage II), and distant metastatic disease (stage III) (39, 60, 61). Primary penile melanoma has also been staged using the AJCC TNM staging for cutaneous melanoma; however, studies investigating the utility of the AJCC staging system in predicting OS and DSS for penile melanoma are lacking. Accordingly, many groups have adopted the same indications for SLNB in cutaneous melanoma for guiding the management of penile melanoma. These include penile melanoma tumors >1 mm and <4.00 mm in depth, and tumors <1.00 mm exhibiting regression, mitoses, or ulceration (62). Further, it has been advocated by some that SLNB should be performed in all patients with penile melanoma without palpable lymph nodes, or in patients with suspicious lymph nodes seen on diagnostic ultrasound or MRI (typically performed for ulcerated tumors or tumors with thickness of ≥1 mm) (63, 64). Larger studies with longer follow-up are needed to further delineate the indications for SLNB in patients with penile melanoma.

Staging of urinary tract melanoma

Finally, no standardized guidelines exist for staging of urinary tract melanomas. Breslow depth was previously not used in the staging of urinary tract melanoma as the depth of invasion was not correlated with OS, likely due to the radial, polypoid growth of tumors (65). A four-stage system, described by Levine et al. in 1980, has been classically used for urethral melanoma staging. This system includes tumors confined to the submucosa (stage A), tumors infiltrating the corpus spongiosum (stage B), tumors extending beyond the corpus spongiosum (stage C), and tumors with metastases to regional lymph nodes (stage D) (39, 66). More recently, AJCC TNM staging has been employed for the staging of urethral melanoma, and contrary to previous studies, the depth of invasion was found to be a predictor of prognosis (18). Studies evaluating the use of SLNB in urethral melanoma are presently lacking. One study demonstrated that patients with clinically negative inguinal lymph nodes who subsequently underwent inguinal lymph node dissection had no difference in recurrence rate or DSS (67). Finally, given its rarity, staging of bladder melanoma has not been addressed in the literature, although some authors suggest that hematuria is indicative of locally advanced disease (43).

TREATMENT

Treatment of female GU melanoma

Surgical resection is the current standard of care for female GU melanoma, as it is the only viable treatment option for attaining long-term survival (1, 68). Radical vulvectomy with either ipsilateral or bilateral inguinofemoral lymphadenectomy was previously the treatment of choice for vulvar melanoma, regardless of tumor thickness, depth of invasion, or site (42, 56). More recently, a number of studies have demonstrated that radical vulvectomy does not improve OS, disease-free survival, or DSS compared to simple vulvectomy, partial vulvectomy, or wide local excision (WLE), all of which carry significantly lower morbidity (8, 42, 52). Additional studies have also noted improved OS after WLE for vulvar melanoma compared to radical surgery (69). Overall, patients diagnosed with metastatic disease have a poor prognosis regardless of the surgical approach, although avoiding excessive risks with more invasive surgery is preferable. As such, the guidelines listed in Tables 2 and 3 have been proposed for WLE surgical margins based on tumor stage (42).

TABLE 2 GU melanoma staging

Female GU staging (vulvar and vaginal)

T-Category, AJCC 8th Edition

T-stage	Tumor thickness	Ulceration status
T1	≤0.80 mm	(i) Without ulceration
		(ii) With ulceration
	0.80–1.00 mm	(iii) With or without ulceration
T2	1.01–2.00 mm	(i) Without ulceration
		(ii) With ulceration
T3	2.01–4.00 mm	(i) Without ulceration
		(ii) With ulceration
T4	>4.00 mm	(i) Without ulceration
		(ii) With ulceration

T-category (proposed by Nagarajan et al. (53))

T-category	Criteria
pT1	Tumor thickness ≤2.00 mm and Mitotic figures <2/mm^2
pT2	Tumor thickness >2.00 mm and/or Mitotic figures ≥2/mm^2

Table continued on following page

TABLE 2 GU melanoma staging (Continued)

Male GU staging (penile) (39, 60, 61)

Stage	Criteria
1	Local disease confined to penis
2	Disease spread to regional lymph nodes
3	Disseminated metastatic disease

Urinary tract staging (39, 66)

Stage	Criteria
A	Tumor confined to submucosa
B	Tumor infiltrating the corpus spongiosum
C	Tumor extending beyond the corpus spongiosum
D	Tumor with metastases to lymph nodes

TABLE 3 Female GU melanoma management

Vulvar melanoma (42)

Stage	Management
0–IA	Wide local excision with 1 cm negative margins; SLNB*
IB–IIA	Wide local excision with 2 cm negative margins; SLNB*
IIB–IIC	Wide local excision with >2 cm lateral and deep, negative margins; SLNB*
III	Wide local excision with negative margins as recommended for stage I or stage II, or consider more extensive local surgery; consider chemotherapy and biotherapy
IV	Wide local excision with negative margins as recommended for stage I or stage II; consider complete lymphadenectomy, radiotherapy, chemotherapy, biotherapy, and resection of metastatic nodes

**Upstage and manage as stage III when SLNB is positive.*

Management guidelines based on AJCC 2002 TNM staging.

Vaginal melanoma (42, 68)

Location	Indicated surgery
Vagina	Wide local excision plus radiotherapy
Vagina	Exenteration if wide local excision is not possible

Groin lymph node management (8)

Clinical finding	Indicated surgery
Stage Ib–III vulvar melanoma	Consider SLNB; if positive, complete inguinofemoral node dissection

Radiotherapy (RT) has also been utilized in vulvar melanoma as preoperative neoadjuvant therapy to reduce tumor size and allow for more conservative surgery. In one study, RT after WLE was associated with a decreased risk of local recurrence and increased survival from 16.1 months to 29.4 months (70). Postoperative RT has been used as adjuvant therapy for patients with groin and pelvic nodal metastases, and for palliative treatment for patients with symptomatic metastatic disease. The RT dosage and fractionation schedules for vulvar melanoma are currently adopted from those for vulvar squamous cell carcinoma (42). RT for vulvar tumors has traditionally been technically challenging due to difficulty directing the external RT beam to the vulva without splatter, and because of the extreme sensitivity of vulvar skin and surrounding mucosal tissue to the effects of RT (42). Interestingly, one study demonstrated no improvement in OS and recurrence-free survival in patients with vulvar melanoma receiving adjuvant RT (69).

Vaginal melanomas are similarly treated with surgical resection, although anatomical constraints of the vagina and cervix may limit the degree of surgical resection due to difficulty achieving negative margins (33). Interestingly, these tumors may exhibit recurrence that is unrelated to inadequate surgical resection, as one study reported that the majority of recurrences were distant or multi-focal even after radical excision (70). Currently, WLE followed by RT is an accepted treatment option for vaginal melanoma. In cases of extensive vaginal melanoma with local metastasis, total pelvic exenteration can be performed to achieve tumor-free surgical margins (68). Overall, the extent of surgical resection remains unclear as some studies have reported no survival advantage from a radical versus conservative surgical resection (9, 42). The indications for RT for vaginal melanoma are similar to those for vulvar melanoma (42). Unfortunately, the vast majority of patients with vaginal melanoma will ultimately die from their disease.

Treatment of male GU melanoma

Surgical resection also remains the current standard of care for male GU melanoma, although different surgical approaches have been suggested depending on the location of the tumor (Table 4). Sanchez-Ortiz et al. reported the successful treatment of seven patients with early-stage penile melanoma using partial penectomy or WLE (14). Bechara et al. also described successful treatment of early-stage penile melanoma in three patients with partial penile amputation or WLE (11). Notably, patients with penile melanoma do not classically present with palpable lymph nodes (11). Even in the absence of clinically appreciable lymph nodes, WLE and SLNB are recommended in patients with penile melanoma (3). In addition, while patients with palpable lymphadenopathy should undergo inguinal lymphadenectomy, those without palpable adenopathy should also be considered for prophylactic modified lymphadenectomy, particularly in the presence of poor prognostic factors (15, 71). Local disease control has been accomplished with WLE in 12 reported cases of scrotal melanoma, although additional studies caution that these patients may still be at significant risk for local recurrence (15, 71). In fact, Papes et al. reported recurrence rates between 15 and 30% after surgical resection in 52 patients with urethral melanoma (39). Finally, adjuvant chemotherapy, including dacarbazine, has also been used after partial penectomy, although no improvement in outcomes have been reported with adjuvant chemotherapy (11).

TABLE 4 Male GU melanoma management

Scrotal		
Location	**Indicated surgery**	**References**
Any site	Wide local excision	(15, 38, 71)
Urethral		
Location	**Indicated surgery**	**References**
Fossa navicularis	≤2 mm—consider glans-preserving partial penectomy	(71, 72)
Distal urethra (penile)	≤2 mm—urethrectomy, perineal urethrostomy	(65, 67, 71, 73, 74)
Posterior urethra (bulb)	En bloc penectomy, total urethrectomy with anterior exenteration	(71)
Penile		
Location	**Indicated surgery**	**References**
Foreskin	Circumcision	(11, 71)
Glans alone	Amputation of glans	(10, 11, 71, 75)
Glans + shaft	Partial or radical penectomy	(11, 71, 76)
Groin lymph node management		
Clinical finding	**Indicated surgery**	**References**
Palpable lymph nodes	Bilateral inguinal lymphadenectomy	(11, 15, 25, 71)
Non-palpable lymph nodes	Consider SLNB or prophylactic modified lymphadenectomy; SLNB	(15, 71)

Treatment of urinary tract melanoma

Urethral melanoma has been treated with combinations of surgical resection and lymphadenectomy, followed by either RT or chemotherapy, with variable outcomes (65). DiMarco et al. reviewed 11 patients with primary urethral melanomas and demonstrated recurrence after urethrectomy at a median of 6.5 months (67). Of these 11 patients, 4 who underwent radical extirpation had a 3-year OS of 27% (67). Lymphadenectomy is generally not recommended for stage I urethral melanoma (62). However, Van Geel et al. recommend ilioinguinal lymph node dissection for patients with groin lymph node metastases from penile melanoma, including urethral involvement (3). Prognosis for patients with stage II urethral melanoma is poor, with a 2-year survival rate approaching 0% regardless of treatment modality (39).

Various treatment modalities have been tried for bladder melanoma, but the rarity of this diagnosis has made identifying effective approaches to treatment challenging (43). For tumors confined to the epithelium which have not yet become invasive, transurethral resection is the surgical approach of choice (20).

However, these tumors typically present late in their clinical course, with therapies including partial cystectomy, radical cystectomy, RT, and chemotherapy (19–22). Regardless of the treatment modality, locally advanced bladder melanoma is associated with a very poor prognosis, with available data demonstrating no survival beyond 3 years after cystectomy (19, 44). For patients who are not surgical candidates, chemotherapy, RT, and interferon-α immunotherapy have been used as alternative treatment options, with similarly poor results (21).

Current treatment strategies for advanced or metastatic melanoma are based on targeted underlying molecular mutations or immune signals in the tumors. Accordingly, targeted treatments have been used to treat mucosal melanomas that have distinct genetic alterations (1). An important consideration regarding the genetics of GU melanoma is that PD-l and PD-L1 have recently found to be highly expressed markers in both vulvar and vaginal melanoma (7, 31). Given these results, PD-1 inhibitors, which have changed the treatment landscape of metastatic melanoma, such as Opdivo (Nivolumab, Bristol-Myers Squibb) and Keytruda (Pembrolizumab, MK-3475, Merck), may have a role in the treatment of GU melanoma. Shoushtari et al. recently retrospectively reviewed mucosal melanoma patients treated with PD-1 inhibitors Nivolumab and Pembrolizumab (including 14 vulvovaginal tumors) and found comparable overall response rates (23%) to PD-1 blockade in patients with cutaneous (26–31%) and acral melanomas (32%). This study found no differences in objective response rate (ORR) by age, sub-site of mucosal melanoma, site of metastasis, and prior melanoma therapy (77). Shoushtari et al.'s results are comparable to a recent pooled study evaluating ORR in patients with mucosal melanoma treated with single agent Nivolumab therapy, demonstrating a 23% ORR; however, this was lower than ORR in cutaneous melanoma (40.9%) (77, 78). Higher response rates were noted in combination therapy with Nivolumab and Ipilimumab, among mucosal melanoma patients, 37.1%, compared to 60% for cutaneous melanoma (78). Additional studies are needed to define the role of PD-1 in GU melanoma subtypes and therapeutic mechanism of its inhibition; PD-1 inhibitors have already changed the treatment paradigm for cutaneous melanoma, and may prove to be a promising treatment for GU melanoma.

Clinical trials have also investigated c-KIT inhibitors, such as imatinib, for the treatment of mucosal melanoma, with an observed response rate of 23.3% and a 1-year OS rate of 51.0% (79). Clinical trials with targeted therapies have not yet been performed in patients with GU melanoma and may offer a potential therapeutic avenue in the future. The rarity of GU melanoma and the variation seen in their molecular signatures makes the investigation of such therapies technically challenging

FUTURE PERSPECTIVES

The management of patients with GU melanoma is hindered by a lack of definitive guidelines for staging and management, as well as high patient morbidity and mortality due to the innately aggressive nature of their disease. The rarity of GU melanoma has resulted in a literature base that is narrow in breadth, providing

limited data regarding its etiology, molecular distinctions, and application of available immunotherapies. Available case reports and series on GU melanoma points to its tendency to present late in disease course and aggressive nature, resulting in death regardless of surgical approach or adjuvant therapies used (1, 39, 42).

The current body of literature describes GU melanoma, specifically vulvar and to a lesser extent scrotal melanoma, to be an extension of cutaneous melanoma, effectively grouping them into similar biological categories. However, studies assessing the molecular genetics of GU melanoma have found a degree of genetic heterogeneity with trends toward more predominant *c-KIT* mutations, but variable trends in *BRAF* and *NRAS* mutations within the subtypes of GU melanoma. In one study, c-*KIT* mutations appear to distinguish female GU melanomas as their own genetic entity distinct from other types of mucosal melanoma (7). Given the few number of cases of GU melanoma and studies regarding molecular genetics, additional studies are needed to build on the current knowledge base to understand if these trends are reflective of cohort-specific differences or rather the result of poor sample size and genetic variability within GU melanoma subtypes.

The staging of GU melanoma, particularly vulvar melanoma, is largely considered as an extension of the AJCC TNM staging for cutaneous melanoma. However, with the introduction of the AJCC 8th Edition TNM staging updates on January 1, 2018, further studies will be required to evaluate the utility of this new staging system on the prognosis of GU melanoma. Particularly, the impact of ulceration and mitoses on determining eligibility for SLNB should be evaluated. Overall, the most recent literature strongly recommends SLNB in GU melanoma work-up to avoid complete bilateral inguinal lymphadenectomy. Generally speaking, the lack of consistency regarding staging among GU melanoma subtypes is one that needs to be addressed in order to more systematically assess prognosis and survival trends.

CONCLUSION

GU melanomas likely possess distinct biological differences from cutaneous melanomas, and possibly from other mucosal melanomas, that are currently difficult to assess given the paucity of available literature. This knowledge gap warrants more thorough studies assessing genetic distinctions, presentations, and standardized staging guidelines for all types of GU melanoma. In particular, there are markedly few studies on male GU melanoma and urinary tract melanoma, which are likely related to the rarity of these diseases. Thus, we advocate for increased systematic reporting of GU melanoma, including in national databases, which will enable data trends to be extrapolated and used in the development of guidelines.

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