Care pathway: Vulvo-vaginal mucosal melanoma

Possible Vulvo-vaginal mucosal melanoma?
Refer to Box 1

REFERRAL

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).

DIAGNOSIS

- For small vulval lesions where there is a high degree of certainty that the diagnosis of melanoma and excisional biopsy should be performed.
- For larger lesions an incisional biopsy or punch biopsy is acceptable.
- 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).

DIAGNOSIS OF VULVO-VAGINAL MUCOSAL MELANOMA

YES

NO — If cutaneous melanoma follow NICE guideline NG 14: https://www.nice.org.uk/guidance/ng14 along with recent evidence

STAGING INVESTIGATIONS

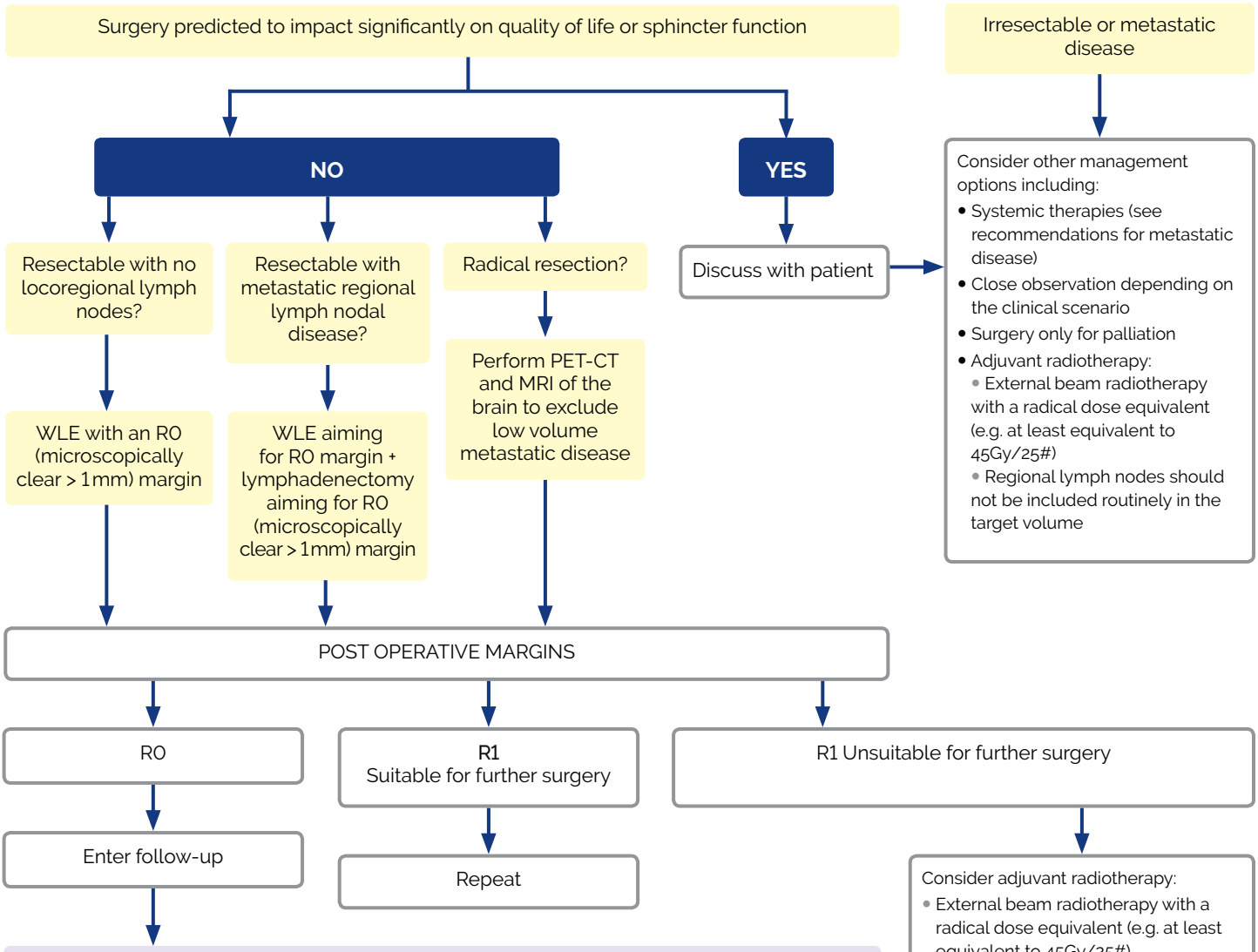
- Local staging should be as for common tumours at the anatomical site (vulva, vagina) and include:
  - External inspection/examination
  - Palpation of inguinal lymph nodes+/-US and FNA or core biopsy
  - Clinical examination including speculum examination and EUA as necessary if there is any suspicion of local recurrence.
  - Cystoscopy, if indicated clinically e.g. urethral involvement.
  - MRI pelvis
- Investigations looking for systemic disease are those generic for all anatomical sites including CT of the thorax, abdomen, and pelvis, including the groins. Consider MRI or CT of brain.
- If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered perform a PET-CT scan and MRI of the brain should be performed pre-operatively to exclude low volume metastatic disease.
- Record histological features - see Box 2
- Molecular Testing should occur as soon as practical, ideally at the time of first diagnosis.
- Test for BRAF, C-KIT, NRAS, GNAQ, GNA11.

SURGICAL PLANNING

- Surgery for vulvo-vaginal melanoma should be performed in centres regularly performing complex vulvo-vaginal surgery, and where the clinicians are regularly managing complex melanoma within a specialist melanoma multidisciplinary team.
- Assess patient's baseline morbidities 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.
- The aim of surgical management of vulval and vaginal melanomas should be to achieve an R0 (microscopically clear > 1mm) margin in the least radical fashion. There is no evidence that radical surgery has an impact on overall survival.
- 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.
- Resectability should be assessed by investigations outlined in the Staging Investigations section above.
- Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease.
- 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 lymph node biopsy is only recommended if it directs adjuvant treatment or clinical trial entry. Following a positive sentinel node there is the option to follow the patient clinical examination or by ultra sound or complete the nodal dissection depending on emerging data and/or consensus opinion.

Surgery predicted to impact significantly on quality of life or sphincter function

Irresectable or metastatic disease



FOLLOW-UP

- All patients should have rapid access to clinical review between appointments or after discharge if they have any concerns
- If appropriate, discuss the advantages and disadvantages of surveillance imaging as set out in NG14 1.9.16 http://optiongrid.org/option-grids/pdf/63/en_gb
- 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 should (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

ADJUVANT SYSTEMIC TREATMENT

- Choice guided by the most contemporary data.
- Emerging data in cutaneous melanoma supports the use of immunotherapy agents and BRAF targeted treatments in the adjuvant setting and consideration should be given for its use in AUG melanoma.

BOX 1

SIGNS AND SYMPTOMS OF POSSIBLE VULVO-VAGINAL MELANOMA

- 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

BOX 2

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 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.

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.

Except for vulval melanomas, 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.

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

METASTATIC DISEASE

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, e.g. anti-CTLA and anti-PD(L)1 monoclonal antibodies in selected fit patients.
4. 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.
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 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.
8. 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.
9. 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.
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

Follow-up

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.