ANO-URO-GENITAL MUCOSAL MELANOMA GUIDELINE

Executive Summary

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Commissioning and funding innovative research, while providing support and information for patients, carers and healthcare professionals

MELANOMA FOCUS

www.melanomafocus.com

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1 INTRODUCTION

Mucosal melanomas mainly occur within the upper aero-digestive tract and sinuses, the conjunctiva, the anorectal region, vagina and vulva, and penis. This guideline relates to mucosal melanomas in the anorectal region, gynaecological tract and penis. It does not address the management of patients with mucosal melanomas in the upper aero-digestive tract and sinuses or in the conjunctiva.

This document is the executive summary which is aimed at practising clinicians. It contains the recommendations and care pathways by anatomical site for anorectal mucosal melanomas, vulval and vaginal mucosal melanomas and penile mucosal melanomas. The general recommendations on patient focussed care and multi-disciplinary meetings and metastatic treatment are the same for all of the anatomical sites, but are repeated within each section for ease of clinical use.

This guidance specifically relates to mucosal melanomas in these areas and the term 'mucosal' was used in our systematic searches. Cutaneous melanomas also occur at these anatomical sites e.g. the shaft of the penis, vulval skin, perineum. Our guidance does not relate to these melanomas which should be managed in the same way as cutaneous melanoma at other sites.

There will be patients where the distinction between 'mucosal' and 'cutaneous' may be difficult to determine; it will be for the specialist melanoma and anatomical site MDTs to decide the best options for intervention taking into account any molecular information and importantly, the opinion of the specialist melanoma pathologist. In these 'grey' cases it is more important to get the intervention right rather than the label.

The recommendations are supported by systematic reviews of the best available evidence. Details of the methods used, evidence reviews and the Guideline Development Group discussions are available in a separate document. There is a further separate document of the appendices and supporting tables. All documentation is available from the Melanoma Focus website:

https://melanomafocus.com/activities/mucosal-guidelines/

2 ANORECTAL MELANOMA

2.1 Recommendations

See the list of abbreviations at the end of this document.

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 Multi-disciplinary 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 loco-regional 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.

Multi-disciplinary team meetings (MDTMs)

5. The specialist melanoma MDT which can be part of the SSMDT, 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 the 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.

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

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

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

Recognition, referral and diagnosis

9. Refer to a colorectal surgeon or a 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*. (See photos in Section 2.2)
   - 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

   **In regions benefiting from local dermatological expertise, it is acceptable for suspicious skin lesions in the perianal area to be referred to a dermatologist rather than a colorectal surgeon.*

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

11. 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

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

13. 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).

Staging Investigations

14. Local staging should be as for common tumours at the anatomical site (anus, rectum) and include:
   - External inspection/examination
   - Palpation of inguinal lymph nodes +/- US and FNA or core biopsy
   - Digital examination
   - Examination Under Anaesthetic [EUA]
   - Proctoscopy +/- flexible sigmoidoscopy
   - MRI pelvis

15. At presentation there should also be staging investigations to look for systemic disease and these are generic for all anatomical sites. They include CT of the thorax, abdomen, and pelvis, including the groins. Also consider MRI or CT of brain.

16. If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered a PET-CT scan and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.

17. 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 lymphatic invasion
- involvement of surrounding structures;
- confirmation of the diagnosis of melanoma with immunostaining with a melanocytic marker
- 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.

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

19. 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.

Molecular Testing

20. Targetable mutations in BRAF have therapeutic significance in both the adjuvant and metastatic setting. Similarly, some activating C-KIT mutations can be targeted and result in tumour responses. Molecular analysis for mutations in both these genes should be performed routinely. Others genes that are known to be mutated in mucosal melanoma should also be part of any molecular diagnostic panel. These include NRAS, GNAQ, GNA11. 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 tested for. Molecular testing should occur takes place as soon as is practical ideally at the time of first diagnosis.

Surgery

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

22. Resectability should be assessed by investigations outlined in the Staging Investigations section above.

23. 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 [APR] can be considered if there is judged to be a significant risk of incontinence from a WLE. This must be carefully discussed with the patient. APR should not be used routinely as a standard of care. There is evidence that radical surgery has no impact on survival.

24. In the event of R1 margins (margin < 1mm), a repeat local excision or radical resection should be performed to obtain an R0 margin. Repeat wide local excision 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.

25. 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.

26. If radical resection (i.e. APR) is being considered, PET-CT and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.

Sentinel Node Biopsy

27. 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.

Adjuvant Systemic Treatment

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

29. 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.

Radiotherapy

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

31. 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.

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

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

Follow-up

34. 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.

35. Clinicians may want to discuss with patients the advantages and disadvantages of surveillance imaging as set out in NG14 1.9.16 http://optiongrid.org/option-grids/pdf/63/en_gb

36. All patients following potentially curative treatment or treatment for relapse should be followed up as follows:

Site of relapse	First three years	Years 3-5
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 site • Baseline CT thorax, abdomen, pelvis including groins 2-3 months post-surgery • 6-monthly CT thorax, abdomen, pelvis including groins • 6-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 site • 12-monthly CT thorax, abdomen and pelvis including groins • 12-monthly CT or MRI of brain (to be discussed with the patient).

- 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

Metastatic disease

Treatment

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

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

39. Consider combination immunotherapy, for example anti-CTLA and anti-PD(L)1 monoclonal antibodies in selected fit patients.

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

41. 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.

42. 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.

43. Not all C-KIT mutations are successfully targeted. Therefore if one is identified, the patient needs to be carefully counselled 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.

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

45. Palliative radiotherapy 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 is currently no data to suggest increased rates of toxicity. This is a consensus view which is the subject of ongoing research.

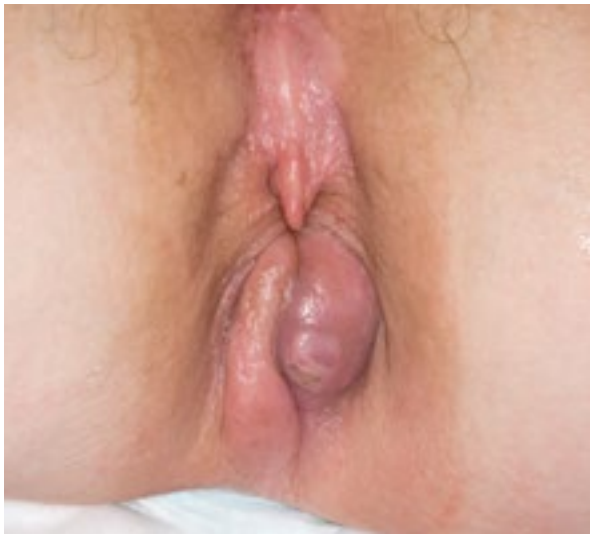
46. Other palliative options for skin metastases that could be considered include:
    - Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446) https://www.nice.org.uk/guidance/ipg446
    - Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410) https://www.nice.org.uk/guidance/ta410

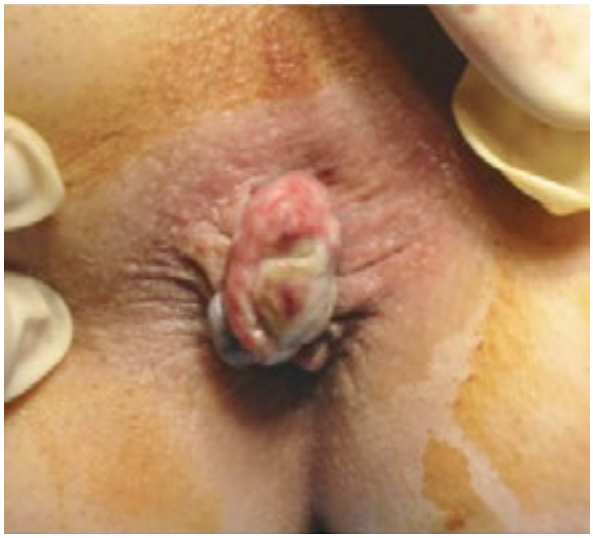
47. For management of supportive care refer to NICE guidance CSG4 https://www.nice.org.uk/guidance/csg4

Follow-up

48. 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.

2.2 Photographs

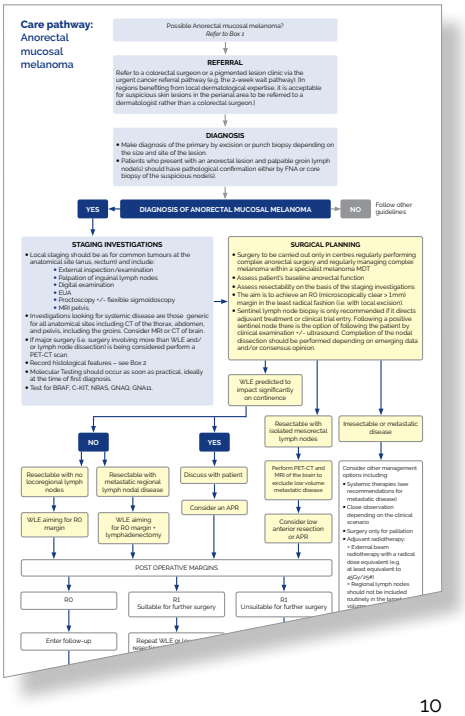




2.3 Care Pathway

Click the button to view the pathway online or download a pdf:

CARE PATHWAY: ANORECTAL MUCOSAL MELANOMA



3 VULVO-VAGINAL MELANOMA

3.1 Recommendations

See the list of abbreviations at the end of this document.

Patient focused care

49. 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.

50. 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 from the MDT
    - Educational material for patients and families regarding signs and symptoms that may indicate that the cancer has recurred, emphasising that the groins are a common site for loco-regional 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

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

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

Multi-disciplinary team meetings (MDTMs)

53. The specialist melanoma MDT which can be part of the SSMDT, 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 MDTMs.
    - The pathology (i.e. the slides with conventional and any immunohistochemical stains, as well as any associated molecular pathology reports) should be reviewed by the 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 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.
    - In some centres there are dermatologists and gynaecologists who have particular expertise in the diagnosis and treatment of vulval diseases. These specialists are often working in joint gynaecology-dermatology clinics or at least there is a close working relationship between the specialists involved. If such a service is present then this team also needs to be involved in the melanoma MDT discussions.
    - 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.

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

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

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

Recognition, referral and diagnosis

57. 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. (See photos in Section 3.2)

    - 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

58. 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.

59. For small vulval lesions where there is a high degree of certainty of a diagnosis of mucosal melanoma, an excisional biopsy should be performed.

60. For larger lesions an incisional biopsy or punch biopsy is acceptable.

61. 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).

62. If the diagnosis is a cutaneous melanoma e.g. of the vulva, the NICE guidelines for Cutaneous Melanoma https://www.nice.org.uk/guidance/ng14, along with recent evidence, should be followed.

Staging Investigations

63. Local staging should be as for common tumours at the anatomical site (vulva, vagina) and include:

    - External inspection/examination
    - Palpation of inguinal lymph nodes+/- US and FNA or core biopsy
    - Clinical examination including speculum examination and EUA as necessary if there is any suspicion of local recurrence
    - Cystoscopy, if indicated clinically e.g. urethral involvement
    - MRI pelvis

64. At presentation there should also be staging investigations to look for systemic disease and these are generic for all anatomical sites. They include CT of the thorax, abdomen, and pelvis including the groins. Also consider MRI or CT of brain.

65. If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered a PET-CT scan and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.

66. For vaginal melanomas 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 lymphatic invasion
- involvement of surrounding structures
- confirmation of the diagnosis of melanoma with immunostaining with immunostaining with a melanocytic marker
- 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

67. 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.

68. 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, except for vulval melanomas.

69. Vulval melanomas should be staged using the skin pTNM staging system.

Molecular Testing

70. Targetable mutations in BRAF have therapeutic significance in both the adjuvant and metastatic setting. Similarly, some activating C-KIT mutations can be targeted and result in tumour responses. Molecular analysis for mutations in both these genes should be performed routinely. Others genes that are known to be mutated in mucosal melanoma should also be part of any molecular diagnostic panel. These include NRAS, GNAQ, GNA11. In the future, mutations in these genes and possibly others may be of clinical relevance or allow entry into clinical trials and these should always be tested for. Molecular testing should occur as soon as practical, ideally at the time of first diagnosis.

Surgery

71. 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.

72. Resectability should be assessed by investigations outlined in the Staging Investigations section above.

73. 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. RT, systemic therapy, close observation depending on the clinical scenario or palliative care.

74. 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.

75. 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 counselling and in the case of the latter, input from urological colleagues.

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

77. If radical resection (e.g. an exenteration) is being considered, PET-CT and MRI of the brain

should be performed pre-operatively to exclude low volume metastatic disease.

Sentinel Node Biopsy

78. 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 +/-or by ultra sound. Completion of the nodal dissection should be performed depending on emerging data and/or consensus opinion.

Adjuvant Systemic Treatment

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

80. 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.

Radiotherapy

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

82. 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.

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

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

Follow-up

85. 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 both evidence of local, regional and systemic relapse.

86. Clinicians may want to discuss with patients the advantages and disadvantages of surveillance imaging as set out in NG14 1.9.16 http://optiongrid.org/option-grids/pdf/63/en_gb

87. All patients following potentially curative treatment or treatment for relapse should be followed up as follows:

Site of relapse	First three years	Years 3-5
Loco-regional relapse	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 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)	• 6-monthly clinical examination according to that used for other malignant tumours at the primary site • 12-monthly CT thorax, abdomen and pelvis including groins • 12-monthly CT or MRI of brain (to be discussed with the patient)

- 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

Metastatic disease

Treatment

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

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

90. Consider combination immunotherapy, e.g. anti-CTLA and anti-PD(L)1 monoclonal antibodies in selected fit patients.

91. The data demonstrates lower response rates from immunotherapy in mucosal melanoma compared to cutaneous melanoma therefore the significant toxicity of combination immunotherapy needs to be carefully discussed with the patient.

92. 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.

93. 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.

94. Not all C-KIT mutations are successfully targeted. Therefore if one is identified, the patient needs to be carefully counselled 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.

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

96. Palliative radiotherapy 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 is currently no data to suggest increased rates of toxicity. This is a consensus view which is the subject of ongoing research.

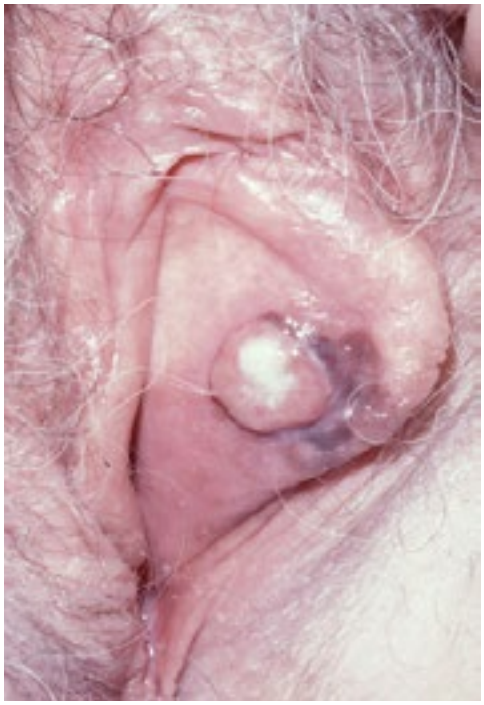
97. Other palliative options for skin metastases that could be considered include
    - Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446) https://www.nice.org.uk/guidance/ipg446
    - Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410) https://www.nice.org.uk/guidance/ta410

98. For management of supportive care refer to NICE guidance CSG4 https://www.nice.org.uk/guidance/csg4

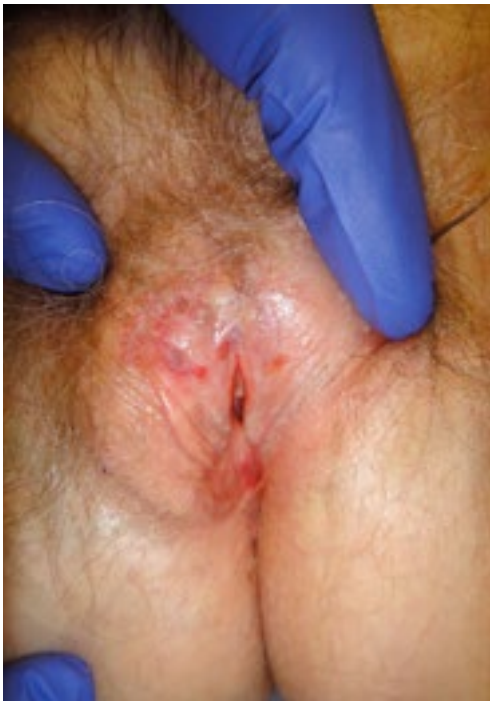
Follow-up

99. If there is/has been loco-regional 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.

3.2 Photographs



A superficial spreading malignant melanoma in vertical growth phase



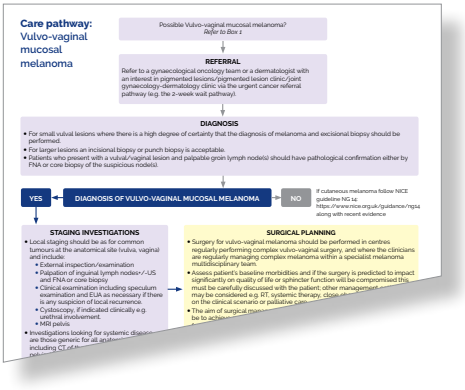
A largely melanotic melanoma affecting the R periclitoral area

Photogtaphs courtesy of Dr Karen L Gibbon Consultant Dermatologist Bart's Health NHS Trust .

3.3 Care Pathway

Click the button to view the pathway online or download a pdf:

CARE PATHWAY: VULVO-VAGINAL MUCOSAL MELANOMA



3 PENILE MELANOMA

4.1 Recommendations

See the list of abbreviations at the end of this document.

Patient focused care

100. 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.

101. Standard care available to all patients countrywide should include:
    - A named cancer nurse specialist and named consultant with contact details
    - A designated keyworker, for example the Clinical Nurse Specialist from the MDT
    - Educational material for patients and families regarding signs and symptoms that may indicate that the cancer has recurred, emphasising that the groins are a common site for loco-regional 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

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

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

Multi-disciplinary team meetings (MDTMs)

104. The specialist melanoma MDT which can be part of the SSMDT and the super-regional penile cancer 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 MDTMs
    - The pathology (i.e. the slides with conventional and any immunohistochemical stains, as well as any associated molecular pathology reports) should be reviewed by the 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.

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

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

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

Recognition, referral and diagnosis

108. 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. (See photos in Section 4.2).
    - 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

109. Be aware that the following may also be symptoms of penile melanoma:
    - Irritation
    - Pruritus
    - Dyspareunia
    - Lower urinary tract symptoms

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

111. 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).

112. If the diagnosis is a cutaneous melanoma e.g. of the shaft, the NICE guidelines for Cutaneous Melanoma https://www.nice.org.uk/guidance/ng14, along with recent evidence, should be followed.

Staging Investigations

113. Local staging should be as for common tumours at the anatomical site (squamous cell carcinoma of the penis) and include:
    - External inspection/examination
    - Palpation of inguinal lymph nodes +/- US and FNA or core biopsy
    - Penile MRI with a pharmacologically-induced erection should be utilised for surgical planning
    - Cysto-urethroscopy, if urethral involvement or lesion close to the perimeatal area

114. At presentation there should also be staging investigations looking for systemic disease and these are generic for all anatomical sites. They include CT of the thorax, abdomen, and pelvis including the groins. Also consider MRI or CT of brain.

115. If radical resection is being considered, PET-CT and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.

116. 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
- 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

117. 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

118. 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.

Molecular Testing

119. Targetable mutations in BRAF have therapeutic significance in both the adjuvant and metastatic setting. Similarly, some activating C-KIT mutations can be targeted and result in tumour responses. Molecular analysis for mutations in both these genes should be performed routinely. Others genes that are known to be mutated in mucosal melanoma should also be part of any molecular diagnostic panel. These include NRAS, GNAQ, GNA11. 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 tested for. Molecular testing should occur as soon as practical, ideally at the time of first diagnosis.

Surgery

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

121. Resectability should be assessed by investigations outlined in the Staging Investigations section above.

122. A patient's baseline morbidities 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.

123. The aim of surgical management should be to achieve an R0 (microscopically clear > 5 mm) margin in the least radical fashion. 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 wide local excision 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. There is no evidence that radical surgery has an impact on overall survival.

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

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

126. If radical resection is being considered, PET-CT and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.

Sentinel Node Biopsy

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

Adjuvant Systemic Treatment

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

129. 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.

Radiotherapy

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

131. 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.

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

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

Follow-up

134. 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 in to local and systemic relapse. Patients should be followed up for both evidence of local, regional and systemic relapse.

135. Clinicians may want to discuss with the patient the advantages and disadvantages of surveillance imaging as set out in NG14 1.9.16 http://optiongrid.org/option-grids/pdf/63/en_gb

136. All patients following potentially curative treatment or treatment for relapse should be followed up as follows:

Site of relapse	First three years	Years 3-5
Loco-regional relapse	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 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)	• 6-monthly clinical examination according to that used for other malignant tumours at the primary site • 12-monthly CT thorax, abdomen and pelvis including groins • 12-monthly CT or MRI of brain (to be discussed with the patient)

• 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

Metastatic disease

Treatment

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

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

139. Consider combination immunotherapy, e.g. anti-CTLA and anti-PD(L)1 monoclonal antibodies in selected fit patients.

140. The data demonstrates lower response rates from immunotherapy in mucosal melanoma compared to cutaneous melanoma therefore the significant toxicity of combination immunotherapy needs to be carefully discussed with the patient.

141. 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.

142. 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.

143. Not all C-KIT mutations are successfully targeted. Therefore if one is identified, the patient needs to be carefully counselled 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.

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

145. Palliative radiotherapy 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 is currently no data to suggest increased rates of toxicity. This is a consensus view which is the subject of ongoing research.

146. 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

147. For management of supportive care refer to NICE guidance CSG4 https://www.nice.org.uk/guidance/csg4

Follow-up

148. If there is/has been loco-regional 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.

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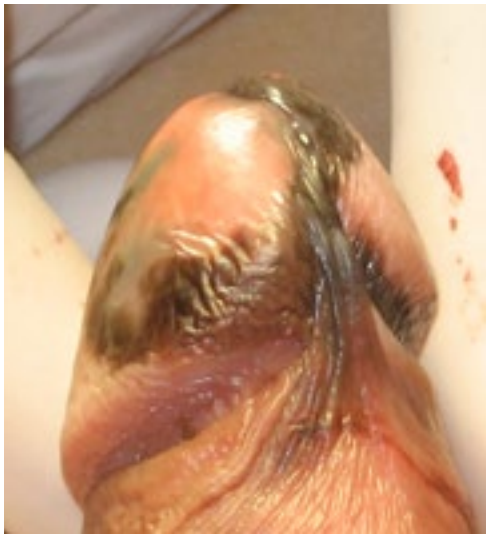
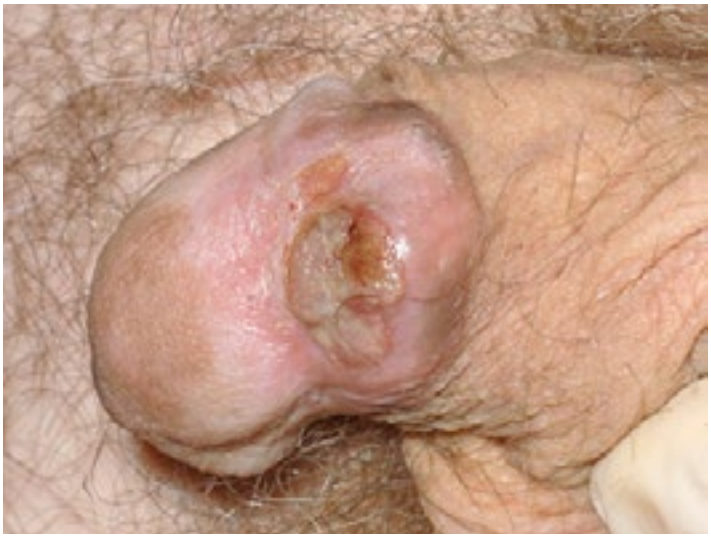


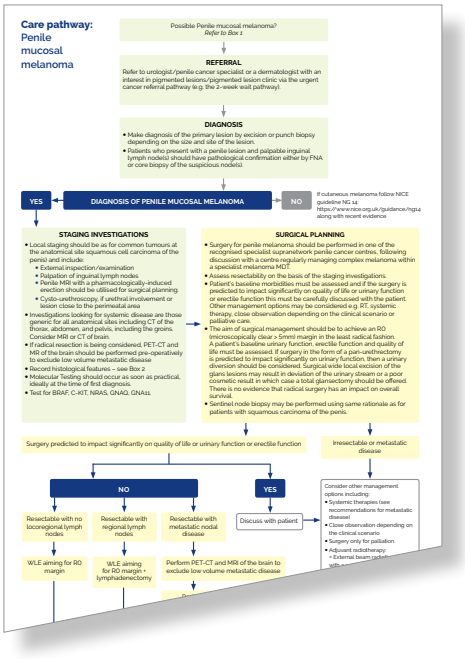


JAMA Dermatol. 2016:15(2):226-227.

4.3 Care Pathway

Click the button to view the pathway online or download a pdf:

CARE PATHWAY: PENILE MUCOSAL MELANOMA



5 USING & IMPLEMENTING THE GUIDELINE

5.1 Potential organisational and financial barriers to applying the recommendations

The main potential organisational barrier to these guidelines relates to the location of the specialist melanoma team which deals with advanced local or metastatic melanoma and the anatomical site specialist surgical team. It is therefore imperative that within a tertiary centre, the surgical teams caring for anorectal, gynaecological and penile cancers and the team caring for those with advanced local or metastatic melanoma prospectively define the communication pathways between them. These teams may not in some areas be geographically co-located and this is acceptable. However, good communication is imperative and if teams are not co-located this is not an excuse for poor collaborative working or information flows. Communication pathways must also include clear procedures, for communicating with secondary and primary care colleagues.

Lead cancer clinicians within tertiary centres must take responsibility for ensuring that these pathways are robust and clearly defined and that there are arrangements for deputising key members of the teams when they are absent.

There should be no financial barriers to these recommendations. In these guidelines we merely have given definition to what is already happening in most tertiary cancer centres both nationally and internationally. Any financial consequence to more robust communications between tertiary teams and secondary and primary care should not be exaggerated as it is likely to be very small.

5.2 Audit criteria

- A member of the treating MDT is named in the case-notes as the designated keyworker.
- There is a record in the case-notes of the following: discussion of management at both the anatomical site MDTM and the specialist melanoma MDTM, communication between the responsible melanoma consultant and other relevant consultants involved in the patient's management especially the surgeon from the anatomical site MDT, and the patient's general practitioner.
- Molecular testing (BRAF, C-KIT, NRAS, GNAQ, GNA11) mutations testing takes place as soon as is practical, ideally at the time of first diagnosis.
- It is anticipated that the number of patients receiving radical surgery will drop with the implementation of these guidelines. Careful audit is required of all patients undergoing surgical treatment radical or otherwise to obtain on-going and dynamic data on surgical practice and outcomes.
- The use of the SACT database will form an important part of any audit of systemic therapy for metastatic disease as well as in the adjuvant setting, and rolling prospective audits of this database should be put in place
- There is a follow-up appointment documented every 3 months for the first 3 years and every 6 months for the following 2 years and a record of the results of the follow up scans.
- Patients are discharged after 10 years of symptom-free survival.

6 RESEARCH RECOMMENDATIONS

There are a number of research questions in the area of AUG mucosal melanoma that need to be addressed. They may not all be easily amenable to randomised studies but nevertheless priority should be given to the topics listed below:

1. The modalities used at follow up and their frequency should be audited on a national basis.

2. There are 2 major imaging research questions: firstly, the utility of brain imaging in follow up, in particularly the yield in relation to the modality used and overall clinical status. Secondly, the frequency and length of imaging follow up using CT thorax/abdomen/pelvis

3. There are good data from prospective studies in patients with AUG melanoma that immunotherapy with immune checkpoint inhibitors yields the best long term results if patients have a good performance status, normal serum LDH and by inference a low volume of disease. However, work needs to be done to better define the patients with AUG melanoma will benefit from immune checkpoint inhibitor therapy

4. The role of targeted therapies for those patients who have actionable mutations has been defined in part in that it is clear that responses are seen. However, some of the targeted agents used are associated with toxicity and durable remissions are rare. Prospective randomised trials are needed to seek better targeted agents and to define their role in relation to immunotherapy, either in combination regimens or as sequential treatment

5. Studies are required to determine the role of adjuvant radiotherapy following curative resection

6. Studies are required to determine the role of sentinel lymph node biopsy

7. We recommend the creation of a national registry for mucosal AUG melanoma with minimum data sets for each anatomical site with the particular purpose of auditing patient management and helping to resolve some of the above questions. In addition, this registry would enable tissue collection and usage for further studies such as the correlation of genomics with treatment outcomes. (Refer to Appendix B1 in the Supplementary Appendix)

7 REVIEW & UPDATES

The guideline was published May 2018 and a full copy of the Guideline and Appendices is available on Website. Melanoma Focus will take administrative responsibility and the Chairman, or someone designated by the Chairman, will take clinical responsibility for maintaining the guideline. GDG members will be asked to notify the chairman at any time, if new evidence makes any aspect of the Guideline unsafe. Annually, the chairman or designated representative will write to the GDG members and the consultees, who comprise many of the leaders in the field, asking if there has been any new evidence which would change the recommendations. At three year intervals, there will be a full search of the literature from the date of the last search to identify any new evidence which would change a recommendation. This will be reviewed by the chairman, or designate, and experts from the each of the clinical areas (Surgery (anorectal, vulvo-vaginal, penile), Radiotherapy, Systemic Therapy and Investigations) the members of that subgroup will meet to review the evidence and agree changes. The re-drafted sections of the Guideline will be sent to the full GDG for agreement before publication. Only if there are several sections that need updating will the full GDG meet. Updates of the guideline should follow the methodology detailed in Melanoma Focus Guideline Development Methodology which also contains further details of the update methods.

Abbreviations

APR	Abdominoperineal resection
AUG	Ano-uro-genital
CLND	Complete lymph node dissection
CNS	Clinical Nurse Specialist
CT	Computed tomography
EUA	Examination under anaesthetic
FNA	Fine needle aspiration
GDG	Guideline Development Group
MDT	Multi-disciplinary team
MDTM	Multi-disciplinary team meeting
MRI or **MR**	Magnetic resonance imaging
PET	Positron emission tomography
SNBx	Sentinel Node Biopsy
SSMDT	Specialist skin cancer multidisciplinary team
US	Ultrasound
WLE	Wide Local excision