**Ano-uro-genital Mucosal Melanoma UK National Guidelines**

H.G. Smith a , I. Bagwan b , R.E. Board c , S. Capper d , S.E. Coupland e , J. Glen f , S. Lalondrelle a, A. Mayberry g , A. Muneer h , K. Nugent i , P. Pathiraja j , M. Payne j , H. Peach k , J. Smith k , S. Westwell l , E. Wilson m , S. Rodwell n , M. Gore a , N. Turnbull n , M.J.F. Smith a.

a The Royal Marsden NHS Foundation Trust, UK

b Royal Surrey County Hospital NHS Foundation Trust, UK

 c Lancashire Teaching Hospitals NHS Foundation Trust, UK

d Christie NHS Foundation Trust, UK

e Royal Liverpool University Hospital/University of Liverpool, UK

f National Clinical Guidelines Centre, UK

g Patient representative, UK

h NIHR Biomedical Research Centre, University College London Hospitals NHS Foundation Trust and Division of Surgery and Interventional Science University College London, UK

i University Hospital Southampton NHS Foundation Trust, UK

j Oxford University Hospitals NHS Foundation Trust, UK

k Leeds Teaching Hospitals NHS Foundation Trust, UK

l Brighton and Sussex University Hospitals NHS Foundation Trust, UK

m North Bristol NHS Trust, UK

n Melanoma Focus, UK

**Corresponding author**

Mr Myles Smith, The Skin Unit, The Royal Marsden Hospital NHS Foundation Trust (myles.smith@rmh.nhs.uk)

**Keywords**

Melanoma, Guideline, Mucosal, Anorectal, Vulvovaginal, Penile Cancer, Penis

# Abstract

Ano-uro-genital mucosal melanomas are rare cancers associated with poor outcomes and limited evidence based management. The United Kingdom (UK) Ano-uro-genital mucosal melanoma guideline development group used an evidence-based systematic approach to make recommendations regarding the diagnosis, treatment and surveillance of patients diagnosed with ano-uro-genital mucosal melanomas. The guidelines were sent for international peer review, and are accredited by The National Institute for Health and Clinical Excellence (NICE). A summary of the key recommendations is presented. The full documents are available on the Melanoma Focus website.

# Introduction

## Aim of the guidelines

The aim of these guidelines is to optimise the care of patients with ano-uro-genital (AUG) mucosal melanomas based on the best available scientific evidence. These guidelines should be used to direct the planning of patient care and to provide an indication of the likely clinical outcomes, as well as facilitating patient counselling and informed decision-making. Where adequate evidence is lacking, the Guideline Development Group (GDG) has, where possible, arrived at an expert consensus. The GDG recognises, however, that each patients is an individual. These guidelines should therefore neither be prescriptive nor dictate clinical care; however, where the clinical care significantly differs from the guidelines, it should be justifiable. In the process of developing these guidelines, gaps in the current evidence have been identified, providing scope for further research and audit.

These guidelines are not intended to guide the management of patients with mucosal melanomas occurring at other anatomical sites or patients with cutaneous melanomas of AUG structures.

### Background

Mucosal melanoma occurs at 4 main anatomical sites – the upper aerodigestive tract, the conjunctiva, and the ano-rectum and uro-genital tracts. The latter two groups are the subjects of these guidelines. Data from Public Health England (PHE) shows that between 2010 and 2013, there were 437 cases of melanoma affecting anorectal and urogenital sites. Of these, 121 cases involved the vulva; 49 cases were vaginal melanoma; and 105 cases involved the ano-rectum. (<https://www.gov.uk/government/organisations/public-health-england>).

Surveillance, Epidemiology, and End Results Program (SEER) data 1 show that age-adjusted incidence rates increased between 1992 and 2011 (p < .05) for both women and men, with estimated annual percentage changes of 3.02% and 5.08%, respectively. There were 2,203 deaths from melanoma in 2010 in England, and about 100 deaths were attributed to AUG melanoma.

## 1.2.2 Anorectal melanoma

Delays in the diagnosis or presentation at an advanced stage of disease in anorectal mucosal melanomas are not uncommon, as these lesions may be mistaken for haemorrhoids or adenomatous polyps 2, 3. Approximately one third of patients present with localised disease, with the potential for curative resection, whilst the remainder present with synchronous regional or distant metastases 2, 4, 5. The prognosis for anorectal melanomas is poor, with 5-year survival rates ranging from 5-33% in patients with localised disease, with no patients with disseminated disease surviving 5 years 2. Though surgery is the primary treatment for localised anorectal melanoma, there is ongoing debate as to the most appropriate strategy, with advocates for both radical (i.e. abdominoperineal resection) and conservative (i.e. wide local excision) operations.

## 1.2.3 Vulvovaginal melanoma

Vaginal melanomas appear to originate from melanocytes that are present in the vaginal mucosa of approximately 3% of women 6. The overall incidence of vaginal melanoma is exceedingly rare, at only 0.46 cases per 1 million women per year. There are no significant differences, between various racial or ethnic groups 7. Although it was first reported in 1887, there have been no more than 500 primary vaginal melanoma cases reported in the literature worldwide 4. It accounts for 2-5% of female genital-tract melanoma, less than 3% of vaginal tumors, and about 1% of melanoma in women 8. It typically affects women in their sixth and seventh decades, and occurs more commonly in the lower third of the vagina and on the anterior vaginal wall compared with other sites 8. The most common presenting symptom is bleeding, although other symptoms can include discharge, dyspareunia or tumor mass 8. These are aggressive tumors; overall 5-year survival ranges from 5% to 25%. Most patients are diagnosed at an advanced stage; about 50% have positive regional lymph nodes and nearly 20% have distant metastases. Tumors are usually pigmented; however, less than 10% are amelanotic which add to diagnostic difficulties 8.

## 1.2.4 Primary Penile Melanoma

Primary penile melanoma is an extremely rare male genital malignancy which is aggressive and associated with a poor prognosis; it mainly affects elderly men from the sixth and seventh decade of life 11. Approximately 200 cases have been described in the literature, representing less than 1.4% of primary penile cancers and less than 0.1% of primary melanomas 12. Early detection of these lesions allows penile preserving surgical procedures to be undertaken. However, patients often present to different specialists such as urology, dermatology and genitourinary medicine, which can lead to a significant diagnostic delay.

## 1.3 Strengths and limitations of the evidence

Due to the rarity of AUG mucosal melanoma and the poor prognosis associated with this disease, there is limited clinical evidence with which to guide decision-making in the management of both localised and metastatic disease. Most reports in the literature consist of retrospective single centre case series, with no randomised controlled trials specifically focusing on patients with this melanoma subtype. As such, the limitations of the available literature regarding AUG mucosal melanoma are considerable.

## 1.4 Risks versus benefits

In evaluating the risks and benefits of any intervention, the GDG has focused on analysing the associated clinical benefit and toxicity. Cost-effectiveness analyses were not performed as this falls outside the remit of these guidelines.

# Methods

These guidelines were convened under Melanoma Focus, a national UK charity with a professional core membership undertaking research and education in the field of melanoma and skin cancers. The guidelines and supporting documentation are available on the Melanoma Focus website (<https://melanomafocus.com/activities/mucosal-guidelines/>).

These guidelines were developed in accordance with the Melanoma Focus methodology (<https://melanomafocus.com/wp-content/uploads/2017/04/Melanoma-Focus-Methods-Manual-V4.2-FINAL.pdf>). The methods are accredited by NICE as rigorous and the guideline carries the NICE kitemark. The guideline was started in 2016, with the first GDG meeting held on 20th July. In all 7 meetings were held over a period of 16 months. GDG members completed a Declaration of Interest form prior to the first meeting, which was subsequently updated. All interests were declared at the first meeting and it was agreed that members who had a commercial interest in a drug or technology under discussion could remain in the room and answer questions from GDG members but could not participate in the discussion or the formulation of recommendations.

Due to the rarity of these cancers, and the limited associated literature, it was decided to perform an all-encompassing initial literature search and then sift references for each question in the database. The original search was conducted by the National Guidelines Centre on 3rd March 2016, with the search repeated to identify new evidence on 8th March 2017 Questions were drafted based on inputs from GDG members. Subgroups of content experts on the GDG worked on each topic, agreeing the criteria for including papers, then appraising and extracting references. Most of the evidence consisted of small case series, for some questions additional criteria were applied to appraise quality, in particular whether the case series included patients from more than one centre. The sub-groups were supported and advised by a guideline methodologist. The subgroups presented the evidence review to the full GDG at the group’s meetings. The full GDG discussed the evidence and formulated evidence statements and recommendations. A great deal of work was done electronically and following update search revisions all GDG members were sent several drafts of chapters for comment.

# Recommendations

## 3.1 General Considerations

### 3.1.1 Patient focused care

1. Cancer centres should name a specific oncologist or surgeon within the specialist melanoma team who is responsible for communication between the cancer centre teams caring for the patient and between the cancer centre and primary and secondary care. Provision should also be made for a deputy when this person is away.

2. Standard care available to all patients countrywide should include:

* A named cancer nurse specialist and consultant with contact details
* A designated keyworker, for example the Clinical Nurse Specialist (CNS) from the Multidisciplinary Team (MDT)
* Educational material for patients and families regarding signs and symptoms that may indicate that the cancer has recurred, emphasising that the groin is a common site for locoregional spread and should be examined regularly
* Easy access to out-patient review
* Easy and prompt access to imaging if symptoms or signs develop
* Early access to palliative support networks

3. Provide and encourage the patient and/or carer an opportunity to discuss prognosis openly.

4. Offer and encourage early referral to services, for example, enhanced supportive care, palliative care support services and support groups.

### 3.1.2 Multidisciplinary Team Meetings (MDTMs)

1. The specialist melanoma MDT and the MDT dealing with the local anatomical site should be linked. Prior to treatment:

* The patient’s management should be discussed at both the anatomical site and the specialist melanoma MDTM
* The pathology (i.e. the slides with conventional and any immunohistochemical stains, as well as any associated molecular pathology reports) should be reviewed by an experienced melanoma pathologist
* The management should be agreed by the melanoma MDT with input from the anatomical site specialists
* Following the melanoma MDT discussion, a named consultant responsible for the patient’s care (‘the responsible melanoma MDT consultant’) should communicate directly with other consultants involved about all aspects of the management of the patient e.g. surgeons from the anatomical site MDT. This communication must be entered into the patient notes by ‘the responsible melanoma MDT consultant’ and copied to the patient’s general practitioner so that all communication can be audited
* The outcome of the MDTM discussion should be discussed with the patient and carer as well as communicated to other health professionals involved in the patient’s care including the G.P.

2. Anatomical site follow-up may be devolved locally in accordance with follow-up guidance below.

3. Patients with proven metastatic disease should be referred directly to the specialist melanoma MDT.

4. Staging should be confirmed and documented at the MDTM and entered in the patient notes and copied to the patient’s G.P.

## 3.2 Recognition, referral and diagnosis

### 3.2.1 Anorectal mucosal melanoma

1. Refer to a colorectal surgeon a dermatologist with an interest in pigmented lesions/pigmented lesion clinic via the urgent cancer referral pathway (e.g. the 2-week wait pathway), patients with any of the following symptoms or signs:

* Bleeding per rectum
* Pain
* Mass or swelling
* Palpable lymph nodes (e.g. in the groin) associated with anal symptoms
* Irregularly outlined pigmented or non-pigmented macule, papule, patch or nodule with or without ulceration
* Atypical haemorrhoids
* Polyps
* Unexplained lumps

2. The anal margin should be carefully inspected, as not all melanomas are pigmented. Consider the use of dermoscopy.

3. Be aware that the presenting symptoms of anorectal melanoma may be similar to those of rectal cancer. The following may also be symptoms of anorectal melanoma:

* Change in continence
* Persistent itching (pruritus)
* Constipation/diarrhoea (change in bowel habit)
* Tenesmus

4. Diagnosis of the primary lesion should usually be made by excision or punch biopsy depending on the size and site of the lesion.

5. Patients who present with an anorectal lesion and palpable groin lymph node(s) should have pathological confirmation either by FNA or core biopsy of the suspicious node(s).

### 3.2.2 Vulvovaginal mucosal melanoma

1. Refer to a gynaecological oncology team or a dermatologist with an interest in pigmented lesions/pigmented lesion clinic/joint gynaecology-dermatology clinic via the urgent cancer referral pathway (e.g. the 2-week wait pathway), patients with any of the following symptoms or signs:

* Pigmentation
* Persistent itching with pigmentation
* Bleeding lesion
* Irregularly outlined pigmented or non-pigmented macule, papule, patch or nodule with or without ulceration
* Groin lymph node(s) enlargement associated with vulval pigmented lesion
* Obstruction of urethral meatus with pigmented lesion

2. Nurse practitioners, who carry out cervical smears, should notify the GP if a patient has a pigmented lesion to arrange urgent cancer referral via pathway (e.g. the 2-week wait pathway) and inform the patient of this.

3. For small vulval lesions where there is a high degree of certainty of a diagnosis of mucosal melanoma, an excisional biopsy should be performed. For larger lesions an incisional biopsy or punch biopsy is acceptable.

4. Patients who present with a vulval/vaginal lesion and palpable groin lymph node(s) should have pathological confirmation either by FNA or core biopsy of the suspicious node(s).

### 3.2.3 Penile mucosal melanoma

1. Refer to urologist/penile cancer specialist or a dermatologist with an interest in pigmented lesions/pigmented lesion clinic via the urgent cancer referral pathway (e.g. the 2-week wait pathway) patients with any of the following symptoms or signs:

* Bleeding from penile lesion
* Urethral discharge/bleeding
* Irregularly outlined pigmented or non-pigmented macule, papule, patch or nodule with or without ulceration on penis or foreskin
* Non-pigmented nodular lesion
* Nodular mass on glans penis
* Ulcerated lesion on glans or prepuce
* Intra-urethral mass (papillary or nodular)
* Palpable urethral lump
* Palpable inguinal lymphadenopathy

2. Be aware that the following may also be symptoms of penile melanoma:

* Irritation
* Pruritus
* Dyspareunia
* Lower urinary tract symptoms

3. Diagnosis of the primary lesion should usually be made by excision biopsy or punch biopsy depending on the size and site of the lesion.

4. Patients who present with a penile lesion and palpable inguinal lymph nodes should have pathological confirmation either by FNA or core biopsy of the suspicious node(s).

### 3.2.4 Cutaneous melanoma found at these anatomical sites

If following investigation of a suspect lesion, a diagnosis of cutaneous melanoma is made at any of these anatomical sites the NICE guidelines for Cutaneous Melanoma (https://www.nice.org.uk/guidance/ng14) along with recent evidence, should be followed.

## 3.3 Staging Investigations

1. Local staging should be as for common tumours at the anatomical site and include:

* External inspection/examination
* Palpation of inguinal lymph nodes +/- US and FNA or core biopsy

2. In the case of anorectal mucosal melanoma, this should be supplemented with:

* Digital examination
* Examination Under Anaesthetic (EUA)
* Proctoscopy +/- flexible sigmoidoscopy
* Magnetic Resonance Imaging (MRI) pelvis

3. In the case of vulvovaginal mucosal melanoma, this should be supplemented with:

* Clinical examination including speculum examination and EUA as necessary
* Cystoscopy, if indicated clinically e.g. urethral involvement
* MRI pelvis

4. In the case of penile mucosal melanoma, this should be supplemented with:

* Penile MRI with a pharmacologically-induced erection allows surgical planning and detects the proximity of the lesion to the distal corpus cavernosum
* Cysto-urethroscopy, if urethral involvement or lesion close to the perimeatal area

5. At presentation there should also be staging investigations looking for systemic disease and these are generic for all anatomical sites. They include Computer Tomography (CT) of the thorax, abdomen, and pelvis including the groins. MRI or CT of the brain should also be considered.

6. If radical resection is being considered, Positron Emission Tomography (PET)-CT and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.

7. The following histological features of the primary should be included in all reports:

* macroscopic size of the tumour
* vertical tumour depth
* presence/absence of ulceration
* cytomorphological subtype (i.e. spindle, epithelioid, mixed)
* presence/absence of perineural and/or lymphovascular invasion
* involvement of surrounding structures
* confirmation of the diagnosis of melanoma with immunostaining with a melanocytic marker, particularly to highlight the presence of any melanoma in situ disease bordering the invasive melanoma
* involvement (or not) of surgical resection margins with either invasive melanoma or melanoma in situ: this may often require immunostaining with a melanocytic marker where there are surgery-induced artefacts

8. Additional features such as presence/absence of pigmentation, presence/absence of necrosis, presence/absence and the composition of an accompanying inflammatory infiltrate should also be noted

9. The presence/absence of lymph node/distant metastases should be recorded according to the anatomical site using the ‘N’ and ‘M’ components of the AJCC/TNM system, as if the melanoma were a carcinoma. Although site-specific staging is lacking from the 8th edition of the AJCC staging system, this is likely to be addressed in the 9th edition.

## 3.4 Molecular Testing

1. Targetable mutations in the gene BRAF (chromosome 7q) have therapeutic significance in both the adjuvant and metastatic settings 13, 14. Similarly, some activating mutations in *c-KIT* (chromosome 4q) can be targeted and result in tumour responses 14. Molecular analysis for mutations in both these genes should be performed routinely. Others genes that are known to be mutated in mucosal melanoma - e.g. the *RAS* family, *NF1* and rarely in *GNAQ* and *GNA11* - should also be part of any molecular diagnostic panel 15. In the future, mutations in these and possibly other genes may be of clinical relevance or allow entry into clinical trials, and these should always be evaluated. Molecular testing should occur as soon as practical, ideally at the time of first diagnosis and in an experienced genomic laboratory.

## 3.5 Surgery

In all cases, resectability should be assessed by site specific investigations outlined in the Staging Investigations section above. If radical resection (e.g. an abdominoperineal resection (APR), an exenteration) is being considered, PET-CT and MRI of the brain should be performed. This will enable exclusion of distant metastases and so radical resection with a curative intent can be appropriately considered. Radical resection with palliative intent, in the presence of distant metastases, may be still an option, but only after clear documented discussion with the patient.

### 3.5.1 Anorectal mucosal melanoma

1. Surgery for anorectal melanoma should be performed in centres regularly performing complex anorectal surgery and regularly managing complex melanoma within a specialist melanoma MDT.

2. The aim of surgical management should be to achieve an R0 (microscopically clear > 1mm) margin in the least radical fashion (i.e. with local excision). A patient’s baseline anorectal function must be assessed and an abdominoperineal resection of the rectum (APR) can be considered if there is judged to be a significant risk of incontinence from a wide local excision (WLE). This must be carefully discussed with the patient. APR should not be used routinely as a standard of care. There is no evidence that radical surgery will improve survival.

3. In the event of R1 margins (margin < 1mm), a repeat local excision or radical resection should be performed to obtain an R0 margin. Repeat WLE should be performed if complete resection will not compromise sphincter function. If sphincter function will be compromised, this must be carefully discussed with the patient; other management options may be considered e.g. APR, RT, systemic therapy or close observation depending on the clinical scenario, while being aware there is evidence that radical surgery has no impact on overall survival.

4. Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease. In the presence of isolated mesorectal nodes, a low anterior resection or APR should be considered.

5. Sentinel lymph node biopsy is only recommended if it directs adjuvant treatment or clinical trial entry. Following a positive sentinel node there is the option of following the patient by clinical examination +/- ultrasound. Completion of the nodal dissection should be performed depending on emerging data and/or consensus opinion.

### 3.5.2 Vulvovaginal mucosal melanoma

1. Surgery for vulvo-vaginal melanoma should be performed in centres regularly performing complex vulvo-vaginal surgery, and are regularly managing complex melanoma within a specialist MDT.

2. A patient’s baseline morbidities must be assessed and if the surgery is predicted to impact significantly on quality of life or sphincter function will be compromised this must be carefully discussed with the patient; other management options may be considered e.g. Radiotherapy, systemic therapy, close observation depending on the clinical scenario or palliative care.

3. The aim of surgical management of vulval and vaginal melanomas should be to achieve an R0 (microscopically clear > 1 mm) margin in the least radical fashion. There is no evidence that radical surgery has an impact on overall survival.

4. The considerations set out in the recommendation above also apply to melanomas near or on the clitoris and distant urethra/urethral meatus. Melanomas at these sites present particularly challenging scenarios and patients with these tumours need careful counseling, and in the case of the latter, input from urological colleagues.

5. Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease.

6. Sentinel lymph node biopsy is only recommended if it directs adjuvant treatment or clinical trial entry. Following a positive sentinel node there is the option of following the patient by clinical examination +/- ultrasound. Completion of the nodal dissection should be performed depending on emerging data and/or consensus opinion.

### 3.5.3 Penile mucosal melanoma

1. Surgery for penile melanoma should be performed in one of the specialist supranetwork penile cancer centres, following discussion with a centre regularly managing complex melanoma within a specialist melanoma MDT.

2. A patient’s baseline comorbidities must be assessed and if the surgery is predicted to impact significantly on quality of life, urinary function or erectile function this must be carefully discussed with the patient. Other management options may be considered e.g. RT, systemic therapy, close observation depending on the clinical scenario or palliative care.

3. The aim of surgical management should be to achieve an R0 (microscopically clear > 5 mm) margin in the least radical fashion. However, the distinct anatomical separation of the glans and distal corpus cavernosum allows deep margins >1mm to be accepted if a glansectomy is performed similar to guidelines for penile squamous cell carcinoma. A patient’s baseline urinary function, erectile function and quality of life must be assessed. If surgery in the form of a pan-urethrectomy is predicted to impact significantly on urinary function, then a urinary diversion should be considered. Surgical WLE of the glans lesions may result in deviation of the urinary stream or a poor cosmetic result in which case a total glansectomy should be offered to ensure clear margins and provide a cosmetically acceptable result. There is no evidence that radical surgery, such as partial penectomy or radical penectomy, has an impact on overall survival.

4. In the event of R1 margins (margin < 5 mm), repeat local excision or radical resection may be performed to obtain an R0 margin.

5. Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease.

6. Sentinel lymph node biopsy may be performed using the same rationale as for patients with squamous carcinoma of the penis.

## 3.6 Adjuvant Systemic Therapy

1. The choice of adjuvant systemic treatment should be guided by the most contemporary data.

2. There is good evidence for the activity of immune checkpoint inhibitors in the metastatic setting for both cutaneous and mucosal melanoma. Currently in cutaneous melanoma there is also evidence that immune checkpoint inhibitors and *BRAF*-targeted agents impact survival in the adjuvant setting. Therefore, consideration should be given to their use in patients with AUG melanoma who are at high risk of relapse.

## 3.7 Radiotherapy

1. The routine use of adjuvant radiotherapy following curative resection in AUG melanoma is not recommended outside of the context of clinical studies.

2. If resection with curative intent only achieves an R1 margin, and radical resection is deemed inappropriate, due to associated morbidity or other clinical reason, then consideration should be given to adjuvant radiotherapy in order to reduce the probability of local recurrence.

3. Regional lymph nodes should not be included routinely in the target volume.

4. If external beam RT is planned in the adjuvant setting it should be given at a radical dose equivalent (e.g. at least equivalent to 45Gy/25#).

## 3.8 Follow-up after potentially curative treatment

1. All patients should have rapid access to clinical review between appointments or after discharge if they have any concerns. Follow-up schedules have been divided into local and systemic relapse. Patients should be followed up for evidence of local, regional and systemic relapse.

2. Site-specific recommended follow-up schedules for the first 5 years after treatment for anorectal, vulvovaginal and penile mucosal melanoma are outlined in Tables 1, 2 and 3, respectively.

3. From years 6-10 patients should be given an annual appointment for clinical examination or open rapid access if available. Patients should be discharged at year 10 post diagnosis.

## 3.8 Metastatic disease

### 3.8.1 Treatment

1. The choice of systemic treatment should be guided by the most contemporary data.

2. Use single agent anti-PD1 antibodies in patients with unresectable Stage III or Stage IV tumours, taking into account any contraindications to this therapy.

3. Consider combination immunotherapy, for example anti-CTLA (cytotoxic T-lymphocyte-associated protein 4) and anti-PD1 (programmed death 1) / PD-L1 (programmed death ligand 1monoclonal antibodies in selected fit patients.

4. The data demonstrate lower response rates from immunotherapy in mucosal AUG melanoma compared to cutaneous melanoma. Therefore, the significant toxicity of combination immunotherapy needs to be carefully discussed with the patient.

5. Consider BRAF + MEK inhibitors as a treatment option for the small number of patients with *BRAF*-mutated unresectable Stage III or Stage IV AUG melanoma.

6. In patients with targetable mutations, consider immunotherapy as the preferred first line option unless the patient has a poor performance status and/or symptomatic bulky disease. However, this is a grey area and the correct sequence of immunotherapy/targeted therapy is yet to be robustly defined by clinical trials.

7. Not all *C-KIT* mutations are successfully targeted. Therefore, if one is identified, the patient needs to be carefully counseled that testing for a *C-KIT* mutation may not change their management. Funding for a C-KIT inhibitor would have to be sought and might not be obtained. This also needs to be discussed with the patient. However, the presence of a *C-KIT* mutation may facilitate entry into clinical trials.

8. There is insufficient evidence to recommend the routine use of chemotherapy or biochemotherapy in the treatment of metastatic disease. Such evidence as there is suggests low response rates.

9. Palliative RT can be considered alongside immunotherapy without interruption of the immunotherapy. Patients receiving *BRAF* inhibitors and palliative radiotherapy should have their systemic therapy withheld during RT. There are currently no data to suggest increased rates of toxicity. This is a consensus view, which is the subject of ongoing research.

10. Other palliative options for skin metastases that could be considered include:

* Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446) (<https://www.nice.org.uk/guidance/ipg446>)
* Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410) (<https://www.nice.org.uk/guidance/ta410>)

11. For management of supportive care refer to NICE guidance CSG4 (<https://www.nice.org.uk/guidance/csg4>)

### 3.8.1 Follow-up

1. If there is/has been locoregional or metastatic disease, follow-up should include CT thorax, abdomen and pelvis including groins, and MRI or CT of brain should usually be at 3-monthly intervals for patients treated with immunotherapy, and 2-monthly intervals for those treated with targeted agents. In patients who have responded or whose disease has not progressed, after 2-3 years the interval between scans can be extended to 6 months up to year 5, and then annually up to year 10.

# Tables and Figures

**Table 1.** Recommended follow-up schedule following potentially curative treatment for anorectal mucosal melanoma.

|  |  |  |
| --- | --- | --- |
|  | **Years 1 - 3** | **Years 4 & 5** |
| **Loco- regional** | 3-monthly clinical examination including:• External inspection/examination• Palpation of inguinal lymph nodes• Digital examination• Proctoscopy• Sigmoidoscopy (as required) | 6-monthly clinical examination including:• External inspection/examination• Palpation of inguinal lymph nodes• Digital examination |
| **Systemic**  | 3-monthly clinical examination according to that used for other malignant tumours at the primary siteBaseline CT thorax, abdomen, pelvis including groins 2-3 months post-surgery6-monthly CT thorax, abdomen, pelvis including groins6-monthly CT or MRI of brain (to be discussed with the patient) | 6-monthly clinical examination according to that used for other malignant tumours at the primary site12-monthly CT thorax, abdomen and pelvis including groins12-monthly CT or MRI of brain (to be discussed with the patient). |

**Table 2.** Recommended follow-up schedule following potentially curative treatment for vulvovaginal mucosal melanoma.

|  |  |  |
| --- | --- | --- |
|  | **Years 1 - 3** | **Years 4 & 5** |
| **Loco- regional** | 3-monthly clinical examination including:* External inspection/examination
* Palpation of inguinal lymph nodes
* Speculum examination
* EUA (if clinically indicated)
* Cystoscopy, if clinically indicated (e.g. urethral involvement)
 | 6-monthly clinical examination including:* External inspection/examination
* Palpation of inguinal lymph nodes
* Speculum examination
* EUA (if clinically indicated)
* Cystoscopy, if clinically indicated (e.g. urethral involvement)
 |
| **Systemic**  | 3-monthly clinical examination according to that used for other malignant tumours at the primary siteBaseline CT thorax, abdomen, pelvis including groins 2-3 months post-surgery6-monthly CT thorax, abdomen, pelvis including groins6-monthly CT or MRI of brain (to be discussed with the patient) | 6-monthly clinical examination according to that used for other malignant tumours at the primary site12-monthly CT thorax, abdomen and pelvis including groins12-monthly CT or MRI of brain (to be discussed with the patient). |

**Table 3.** Recommended follow-up schedule following potentially curative treatment for penile mucosal melanoma.

|  |  |  |
| --- | --- | --- |
|  | **Years 1 – 3** | **Years 4 & 5** |
| **Loco- regional** | 3-monthly clinical examination including:* External inspection/examination
* Palpation of inguinal lymph nodes
* Cystourethroscopy, if urethral involvement or lesion close to the perimeatal area
 | 6-monthly clinical examination including:* External inspection/examination
* Palpation of inguinal lymph nodes
* Cystourethroscopy, if urethral involvement or lesion close to the perimeatal area
 |
| **Systemic**  | 3-monthly clinical examination according to that used for other malignant tumours at the primary siteBaseline CT thorax, abdomen, pelvis including groins 2-3 months post-surgery6-monthly CT thorax, abdomen, pelvis including groins6-monthly CT or MRI of brain (to be discussed with the patient) | 6-monthly clinical examination according to that used for other malignant tumours at the primary site12-monthly CT thorax, abdomen and pelvis including groins12-monthly CT or MRI of brain (to be discussed with the patient). |

**Acknowledgements**

Mr Asif Muneer is supported by the NIHR Biomedical Research Centre University College London Hospital.

Dr S Lalondrelle, Mr MJF Smith and Professor M Gore are supported by the NIHR Biomedical Research Centre The Royal Marsden Hospital.

# References

 1. Bishop KD, Olszewski AJ. Epidemiology and survival outcomes of ocular and mucosal melanomas: a population-based analysis. Int J Cancer 2014;134:2961-71.

 2. Falch C, Stojadinovic A, Hann-von-Weyhern C, Protic M, Nissan A, Faries MB, Daumer M, Bilchik AJ, Itzhak A, Brucher BL. Anorectal malignant melanoma: extensive 45-year review and proposal for a novel staging classification. J Am Coll Surg 2013;217:324-35.

 3. Zhang S, Gao F, Wan D. Effect of misdiagnosis on the prognosis of anorectal malignant melanoma. J Cancer Res Clin Oncol 2010;136:1401-5.

 4. Chen L, Xiong Y, Wang H, Liang L, Shang H, Yan X. Malignant melanoma of the vagina: A case report and review of the literature. Oncol Lett 2014;8:1585-88.

 5. Kelly P, Zagars GK, Cormier JN, Ross MI, Guadagnolo BA. Sphincter-sparing local excision and hypofractionated radiation therapy for anorectal melanoma: a 20-year experience. Cancer 2011;117:4747-55.

 6. Nigogosyan G, Delapava S, Pickren JW. Melanoblasts in Vaginal Mucosa. Origin for Primary Malignant Melanoma. Cancer 1964;17:912-3.

 7. Hu DN, Yu GP, 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.

 8. Gokaslan H, Sismanoglu A, Pekin T, Kaya H, Ceyhan N. Primary malignant melanoma of the vagina: a case report and review of the current treatment options. Eur J Obstet Gynecol Reprod Biol 2005;121:243-8.

 9. Piura B. Management of primary melanoma of the female urogenital tract. Lancet Oncol 2008;9:973-81.

 10. Hockel M, Dornhofer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol 2006;7:837-47.

 11. 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.

 12. 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;39:823-31.

 13. Ascierto PA, Flaherty K, Goff S. Emerging Strategies in Systemic Therapy for the Treatment of Melanoma. Am Soc Clin Oncol Educ Book 2018;38:751-58.

 14. Ponti G, Manfredini M, Greco S, Pellacani G, Depenni R, Tomasi A, Maccaferri M, Cascinu S. BRAF, NRAS and C-KIT Advanced Melanoma: Clinico-pathological Features, Targeted-Therapy Strategies and Survival. Anticancer Res 2017;37:7043-48.

 15. Rabbie R, Ferguson P, Molina-Aguilar C, Adams DJ, Robles-Espinoza CD. Melanoma subtypes: genomic profiles, prognostic molecular markers and therapeutic possibilities. J Pathol 2019;247:539-51.