This article describes the case of a 77-year old patient in whom a brownish bleeding glans lesion led to the diagnosis of a stage pT4b ulcerating melanoma of nodular subtype on excision biopsy, with a suspect lymph node in the left inguinal region. There was no evidence of nodal or distant metastatic disease. Punch biopsy confirmed nodal disease on the left side. Consequently, a complete glansectomy combined with an iliacofemoral lymphadenectomy was performed on the left side, as well as a sentinel procedure on the right side. Pathology showed residual melanoma in situ in the glans and one necrotic adenopathy (1/8) in the inguinal lymphadenectomy. For this node positive melanoma, the multidisciplinary team meeting agreed to start with nivolumab. Based on the ‘Melanoma Focus’ ano-uro-genital (AUG) mucosal melanoma guidelines, the current recommendations of practice are highlighted. However, the available evidence on AUG mucosal melanoma, and especially penile mucosal melanoma, is very limited.

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The case was discussed at the multidisciplinary team meeting as well as with our colleagues of oncological surgery. Complete glansectomy was preferred for local control, combined with an iliaco-femoral lymphadenectomy on the left side and a sentinel biopsy on the right side. On FDG-PET/CT scan, a sole adenopathy in the left sided inguinal area was confirmed with no further evidence for metastases. Surgery was performed as planned without any perioperative complications. Pathology showed residual melanoma in situ in the glans, in the absence of an invasive component. Section margins and the sentinel biopsy were negative. One necrotic adenopathy was found to be positive (1/8) in the inguinal lymphadenectomy. In the iliac lymphadenectomy specimen, 9 negative lymph nodes were found. For this node positive melanoma, the multidisciplinary team meeting agreed to adjuvant therapy with nivolumab. At one year of follow-up, the patient was doing well and there was no sign of recurrence on the last staging.

**SYMPTOMS AND DIAGNOSIS**

Often the diagnosis of AUG melanomas is made rather late, due to the location and the rather atypical and diverse aspect of these lesions. Given the rareness of the disease it is frequently overseen as a possible diagnosis. These lesions are often an irregularly outlined, pigmented or non-pigmented macule, papule or nodule with or without ulceration on the penis, the foreskin or in the urethra. These lesions can itch or bleed, and can even cause irritative miction symptoms. In typical and small lesions, an excision biopsy can be proposed. When the diagnosis is clinical-ly less evident or the lesion is larger, a punch biopsy is a good alternative.

**STAGING AND MOLECULAR TESTING**

**STAGING**

As in other penoscrotal malignancies, the inguinal areas should be examined for enlarged lymph nodes. Ultrasound and FNA or core biopsy are optional in case of doubt. A cystoscopy is advised if the lesion is close to or involving the meatus. In every AUG melanoma staging investigations should find place, consisting of a CT thorax-abdomen-pelvis with imaging of the brain in non-localised disease. A penile MRI with artificial erection can help to determine the local extent but rarely changes practice. If major surgery (more than local excision and lymph nodes) is being considered, a PET-CT should be carried out to exclude low-volume metastatic disease.

**MOLECULAR TESTING**

The majority of melanomas contain potentially actionable genetic mutations. While a targetable mutation in the *BRAF* gene occurs in approximately 50% of cutaneous melanomas, at around 3-15% this is much rarer in AUG melanoma. Despite this low incidence, this mutation should be traced in all AUG mucosal melanoma patients, due to the existence of an effective and licenced treatment option for a small subset of patients. Mutations in *C-KIT* can be identified in 7-17% of all patients with mucosal melanoma and are also predictive of tumour response to targeted inhibition. Especially mutations or amplifications in exons 11 and 13 of the *C-KIT* gene have most
frequently been associated with durable clinical benefit from KIT inhibitors. Molecular analysis for mutations in other genes known to be mutated in melanoma is recommended if a patient with AUG mucosal melanoma is considered for a clinical trial. These include NRAS, GNAQ, GNA11.

SURGICAL TREATMENT
The surgical planning is evidently dependent on the stage and location of the lesion. Given the rare nature of the disease, only small case series, comparing radical excision with local excision, are reported. In women with urethral melanoma (N=11), 25% survived following radical surgery compared to 14% in those with partial urethrectomy. However, the single survivor in the radical group was only followed-up for 2 months, whilst the range of follow-up for all 11 patients was 2-53 months. The recurrence rate was 50% in the radical surgery group and 57% in the partial surgery group. No multivariable analysis controlling for possible confounding factors was undertaken.

In men with genitourinary melanoma (N=16), of those with mucosal melanoma (N=6; excluding those with melanoma of the scrotum and shaft), there was 40% survival in the partial penectomy group (3/5), and 100% in the group who had WLE (1/1). Recurrence rates were 20% in the partial penectomy group and 0% in those who underwent WLE. No multivariable analysis controlling for possible confounding factors was undertaken.

LYMPH NODES
Although resection of involved lymph nodes results in improved local control, there is insufficient data to support a survival benefit. As in other penile malignancies, it is recommended to perform a sentinel node procedure. The drainage to regional lymph nodes has been well characterised.

ADJUVANT SYSTEMIC THERAPY – AFTER CURATIVE RESECTION
In mucosal melanoma, there is a significant risk of inoperable local and/or distant relapse of disease following surgical excision. As in other cancers, this risk is determined by features of the primary tumour and involvement of regional lymph node metastases. Currently, there are no studies regarding adjuvant systemic therapy with more than one case of penile mucosal melanoma included.

For mucosal melanoma in general, there is convincing evidence for the use of checkpoint inhibitors in the metastatic setting. In cutaneous melanoma with high risk of relapse these have a role in the adjuvant setting as well, despite not being addressed by the NICE guidelines. For mucosal melanoma, a randomised non-stratified study showed a trend towards improved survival with chemotherapy (temozolomide + cisplatin) or immunotherapy (IFN a-2b) compared to no systemic adjuvant treatment after complete resection of stage II or III disease. In this study population 103/189

| TABLE 1. Overview of the currently recommended manner and interval of follow-up for penile mucosal melanoma, after treatment with curative intent. |
|-----------------------------------------------|-----------------------------------------------|
| Loco-regional relapse | Systemic relapse |
| First 3 years | 3-monthly clinical examination including:  
- External inspection/examination  
- Palpation of inguinal lymph nodes  
- If urethral involvement if lesion close to the perimeatal area: cystourethroscopy  
• 3-monthly clinical examination according to that used for other malignant tumours at the primary site  
• Baseline CT thorax, abdomen, pelvis including groins 2-3 months post-surgery  
• 6-monthly CT thorax, abdomen, and pelvis including groins  
• 6-monthly CT or MRI of brain (to be discussed with the patient) |
| Years 3-5 | 6-monthly clinical examination including:  
- External inspection/examination  
- Palpation of inguinal lymph nodes  
- If urethral involvement if lesion close to the perimeatal area: cystourethroscopy  
| Years 6-10 | Annual appointment for clinical examination or open rapid access if available. |
| Year 10 | Patients should be discharged at year 10. |
patients had ano-uro-genital melanoma with one case of penile melanoma. At this moment, the true benefit of adjuvant systemic therapy in mucosal melanoma remains uncertain. It is recommended to take the most contemporary data into account.

**RADIOThERAPY**

Radiotherapy is known to be an adjuvant treatment modality in cutaneous melanoma. In penile mucosal melanoma it may have a role in improving local control and overall survival in the setting of incomplete resection where further surgery is not possible. However, this can only be suggested as there are currently no studies regarding adjuvant radiotherapy in this subtype. For positive microscopic margins following curative resection, further surgery to obtain clear margins is currently preferred. However, adjuvant radiotherapy to the primary site can be considered to reduce the probability of local recurrence when further surgery is not feasible or is declined by the patient. Alternative approaches are watchful waiting or a trial of systemic therapy.

In metastatic regional nodal disease in the absence of further metastatic disease, lymphadenectomy is the first choice of treatment. Prophylactic irradiation of regional nodal basins has no role in mucosal melanoma.

**FOLLOW-UP**

After curative surgery for ano-uro-genital mucosal melanoma there is a high rate of loco-regional and/or systemic relapse, especially in the first three years post diagnosis. Early detection of relapse is essential to preserve surgery as an option for local control. Additionally, better response to immunotherapy is expected when metastatic spread is detected earlier. For penile mucosal melanoma, there is no data regarding follow-up available. Neither are there internationally agreed standards on the follow-up after potentially curative treatment or treatment for relapse. Based on consensus, all patients should have rapid access to clinical review (Table 1).

**MANAGEMENT OF METASTATIC DISEASE**

The poor prognosis of metastatic mucosal melanoma made the rise of systemic therapy strongly anticipated. In cutaneous melanoma, a great improvement in progression-free and overall survival has been observed since the introduction of targeted (e.g. BRAF inhibitors) and immune mediated therapy (e.g. CD1 inhibitors, CTLA-4 inhibitors). At the time of writing, there are no randomised controlled trials on mucosal melanoma in the metastatic setting. The available evidence does not differentiate between sites of primary disease. Currently, it is recommended to use PD1-inhibiting immunotherapy in patients with unresectable stage III or IV tumours. In selected fit patients the use of combined immunotherapy (e.g. anti-CTLA and anti-PD1 antibodies) should be given consideration.

A subgroup analysis of 84 patients with metastatic mucosal melanoma from the prospective KEYNOTE studies, demonstrated the efficacy of pembrolizumab. An overall response rate of 19% was described. Based on pooled data from 6 studies, an objective response rate of 23% and 37% for nivolumab (N=86 patients with mucosal melanoma) and a combination of nivolumab and ipilimumab (N=35) respectively was reported. Immunotherapy appears to have a lower response rate in mucosal melanoma compared to cutaneous melanoma.

For malignant melanoma in general, inhibition of BRAF ± MEK is recommended by the NICE guidelines. As previously mentioned, these BRAF mutations are less common in mucosal melanomas. In Asia however, larger numbers have been reported and a single site study demonstrated a similar efficacy of BRAF inhibitors in mucosal and cutaneous melanomas with proven BRAF mutations. In those patients with BRAF mutations the administering of BRAF and MEK inhibitors should be considered. In contrast to immunotherapy, the currently preferred treatment modality, the administering of BRAF inhibitors should not be continued during palliative radiotherapy.

C-KIT gene abnormalities can be identified in 25% of mucosal melanomas. Responses to C-KIT targeted therapy (e.g. imatinib, sunitinib) have been reported in ano-uro-genital mucosal melanomas but the true benefit remains unclear. Data from the ongoing PIANO trial may provide the awaited evidence. At this moment, testing for C-KIT mutations can be discussed with the patient although this often does not change treatment. There is insufficient data to recommend the use of chemotherapy or bio-chemotherapy in metastatic mucosal melanoma, although some activity of carboplatin paclitaxel has been suggested. Follow-up of metastatic disease should include CT thorax, abdomen and pelvis including the groins, and MRI or CT of the brain. This should take place on a 3-month interval for patients treated with immunotherapy, and 2-monthly for patients treated with targeted agents. After 2-3 years, the interval of imaging can be extended to 6 months. From year 5 onwards, annually up to year 10.

**CONCLUSION**

The rarity, location and diverse aspect of penile mucosal melanoma often results in a late diagnosis. Therefore, awareness is essential in a bid to improve its poor prognosis. On clinical suspicion, a biopsy and adequate staging after confirma-
The current recommendations are based on data of AUG mucosal melanoma and mucosal melanoma in general. In selected cases considered for major surgery, a PET/CT should be performed to exclude occult metastatic disease. Surgery is the leading treatment modality for mucosal melanoma. In penile mucosal melanoma, this should be accompanied by a bilateral sentinel procedure. Adjuvant radiotherapy can be considered in case of positive section margins. Adjuvant immunotherapy appears to be promising.

Immune and targeted mediated therapy are promising modalities in the metastatic setting.

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