Ano-uro-genital Mucosal Melanoma

Full Guideline

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Commissioning and funding innovative research, while providing support and information for patients, carers and healthcare professionals
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1 How to use this document

This document contains the background information, methodology, evidence reviews and the Guideline Development Group (GDG) discussion. It supports the recommendations made regarding the management of Ano-uro-genital (AUG) mucosal melanoma. The recommendations and care pathways are also contained in the separate Executive Summary **** which focuses on the management of patients with this condition and is therefore more accessible for practising clinicians. For convenience, the recommendations are repeated in this document—the numbering reflects that of the Executive Summary. The Appendices with the evidence tables, search strategies and other background information are also available ***** here. The abbreviations used in the document are detailed at the end of the document here.
2 Introduction

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

2.1 Epidemiology

Mucosal melanoma occurs at 3 main sites – the upper aerodigestive tract, the conjunctiva, and the ano-rectum and uro-genital tracts. The latter group is the subject of this guideline. Data from Public Health England (PHE) shows that between 2010 and 2013, there were 437 cases of melanoma affecting ano-rectal 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 (1,2) shows 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 ano-uro-genital (AUG) melanoma.

There may be variations in survival across different cancer networks, and poorer survival may be attributable to late presentation or delays in diagnosis and initiation of treatment.

2.2 Current practice

It is unclear to what extent current practice for skin melanoma should inform decisions for people with AUG melanoma. It is also unclear how the American Joint Committee on Cancer (AJCC) Tumor Node and Metastasis (TNM) cutaneous melanoma staging system applies to this group of patients.

At present, even the 8 edition of the TNM staging system would not appear to be appropriate or accurate, suggesting that future revisions of the AJCC/TNM staging should consider including a small section on these tumours (https://cancerstaging.org/references-tools/quickreferences/documents/melanomasmall.pdf).

The majority of AUG melanomas are diagnosed as a result of appearance, in the case of vulval melanoma, or by bleeding from the ano-rectum or uro-genital tracts. Many will be referred via the 2-week wait process.

Most will have either a biopsy or, less commonly, complete excision of the melanoma, pathological analysis, and subsequent wide local excision (WLE). There remains some uncertainty about optimal final excision margins for cutaneous melanoma, and this topic is the subject of current research. This is especially relevant to this group, who are more likely to have more advanced primary disease.

Imaging (for example CT, MRI or PET-CT) for staging purposes is indicated for all people diagnosed with AUG melanoma. Sentinel node biopsy (SNB) is used to stage skin melanomas according to the AJCC staging system. It is also used to identify people who might be eligible for adjuvant therapy clinical trials and to stratify during analysis of those trials. However, SNB has not been shown to confer any survival advantage and the cost effectiveness of SNB is uncertain. Its applicability to people with AUG melanoma is unclear. There is thought to be variation in practice in the use of CT and PET-CT imaging for people with more advanced disease.
Adjuvant chemotherapy and immunotherapy are not currently indicated for the management of skin melanoma and continue to be the subject of research trials. Adjuvant radiotherapy for stage IIIB and IIIC melanoma is used on the basis of one randomised study showing reduced risk of loco-regional recurrence, but it does not appear to confer a survival advantage. The relevance of these findings to people with AUG melanoma is uncertain, especially as the sites of their disease frequently limit the extent of curative surgical resection. Some people with small numbers of apparently localised metastases to other organs may also be offered surgical resection, although this is not supported by randomised trial evidence.

People whose metastatic melanoma carries CKIT mutations may be treated with specific CKIT inhibitors. Other drugs used in people with advanced skin melanoma, such as BRAF and MEK inhibitors, are less likely to be relevant to people with AUG melanoma. These drugs have a very rapid effect on tumours but unfortunately the majority of people who take them develop resistance and the tumour relapses.

People with systemic metastases whose tumours are not found to carry BRAF mutations are usually treated with immunotherapies using ipilimumab, or with a PD1 inhibitor. The utility of these treatments for patients with AUG melanoma is uncertain. Chemotherapy with dacarbazine may be used but response rates are low.

Radiotherapy may be used to treat isolated cerebral metastases and for palliation.

2.3  Strengths and limitations of the evidence

Mucosal melanomas are rare and, as with other rare cancers, there is a paucity of Level 1 evidence to guide the management of patients with these tumours. Therefore, the main principles used in the creation of these guidelines has been to elicit as much information as possible from prospective and retrospective series, particularly the latter when AUG melanomas have been included within prospective trials and studies of cutaneous melanoma.

There is general agreement in the literature that AUG melanomas have a poor prognosis and appear to be more aggressive than cutaneous melanomas; however, that this behaviour may be explained at least in part, by the late diagnosis of primary lesions and their consequent thickness at diagnosis.

There is also very good evidence that AUG melanomas are distinct disease entities to cutaneous melanoma as evidenced by the substantial differences seen in their molecular profiles (3)

The lack of randomised data should not prevent those treating clinicians AUG patients from coming together and producing agreed guidance and algorithms, which can then be audited with a view to furthering our knowledge of the behaviour of these cancers. Further, such guidelines would highlight questions that need to be taken forward into prospective studies, randomised clinical trials and research, where possible.

2.4  Risks versus benefits

The risks of producing clinical guidance based on low levels of evidence are that patients may not receive what is subsequently discovered to be the best treatment. However, unless there is a degree of uniformity and consistency in how AUG melanoma patients are treated in England, it is
unlikely that these rare tumours further useful information will be obtained from clinical evidence, because future case series will suffer from the same problems as those in the past.

The benefits of tertiary centres adhering to the same proposed guidelines and algorithms are that within a relatively short period of time more accurate outcome data can be obtained, which will then form a robust basis to build our knowledge on, AUG melanoma patients. Furthermore, such data are likely to encourage international collaborations, which would not only include the collating of larger data sets, but also to stimulate the development of prospective randomised clinical trials.

2.5 Acknowledgements

In final document, thank Melanoma Focus, Jess and the NCGC, BAD and consultees here
3 Scope and purpose

3.1 Aim of the guideline

The aim of this guidance on AUG melanoma treatment is to improve patient care by providing clinicians with the best advice available for patient management and the evidence on which that guidance has been based. This guidance will also help to reduce variations in practice across England, and may contribute towards reducing inequality of access to the best advice and therapy.

3.2 Population

3.2.1 Groups that will be covered:
- Children, young people and adults with primary AUG melanoma. (No data on children/adolescents but these guidelines should be used in these patients in the absence of evidence)
- Subgroups identified as needing specific consideration will be considered during development of the guideline.

3.2.2 Groups that will not be covered:
- People with primary conjunctival melanoma.
- People with mucosal melanomas at other sites e.g. upper GI tract, head and neck,
- People with cutaneous melanoma presenting with secondary spread to an AUG site

3.3 Healthcare setting

All primary, secondary and tertiary care settings in which NHS-funded care is provided.

3.4 Clinical management

3.4.1 Key clinical issues that will be covered
- The specific information and support needs of people with AUG melanoma and their carers at diagnosis, at treatment planning, and during and after treatment.
- The best approach to increasing clinical diagnostic accuracy and appropriate prompt excision.
- The best approach to resolving clinico-pathological diagnostic uncertainty for borderline melanocytic lesions.
- The best approach for mutation testing of tumours for prognostic and predictive purposes.
- The most effective method of staging melanoma:
- The role of sentinel lymph node biopsy in newly diagnosed melanoma.
- Imaging for newly diagnosed and recurrent AUG melanoma.
- The most effective surgical treatment for stage 0-II AUG melanoma.
- The most effective surgical treatment for stage III AUG melanoma (including the effectiveness of sentinel lymph node biopsy).
- The indications for adjuvant radiotherapy for stage I-III AUG melanoma after resection.
- The most effective treatment for relapsed loco-regional melanoma metastases.
- The role of systemic anti-cancer therapy in the treatment of metastatic melanoma including targeted treatment and immunotherapy.
- The optimum methods, setting and frequency of follow-up for people with AUG melanoma.
3.5 Clinical issues that will not be covered

- Awareness and prevention of melanoma.
- End-of-life care.
- Complementary therapies.

3.6 Main outcomes

- Overall survival.
- Disease-free survival.
- Progression-free survival.
- Melanoma-related morbidity.
- Melanoma-related mortality.
- Treatment-related morbidity.
- Treatment-related mortality.
- Psychological wellbeing.
- Number and length of admissions to hospital after diagnosis.
- Number and severity of adverse events.
- Health-related quality of life.
- Cost effectiveness.
- Patient-reported outcomes.

3.7 Economic aspects

- Developers will search for evidence of both clinical and cost effectiveness and take this into account when making recommendations involving a choice between alternative interventions for AUG Melanoma.

3.8 Review Questions

The questions that the guideline included:

<table>
<thead>
<tr>
<th>Question</th>
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<tbody>
<tr>
<td>What are the individual information and support needs of patients with AUG melanoma?</td>
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4 Methodology

The guideline was convened by Melanoma Focus, a national charity with a professional core membership undertaking research and education in the field of melanomas and skin cancers ([http://melanomafocus.com/activities-2/um-guidelines-resources/](http://melanomafocus.com/activities-2/um-guidelines-resources/)). The development of the guideline was started by Dr Jerry Marsden, who is dermatologist with an interest and expertise in mucosal melanoma. Dr Marsden led the initial scoping, scoping search and advertising for guideline development group (GDG) members. Dr Marsden stepped down as the GDG lead, following the initial GDG establishment phase, as he is a trustee of Melanoma Focus and Prof. Martin Gore, a medical oncologist with an interest and expertise mucosal melanoma, became the ultimate GDG chairman of the guideline development group. Prof Gore was responsible for selecting the GDG, finalising the scope and led the GDG discussions.


4.1 Recruitment of GDG

The guideline development was advertised on the Melanoma Focus Website along with a downloadable application pack for those interested in applying to be a member of the GDG. In addition a letter was sent out to clinicians, teams and patient and professional organisations telling them of the planned development, and giving details of how to apply for membership of the GDG. They were asked to cascade the letter to those interested. Twenty people applied to be on the GDG.

The GDG comprised the following membership professions. A list of the actual members is to be found in the supplementary Appendix.

1. Gynaecological surgical oncologist
2. Urological surgical oncologist
3. Colorectal surgical oncologists
4. 2 plus chairman - Medical oncologists
5. 2 - Clinical oncologist
6. 2 - Surgeons with a major interest in melanoma
7. 2 – Pathologists with expertise in melanoma and gynaecological, urological or colorectal oncology
8. 1 - Radiologist with expertise in melanoma and gynaecological, urological or colorectal oncology
9. 1 - Specialist cancer nursing with expertise in managing patients with colorectal oncology
10. 1 – Patient representative
11. 1- Surgical Research Registrar who acted as rapporteur
The guideline was unsuccessful in recruiting a second patient representative and a melanoma clinical nurse specialist.

4.2 Scoping

The scope and review questions were drafted and posted on the Melanoma Focus website. It was circulated amongst the melanoma community via Melanoma Focus’s mailing lists and sent to GDG applicants. The scope and review questions are detailed in Chapter 3.

4.3 Search, sifting and selection and evidence review

AUG melanoma is a rare condition and the evidence is almost exclusively limited to observational studies, mainly case series or retrospective review. It was decided to carry out a wide single search with the aim of capturing all of the research evidence. The search was undertaken in July 2016 with an update search in March 2017. The information scientists at the National Clinical Guidelines Centre (NCGC) (http://www.ngc.ac.uk/) conducted the searches and the initial sifting of the literature. These are detailed in Appendix B6 appendix in the supplementary APPENDIX document LINK.

The methods of the evidence reviews are detailed in the methodology manual as above. The NCGC provided methodological expertise and assistance at the start of the guideline; however but, most of the selection and reviewing of evidence was undertaken by GDG members with expertise in the topic.

The NCGC research fellow initiated the surgery question (Q2), which was the only question for which controlled trial evidence was found, and therefore the use of GRADE (http://www.gradeworkinggroup.org/) methodology was possible. Working with the GDG members with expertise on the topic, she undertook a GRADE review and presented it to the GDG. For further information on the definition of terms used in the review see the 2011 series in the Journal of Clinical Epidemiology (4)

The NCGC research fellow also selected the evidence, following the development of protocols with the GDG, for the follow-up and lymph node questions, and the GDG members with expertise in the topics reviewed the evidence and presented it to the GDG. For the radiotherapy and systemic therapy questions, GDG members undertook the selection and evidence review and presentation to the GDG. In this guidance histopathological staging of the primary site was developed through a consensus of histopathologists on the GDG with input from the Royal College of Pathology. There are no relevant prospective Phase III data to guide staging investigations or follow up, and therefore a pragmatic approach was taken to use those investigations that have been agreed for the loco-regional staging of common tumours at the anatomical sites in question.

For the detection of systemic disease, we have employed the common strategies used pre-operatively for patients with high-risk cutaneous melanoma e.g. stage III disease. Similarly, in the absence of robust randomised data, there were 2 principles that guided the development of the follow-up recommendations: firstly, the strategies and schedules used in randomised trials; and secondly, the emerging data that there is a sub-set of patients who obtain durable clinical remissions lasting many years following immunotherapy, and these patients appear to have relatively low volumes of disease and normal serum LDH.
There are no data on multidisciplinary care in AUG melanoma, and therefore the general principles of multidisciplinary care are re-stated in these guidelines but with one addition; we are emphasising the importance of communication between different multidisciplinary teams (MDT) because very often patients require input from melanoma specialists as well as anatomical site specialists.

4.4 Consultation

The relevant professional and patient colleges, societies and organisations were identified and nominations for individuals to review the guideline were sought from GDG members. Individuals were asked to forward the document on to colleagues. The consultation was also posted on the Melanoma Focus website and anyone could comment. XXX Organisations and XXX individuals were invited to review the draft guideline and XXX organisations and XXX individuals sent in comments. Comments were processed and used according to the methods detailed in the handbook.
5 General guidance

Where there was no specific evidence, the GDG made recommendations based on discussion and consensus. This chapter contains summaries of the issues discussed for each topic.

5.1 Patient Focussed care - What are the individual information and support needs of patients with AUG melanoma?

The GDG recognises that there is a lot of good general information on patient-focussed care; however, for patients with these rare condition AUG melanomas, there is relatively little. Only one leaflet was found on the Dermnetnz website. (http://www.dermnetnz.org/topics/mucosal-melanoma) Recommendations for the patient focussed care were based on the experience of GDG members, and in particular the patient representative, who had had experience of caring for a family member with AUG Melanoma.

The gaps identified were:

**Information** – it is difficult to find well-validated information for this these rare AUG melanomas. Patients and their carers need a portal of entry for advice.

**Prognosis** – In many cases, a discussion of prognosis was avoided. While many patients will not want a frank discussion about their prognosis, some do and the opportunity should be given. In addition, with the patient’s permission, relatives may want the opportunity to discuss, discuss this directly with the clinician.

**Communication, Co-ordination and Planning** – there was a lack of communication amongst healthcare professionals, and patients and carers are asked for the same information over and over. When there is a crisis, carers may not know who they should to call. There was also little planning for events, therefore when a patient becomes very unwell, there can be a wait for necessary equipment. There was a discussion about the advantages and disadvantages of early referral to palliative care services.

**Information for patients and carers** - In addition to the recommendations, a three patient information leaflets, one for each anatomical site, will be written, based on the recommendations in the guideline, which will be distributed via the cancer nursing networks. Melanoma Focus are also adding information on mucosal melanoma to their database of FAQ’s for the helpline, providing online counselling and a patient decision-making tool.

<table>
<thead>
<tr>
<th>Recommendations for all AUG Mucosal Melanomas - Patient focused care</th>
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<tr>
<td>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 way.</td>
</tr>
</tbody>
</table>
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 groins are a common site for local 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.

5.2 Multi-disciplinary Team Meetings (MDT) - What is the best way of ensuring effective multi-disciplinary care for people with AUG melanoma?

The principles of MDT meetings and their importance for patient care has been well-established and discussed in many arenas. AUG melanoma presents the problem that almost invariably the expertise of more than one MDT is required. Knowledge of melanoma is essential when planning treatment, but so too is the knowledge and experience of the management of tumours at the particular AUG anatomical site, particularly in relation to the possibly required surgery.

GDG members quickly and unanimously came to the conclusion that teams in secondary and especially tertiary care need to have clearly defined pathways between the MDTs that are likely to be involved in the care of patients with AUG melanoma. There was also unanimity that in view of the rareness of this group of tumours, care should be delivered in tertiary centres with subsequent follow-up being either at that centre or within secondary or primary care, depending on local circumstances and expertise. Follow-up should be clearly defined by the tertiary centre.

Patient management must be discussed, by both the specialist melanoma team, which deals with patients who have advanced local or metastatic disease, and the relevant team that is defined by the anatomical site of the mucosal melanoma. The tumour staging of patients should be undertaken according to the guidance set out in this document. Ideally, a member of the specialist melanoma team should be present at the anatomical site team meeting and/or vice versa. Failing this, a named consultant from each team should be in direct communication after both MDT meetings to discuss and agree the final recommendation for the patient management. This function must not be delegated to the CNS or junior medical staff.

As with all MDT meeting decisions, clear annotations must be made that define treatment and follow up. In particular, it must be clearly documented within the patient notes which particular
The clinical team will be responsible for steering the patient through the treatment pathways, even though the patient may have to attend 2 different clinics for a time. It will be the responsibility of that ‘lead’ team to ensure that the first follow-up appointments are communicated to the patient.

The anatomical site specialist pathologist should be encouraged to seek a second opinion on the pathology should there be any doubt about the diagnosis. It is unnecessary and wasteful for the radiology to be reviewed by 2 radiologists, unless there are doubts about the findings.

We are recommending that the primary responsibility for reviewing the imaging is the radiologist at the anatomical site specific MDT meeting, since they are in the best position to give an accurate assessment of any loco-regional spread of the disease and they will also have generic expertise in the diagnosis of metastatic cancer.

Table: Recommendations for all AUG Mucosal Melanomas - Multi-disciplinary team meetings

5. 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 MDTs.
- 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 MDT discussion, a named consultant responsible for the patient’s care should communicate directly with other consultants involved about all aspects of the management of the patient. This communication must be entered into the patient notes and copied to the patient’s general practitioner so that all communication can be audited.

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

5.3 Recognition and referral - What are the signs and symptoms that should trigger non-specialists to refer a patient for a suspected AUG melanoma?

Patients with AUG melanomas tend to present later than those with skin melanomas, as the lesions are usually not readily visible. When the patients do present, AUG melanoma may not be suspected. AUG melanoma, being such a rare condition, non-specialists are unlikely to have seen it or previously learned much about it. The aim of this section is to assist non-specialists clinicians in recognising the key signs and symptoms and providing guidance on the optimal referral pathway. The GDG recognised that practice and family planning nurses who carry our cervical smears, if aware of the signs, may be able to identify and report lesions. Some photographs have been provided to assist in recognising the lesions.
Recomendations for Ano-Rectal Mucosal Melanoma - Recognition and referral

7. Refer to a colorectal surgeon or dermatologist with an interest in pigmented lesions 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.
   - Bleeding
   - Pain
   - Mass or swelling
   - Palpable lymph nodes associated with anal symptoms (e.g. in the groin)
   - Tenesmus
   - Pigmented lesions (refer to photos in section 9.2)
   - Atypical haemorrhoids
   - Polyps
   - Unexplained lumps

8. The anal margin should be carefully inspected, as not all melanomas are pigmented.

9. Be aware that the presenting symptoms of ano-rectal melanoma are similar to those of rectal cancer. The following may also be symptoms of ano-rectal melanoma:
   - Change in continence
   - Persistent itching (syn. Pruritus)
   - Constipation/diarrhoea (change in bowel habit).

10. Patients who present with an ano-rectal lesion and palpable groin lymph node(s) should also be referred for an ultrasound and biopsy of the suspicious node.

11. Diagnosis of the primary tumour should usually be made by excision- punch- or fine needle biopsy.

Recomendations for Vulval-Vaginal Mucosal Melanoma - Recognition and referral

53. Refer to a dermatologist with an interest in pigmented lesions/pigmented lesion clinic/joint gynaecology-dermatology clinic or a gynaecological oncology team via the urgent cancer referral pathway (e.g. the 2-week wait pathway), patients with any of the following symptoms or signs.
   - Melanocytic pigmentation (refer to photos in section 9.2)
   - Persistent itching
   - Lump or an ulcer
   - Bleeding
   - Difficulty in passing urine/urethral obstruction
   - Lump in the groin
   - Irregularly-edged pigmented lesion (black or dark brown, red, white or patchy coloured.
   - Vulval/vaginal lesion(s) with ulceration or contact bleeding
- Groin lymph node(s) enlargement
- Obstruction of urethral meatus
- Distant metastasis

54. Be aware that the pain/discomfort and discoloration (pigmented patches) may also be symptoms of vulvovaginal melanoma

55. 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 two week wait pathway).

56. Patients who present with vulva/vaginal lesions and loco-regional lymphadenopathy should be considered for ultrasound and FNA or core biopsy of lymph nodes.

57. Diagnosis of the primary tumour should usually be made by excision, punch- or fine needle biopsy.

**Recommendations for Penile Mucosal Melanoma - Recognition and referral**

96. Refer to a dermatologist with an interest in pigmented lesions/pigmented lesion clinic or urologist 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
- Presence of mole/lump on penis
- Pigmented lesion on glans 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

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

98. Patients who present with a penile lesion and palpable inguinal lymph nodes should also be referred for an ultrasound and FNAC/biopsy of the inguinal node.
Diagnosis of the primary tumour should usually be made by excision biopsy or punch biopsy.
Ano-rectal melanoma

![Image of ano-rectal melanoma]

Fig. 1. Amelanotic melanoma of anal canal

Early vulval melanoma  Common appearance of a *vulval* melanoma

![Image of early vulval melanoma]

Penile melanoma

5.4 Staging- What is the best approach to staging AUG melanoma patients with Stage I-III disease?

At present the 8th Edition of the American Joint Committee on Cancer (AJCC) Tumor Node and Metastasis (TNM) staging system is the main one used for the clinical and pathological staging of most (but not all) mucosal melanomas (5).

Staging of the vulvovaginal and penile mucosal melanomas are addressed in Chapter 47 “Melanomas of the Skin” of this (and also the 7th) Edition of the AJCC/TNM system (6). Whilst this may be appropriate for the smaller melanomas arising in the labia majora or from the penile foreskin or shaft, it may not be considered sufficiently accurate since the skin melanoma staging system does not necessarily take into account the particular anatomical structures of these regions (e.g. labia minora, glans penis, urethra etc.). However, alterations in the AJCC/TNM staging systems can only be based on evidence in the literature, and it is likely that due to the rarity of the vulvovaginal and urogenital melanomas that change has not been (or could not be) instigated as yet. Interestingly, cervical mucosal melanomas have also been clinical staged by some investigators using the FIGO (International Federation of Gyneacological Oncologists) staging system, which is actually designed for cervical carcinomas (7).

It is important to note that there is no specific AJCC system for mucosal melanomas of the anus (4). This is clearly stated at the beginning of the Anus Chapter in both the 7th and 8th AJCC/TNM staging systems. Despite this, clinical investigators are utilizing a mixture of both the skin melanoma and anal carcinoma staging systems in describing clinical and pathological disease extent. Future multicentre collaborative studies would possibly overcome this deficit, and allow for evidence-based treatment evaluations.

Interestingly, there are separate chapters in the AJCC/TNM addressing the mucosal melanomas of the Head and Neck (8,9) and of the Conjunctiva (9,10) respectively, in this large volume. The Head- and-neck mucosal melanoma staging system was introduced into the AJCC in 2010, whilst that for the conjunctiva melanomas appeared earlier in 1992. More recently used and alternate staging systems of the head-and-neck melanomas (11,12) have been demonstrated by comparative studies with the TNM staging to be less precise in their prognostication (13,14). The presence of these separate chapters for specific anatomical sites raises the question whether it could not be possible to add distinct chapters on “Vulvovaginal melanoma”, “Penile melanoma” and “Anal Melanoma” to future volumes of the AJCC, if the scientific evidence were to be collated across centres. Alternatively, a specific AJCC/TNM staging chapter dedicated to mucosal melanomas – including all organ systems – could be considered.

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### Recommendations for Ano-Rectal Mucosal Melanoma - Staging Investigations

12. Local staging should be as for common tumours at the anatomical site (anus, rectum) and include:

- External inspection/examination
- Palpation of inguinal lymph nodes
- Digital examination
- Examination Under Anaesthetic [EUA], Proctoscopy + flexible +/- sigmoidoscopy
13. 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 MR or CT of brain.

14. If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered a PET-CT scan should be performed.

15. Carry out BRAF, NRAS and CKIT mutational testing

---

**Recommendations for Vulval-Vaginal Mucosal Melanoma – Staging Investigations**

58. Local staging should be as for common tumours at the anatomical site (vulva, vagina) and include:
   - External inspection/examination
   - Palpation of inguinal lymph nodes
   - EUA including speculum examination
   - Cystoscopy, if indicated clinically e.g. urethral involvement.

59. 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 MR or CT of brain.

60. If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered a PET-CT scan should be performed

61. Carry out BRAF, NRAS and CKIT mutational testing

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**Recommendations for Penile Mucosal Melanoma - Staging Investigations**

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

101. 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 MR or CT of brain.
102. If radical penile surgery is being considered, PET-CT and MR of the brain should be performed pre-operatively to exclude low volume metastatic disease.

103. Carry out BRAF, NRAS and CKIT mutations testing
6 Surgical treatment

6.1 Introduction

Stage 0-3 malignant melanomas originating from the anorectal or urogenital mucosae represent potentially curable disease. However, as a consequence of the rarity of these malignancies, there is limited evidence in the literature regarding their optimal management to guide clinicians. A common theme encountered in the surgical treatment of AUG melanomas at these sites is the debate regarding whether the initial strategy should be radical or conservative. As the prognosis of patients with metastatic disease in this setting is poor, a radical approach is sometimes suggested as an approach that may appear to offer increased likelihood of controlling local disease, and thereby preventing disease dissemination by removing the source. However, as has been noted with other malignancies, with the archetypal example being breast cancer, radical surgery does not necessarily equate to improved patient outcomes and wide negative margins may not confer additive survival benefit over narrow negative margins. Survival in mucosal melanomas is not usually determined by local disease but by metastatic disease, which occurs in the majority of patients regardless of local interventions. As survival may often be limited in the presence of metastatic disease, even in the era of effective systemic therapy, particular attention must be paid to the quality of life afforded by the initial surgical management. Due to their anatomical location, radical resections of melanomas are accompanied by a considerable risk of post-operative morbidity in terms of continence, sexual dysfunction and their resultant psychosocial impact. Hence, the key questions that must be answered in determining the optimal management of potentially curative disease are whether an initial radical approach improves survival in these patients and, if not, how loco-regional disease may be best controlled whilst maximising a patient’s quality of life.

6.2 Review question: What is the most effective surgical treatment for stage 0-III AUG melanoma to achieve clear margins and loco-regional disease control? And what are the appropriate margins?

For full details see review protocol in the appendix for this chapter in the supplementary APPENDIX document.

Table 1: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>AUG melanoma patients stage 0-III stratified by type of melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vulvovaginal</td>
</tr>
<tr>
<td></td>
<td>Urogenital</td>
</tr>
<tr>
<td></td>
<td>Anorectal</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention(s)</th>
<th>Vulvovaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vulvectomy, modified vulvectomy or vaginal surgery</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Urogenital (including penile)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total or partial penectomy or glansectomy</td>
</tr>
</tbody>
</table>
Anorectal
Wide local excision including trans-anal excision (TAE) and Trans-anal Endoscopic Micro-Surgery (TEMS)
Abdominoperineal resection (APR)
Abdominoperineal excision (APE)
Hemi abdominoperineal rectal resection

Comparison
The more radical surgical treatment in comparison with the more conservative

Outcomes
Patient-reported outcomes
Morbidity
Negative resection rate (R0 vs. R1 vs. R2)
Local recurrence-free survival (LRFS)
Overall survival (OS)
Disease-free survival (DFS)
Quality of Life

Study design
Systematic reviews, randomised control trials and non-randomised observation studies.

Pre-specified subgroups
Margins (R0 or R1)
Stage
Anatomical location
Thickness

6.3 Clinical evidence

We searched for randomised trials and non-randomised observational studies comparing the effectiveness of radical surgery with local surgery for people with anorectal, urogenital or vulvovaginal melanoma. No randomised controlled trials were identified. Thirty-six observational cohort studies, eight case-series and three systematic reviews were identified as matching the review protocol. Included studies are grouped by strata and summarised in Table 2 below. Further discussion and the evidence for effectiveness is summarised in sections 6.3.1, 6.3.3 and 6.3.2. See also, the appendix for this chapter in the supplementary APPENDIX document including forest plots in Appendix A1.2, study evidence tables in Appendix A1.3, GRADE tables in Appendix A1.4 and excluded studies list in AppendixA1.5 of this chapter. With respect to some of the excluded studies, if multiple studies were published from the same institution and the period of patient enrolment overlapped between multiple publications, the study with the longest time period was included in the review.

Due to the non-randomised nature of the evidence, the included studies on AUG melanomas offer more potential for bias; for example, in patient selection where the composition of treatment groups may differ in terms of important characteristics leading to possible confounding of the relationship between type of surgery and patient outcomes. While some studies conducted multivariable analysis, in order to control for possible baseline differences between groups (e.g. stage of melanoma, tumour depth and size, different use of adjuvant treatment, and widely variable lengths of follow-up time), very few studies included the type of surgical treatment in their multivariable analysis. Therefore, the majority of the evidence included is at high risk of bias. Lack of controlling for differences in the presence of possible confounders within the population of different studies may contribute to inconsistency in the study results. This is taken into account in the GRADE quality ratings for those studies where unadjusted raw data were available to enter into meta-analysis. Some studies included small percentages of patients with distant metastases (stage IV), who are considered outside the population focus for this question (stage 0-III). Where necessary the
indirectness of the study population is noted in the clinical evidence tables for these particular studies. For further information on the GRADE methodology and terminology see the series by Guyatt et al. (15,16)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and comparison</th>
<th>Population</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strata 1: Anorectal</td>
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<tr>
<td>Antoniuk (17)</td>
<td>Transanal local excision</td>
<td>Primary malignant melanoma</td>
<td>5-year survival (rate)</td>
<td>No statistical analysis performed (case series).</td>
</tr>
<tr>
<td>USA</td>
<td>Abdominoperineal resection</td>
<td>n=15</td>
<td>Disease-free survival (median)</td>
<td></td>
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<tr>
<td></td>
<td>Follow-up duration not reported</td>
<td></td>
<td>Overall survival (median)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Local recurrence (rate)</td>
<td></td>
</tr>
<tr>
<td>Belli (18)</td>
<td>Local excision</td>
<td>Anorectal melanoma n=40</td>
<td>Overall survival (median and rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Italy</td>
<td>Radical surgery</td>
<td>Median follow-up time: 75 months</td>
<td>5-year survival (rate)</td>
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<td></td>
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<td>Disease-free survival (median and rate)</td>
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<td></td>
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<td>Local recurrence (rate)</td>
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<tr>
<td>Bullard (19)</td>
<td>Wide local excision</td>
<td>Anorectal melanoma n=15</td>
<td>Local recurrence (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>USA</td>
<td>Abdominoperineal resection</td>
<td>Median follow-up time: 16 months</td>
<td>Overall survival (rate)</td>
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<td></td>
<td></td>
<td></td>
<td>Disease-free survival (rate)</td>
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<tr>
<td>Che (20)</td>
<td>Wide local excision</td>
<td>Anorectal melanoma n=56</td>
<td>5-year overall survival (rate and median)</td>
<td>Effectiveness of surgery type not statistically significant at the univariate level so not entered into the multivariable analysis</td>
</tr>
<tr>
<td>China</td>
<td>Abdominoperineal resection</td>
<td>Follow-up range: 4-144 months</td>
<td>Local recurrence (rate)</td>
<td></td>
</tr>
<tr>
<td>Choi (21)</td>
<td>Wide local excision</td>
<td>Anorectal melanoma n=19</td>
<td>5-year overall survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Korea</td>
<td>Abdominoperineal resection</td>
<td>Follow-up duration not reported</td>
<td>Overall survival (mean)</td>
<td></td>
</tr>
<tr>
<td>David (22)</td>
<td>Wide local excision</td>
<td>Anorectal melanoma</td>
<td>Local recurrence (rate)</td>
<td>No multivariable analysis.</td>
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<tr>
<td></td>
<td>Abdominoperineal resection</td>
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<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
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<tr>
<td><strong>India</strong></td>
<td>resection</td>
<td>n=17</td>
<td>Mean follow-up: 8 months</td>
<td></td>
</tr>
<tr>
<td>Droesch (23)</td>
<td>Systematic review – identified and included as a reference checking document.</td>
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<tr>
<td><strong>Hicks 2014 USA</strong></td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Anorectal melanoma n=18 Median follow-up: 18.5 months</td>
<td>Overall survival (median and rate) Recurrence (median and rate)</td>
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<tr>
<td><strong>Iddings (24) Chen (25) USA</strong></td>
<td>Transanal excision Abdominoperineal resection</td>
<td>Anorectal melanoma without distant metastases n=183 Follow-up duration not reported</td>
<td>Overall survival (median) 5-year survival (rate)</td>
<td>Multivariable analysis provided in Chen 2016 for similar cohort of patients.</td>
</tr>
<tr>
<td><strong>Ishizone (26) Japan</strong></td>
<td>Local excision Abdominoperineal resection</td>
<td>Anorectal melanoma n=79 Follow-up duration not reported</td>
<td>Overall survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Kanaan (27)</td>
<td>Systematic review – identified and included as a reference checking document.</td>
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<tr>
<td><strong>Knowles (28) Australia</strong></td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Anal melanoma n=16 Follow up: 18 years</td>
<td>Local recurrence (rate) Disease-free survival (mean)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td><strong>Konstadoulakis (29) USA</strong></td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=15 Follow-up duration not reported</td>
<td>Local recurrence (rate) Overall survival (median and rate) Average hospital stay (mean)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td><strong>Luna-Perez (30) Mexico</strong></td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=15 Follow-up duration not reported</td>
<td>Local recurrence (rate) Overall survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td><strong>Malik (31)</strong></td>
<td>Local excision Abdominoperineal</td>
<td>Primary anorectal melanoma</td>
<td>Local recurrence (rate)</td>
<td>No statistical analysis performed (case)</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
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<tr>
<td>USA</td>
<td>resection</td>
<td>n=19</td>
<td>Overall survival (rate)</td>
<td>series)</td>
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<td>Matsuda</td>
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<td>Moozar (33)</td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=14 Minimum follow-up 28 months</td>
<td>Overall survival (median)</td>
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<tr>
<td>Nilsson (34)</td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=251 Follow-up duration not reported</td>
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<td>Effectiveness of surgery type not statistically significant at the univariate level so not entered into the multivariable analysis.</td>
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<tr>
<td>Perez (35)</td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma without metastatic disease n=65 Median follow-up: 20 months</td>
<td>Recurrence-free survival (median) Recurrence-free 5-year survival (rate) Disease-specific survival (median) Disease-specific 5-year survival (rate)</td>
<td>Effectiveness of surgery type not statistically significant at the univariate level so not entered into the multivariable analysis.</td>
</tr>
<tr>
<td>Pessaux (36)</td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=40 Follow-up duration not reported</td>
<td>Morbidity (rate) Duration of hospital stay 5-year overall survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Ramakrishnan (37)</td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Stage I patients with anorectal melanoma n=63 Follow-up duration not reported</td>
<td>Local recurrence Overall survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Ross (38)</td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=32</td>
<td>Local recurrence Disease-free survival (median)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
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<tr>
<td>Roumen (39)</td>
<td>Local surgery Abdominoperineal resection</td>
<td>Follow-up duration not reported Primary anorectal melanoma n=63</td>
<td>Local recurrence 5-year survival (rate) Overall survival (median and rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>The Netherlands</td>
<td></td>
<td>Follow-up duration not reported</td>
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</tr>
<tr>
<td>Slingleluff (40) USA</td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=24 Duration of follow-up 26.4 months</td>
<td>Disease-free survival (mean) Overall survival (median and rate)</td>
<td>Surgery type not significant in Cox multivariable analysis.</td>
</tr>
<tr>
<td>Thibault (41) USA</td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=50 Follow-up range: 66 months to 44 years</td>
<td>Recurrence (rate) Disease-free survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Wang (42) China</td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=43 Median follow-up time: 20 months</td>
<td>5-year overall survival (median and rate) Disease-free survival (median and rate)</td>
<td>Surgery type not significant at univariate level so not entered into multivariable analysis.</td>
</tr>
<tr>
<td>Weyandt (43) Germany</td>
<td>Wide local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=19 Follow-up range: 15-119 months</td>
<td>Overall survival (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td>Yen (44) Taiwan</td>
<td>Wide local excision Radical excision</td>
<td>Primary anorectal melanoma n=22 Follow-up duration not reported</td>
<td>5-year overall survival (rate) 2-year disease-free survival (rate) Local recurrence (rate)</td>
<td>Surgery type not significant at univariate level. No multivariable analysis.</td>
</tr>
<tr>
<td>Zhang (45) China</td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=54</td>
<td>5-year overall survival (rate) Overall survival</td>
<td>Surgery type not significant at univariate level. No multivariable analysis.</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
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</tr>
<tr>
<td><strong>Zhou (46) China</strong></td>
<td>Local excision Abdominoperineal resection</td>
<td>Primary anorectal melanoma n=57 Median follow-up: 37 months</td>
<td>Survival time (median) 5-year survival (rate) Local tumour recurrence (rate)</td>
<td>No multivariable analysis.</td>
</tr>
<tr>
<td><strong>Strata 2: Urogenital</strong></td>
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<tr>
<td>DiMarco (47) USA</td>
<td>Radical expiration Partial urethrectomy</td>
<td>Primary localised urethral melanoma n=11 Range of follow-up: 2-53 months</td>
<td>Recurrence (rate) Overall survival (rate)</td>
<td>Case-series only: no analysis.</td>
</tr>
<tr>
<td>Sanchez-Ortiz (48) USA</td>
<td>Radical penectomy Partial penectomy Wide local excision</td>
<td>Genitourinary melanoma n=16 Range of follow-up: 20-210 months</td>
<td>Recurrence (rate) Overall survival (rate)</td>
<td>Case-series only: no analysis.</td>
</tr>
<tr>
<td><strong>Strata 3: Vulvovaginal</strong></td>
<td></td>
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</tr>
<tr>
<td>Aziz (49) UK</td>
<td>Radical vulvectomy Wide local excision + lymph node dissection Wide local excision</td>
<td>Primary melanoma of the vulva n=9 Duration of follow-up time unclear</td>
<td>Overall survival (rate)</td>
<td>Case-series only: no analysis.</td>
</tr>
<tr>
<td>Bradgate (50) UK</td>
<td>Local excision Radical vulvectomy</td>
<td>Primary melanoma of the vulva (2% stage IV) n=50 Follow up: 6-25 years</td>
<td>Age-adjusted 5-year survival (rate)</td>
<td>Surgery type was not significant at univariate level so was not entered into multivariable analysis.</td>
</tr>
<tr>
<td>Catalano (51) Italy</td>
<td>Local excision Radical surgery</td>
<td>Primary melanoma of the vulva (13% stage IV) n=9 Average follow up: 50.2 months</td>
<td>Dead from disease at follow-up (rate) Local recurrence (rate)</td>
<td>Case-series only: no analysis.</td>
</tr>
<tr>
<td>Huang (52)</td>
<td>Conservative surgery (not defined)</td>
<td>Primary melanoma of the vagina (16%) 5-year survival (rate and median)</td>
<td>Surgery type was not significant at univariate</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------</td>
<td>------------</td>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>China</td>
<td>Radical surgery (including hysterectomy)</td>
<td>stage IV) n=31  Median follow up: 20.2 months</td>
<td>level so was not entered into multivariable analysis.</td>
<td></td>
</tr>
<tr>
<td>Irvin (53) USA</td>
<td>Wide local excision</td>
<td>Primary vaginal melanoma n=7  No follow-up information</td>
<td>Dead of disease (rate)  Local regional control (narrative)</td>
<td></td>
</tr>
<tr>
<td>Konstadoulakis (54) USA</td>
<td>Wide local excision Radical surgery</td>
<td>Primary melanoma of the female genital tract n=25  Mean follow-up: 74 months</td>
<td>5-year survival (rate)  Local recurrence (rate)</td>
<td></td>
</tr>
<tr>
<td>Look (55) USA</td>
<td>Wide local excision</td>
<td>Primary melanoma of the vulva n=16  Mean follow-up: 24 months</td>
<td>Recurrence (rate)  Overall survival (rate)</td>
<td></td>
</tr>
<tr>
<td>Miner (56) USA</td>
<td>Wide excision</td>
<td>Primary melanomas of the vagina n=35  No follow-up information</td>
<td>Recurrence-free survival (median)</td>
<td></td>
</tr>
<tr>
<td>Phillips (57) USA</td>
<td>Radical hemivulvectomy</td>
<td>Primary untreated melanoma of the vulva. n=71  No duration of follow-up information</td>
<td>Local recurrence (rate)</td>
<td></td>
</tr>
<tr>
<td>Scheistrøen (58) Norway</td>
<td>Local excision Vulvectomy and vulvectomy + groin dissection</td>
<td>Primary melanoma of the vulva n=75  Median follow-up time: 99 months</td>
<td>Local recurrence (rate)  Disease-free survival (risk ratio)  Type of surgery entered into Cox multivariable analysis for subgroup of those with stage I disease.</td>
<td></td>
</tr>
<tr>
<td>Sugiyama (60)</td>
<td>Conservative surgery</td>
<td>Primary melanoma of the vulva</td>
<td>5-year disease-specific survival (rate)  Type of surgery not significant in multivariable analysis.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>USA</td>
<td>Wide local excision</td>
<td>n=644</td>
<td>Survival (narrative)</td>
<td>Type of surgery not evaluated in multivariable analysis.</td>
</tr>
<tr>
<td></td>
<td>Hemivulvectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radical vulvectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimble (61)</td>
<td></td>
<td>Primary melanoma of the vulva</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td>n=84</td>
<td>Survival (narrative)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median follow-up time: 193 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xia (62)</td>
<td>Wide local excision</td>
<td>Lesions confined to the vagina</td>
<td>Positive margins (rate)</td>
<td>No multivariable analysis</td>
</tr>
<tr>
<td>China</td>
<td>Hemivulvectomy</td>
<td>and diagnosed with melanoma</td>
<td>Overall survival (median)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radical excision</td>
<td>n=44</td>
<td>Progression-free survival (narrative)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median follow-up time: 18.9 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 6.3.1 Anorectal melanoma – Narrative summary

Twenty-eight studies were identified that compared the effectiveness of radical surgery with local excision for anorectal melanoma. Twenty-four studies were non-randomised observational cohort studies. (18–22,24,26,28–30,34,63) A recent twenty-fifth observational study (25) was also included as providing supplementary data for an already included study. (24) Three case series that included data to allow a comparison between surgery types were also included. (17,31,33) Three systematic reviews were identified. (23,27,32) A recent twenty-fifth observational study (25) was also included as providing supplementary data for an already included study. (24) Three case series that included data to allow a comparison between surgery types were also included. (17,31,33) Three systematic reviews were identified. (23,27,32) A recent twenty-fifth observational study (25) was also included as providing supplementary data for an already included study. (24) Three case series that included data to allow a comparison between surgery types were also included. (17,31,33) Three systematic reviews were identified. (23,27,32) It was not possible to analyse results based on melanoma thickness (as this was described in various ways depending on whether the lead authors were predominantly colorectal or subspecialist melanoma surgeons). Similarly, there was variability in the description of anatomical location that hindered categorisation, such as using either locations such as anus/rectum/perianal, or noting the distance from the anal verge, or stating whether the tumour was below/at/or above the dentate line. Therefore, no sub-group analysis could be undertaken based on either tumour thickness or anatomical location; however, if this information was provided within the studies it was detailed in the clinical evidence tables for each included paper in Appendix A1.3.
6.3.1.1 Overall survival

Twenty-three studies (n=895) provided evidence on overall survival. (17–22, 24, 26, 28–31, 34, 63) Low quality evidence from the meta-analysis of 23 studies suggested that the chances of overall survival may be reduced for those who underwent more radical surgery, such as APR compared to those who underwent more conservative surgery, such as WLE (RR 0.8 [95% CI 0.6-1.07]); however, there was considerable uncertainty in the result. This uncertainty therefore means the effect estimate could be consistent with NO difference in overall survival based on which surgery type was performed.

Sub-groups were explored to see if differences in these pre-specified categories explained the heterogeneity in the results. Twelve studies (n=447) that specified they included a population of only those with R0 margins could be analysed separately. This sub-group analysis also suggested that chances of OS may be reduced for those who underwent more radical surgery, such as APR, compared to those who underwent more conservative surgery, such as WLE (RR 0.87 [95% CI 0.6-1.28]); however, the imprecision of the effect of this comparison was increased. Stage was also explored as a sub-group analysis. Available information in papers allowed for a comparison of the sub-groups for Stage I patients only with those patients who were Stage I & II (those without distant metastases). Meta-analysis of three papers (n=52) in patients with stage I only suggested that the original effectiveness of surgical procedure on OS was strengthened in this sub-group (RR 0.65 [95% CI 0.23-1.83]) but less in the six studies (n=272) from the sub-group of patients with stage I & II (no distant metastases; RR 0.86 [95% CI 0.5-1.48]). However, again it must be noted that there was very serious imprecision concerning the data provided. This evidence is summarised in Table 3. Forest plots are available in Appendix A1.2 and GRADE tables in Appendix A1.4 in the supplementary appendix.

Of the two studies that explored the effect of surgical procedure in multivariable cox regression analysis, one (25) reported that surgical procedure did not have a significant effect on survival when controlling for stage, tumour location or year of diagnosis. The second (40) reported that initial surgical type was not a significant factor for survival when controlling for stage, sex, age, race, and initial chemotherapy or immunotherapy.

Fourteen studies reported data for duration of overall survival in patients with anorectal melanoma (see...
These data were provided in a variety of ways (mean and median with variance measures of 95% confidence interval, standard deviation [SD] or interquartile range [IQR]), which precluded any 'pooling' of results. Therefore, individual duration estimates are provided in tables for interest only (no meta-analysis and GRADE ratings provided).

6.3.1.2 Disease-free survival

Seven (n=229) provided evidence on disease-free survival. (18,19,35,38,41,42,44) No clinically important differences between surgical procedures were found for rate of disease-free survival (RR 1.08 [95% CI 0.61-1.91]). Consideration of sub-groups suggested that this effect was stronger for those five studies (n=152) with only R0 margins achieved (RR 0.86 [95% CI 0.39-1.92]), and stronger still when considering the two studies (n=32) in only those patients with stage I & II disease (RR 0.52 [95% CI 0.12-2.26]); however, there is serious imprecision around both of these sub-group results.

This evidence is summarised in the Forest plots are available in Appendix A1.2 and GRADE tables in Appendix A1.4 in the supplementary appendix.

Seven studies reported data for duration of disease-free survival (see Table 7). This data was reported in a variety of ways (mean and median with variance measures of 95% confidence interval, SD [Standard Deviation] or IQR [Inter-quartile Range], which precluded pooling of results. Therefore individual duration estimates are provided in tables for interest only (no meta-analysis and GRADE ratings provided).

6.3.1.3 Local recurrence

Nineteen studies (n=638) provided evidence on local recurrence that could be meta-analysed and assessed using GRADE. (17–22,24,26,28–31,34,35,37–39,41,42,44,46,63) Low quality evidence from the meta-analysis suggests that those patients who have undergone radical surgery are less likely to experience local recurrence than those who underwent local excision (RR 0.71 [95% CI 0.44-1.14]). However, there was considerable uncertainty in the analysis. The uncertainty means the effect estimate could suggest that there is no difference in local recurrence based on the surgical procedure performed.

Consideration of sub-groups suggested that this effect was stronger for those with only R0 margins achieved (RR 0.49 [95% CI 0.23-1.04]; 9 studies, n=272). When considering the different stage sub-groups, there was a stronger effect for those patients with stage I disease only (3 studies, n=52) (RR 0.29 [95% CI 0.02-3.72]). Five studies (n=106) in the sub-group of those patients with stage I & II disease (no distant metastases) showed no difference in local recurrence based on the surgical procedure performed (RR 0.70 [95%CI 0.32-1.94]). However, for all these sub-group analyses, there was substantial uncertainty around the results. This evidence is summarised in Table 5. Forest plots are available in Appendix A1.2 and GRADE tables in Appendix A1.4 in the supplementary appendix.

6.3.1.4 Resection rate and margins

Four studies examining outcomes on anorectal melanoma offered data on resection rates and appropriate surgical margins. One study (35) showed that risk of microscopically incomplete tumour resection were slightly higher after wide local excision (22.5%) when compared with APR (16%); however, no comment regarding the clinical significance of this difference was offered. A second study (36) indicated that the 5-year OS was better for those patients with R1 microscopically positive margins (26%) than those with R0 margins (19%), although this was not statistically significant.
(p=0.402). In the same study in the sub-group of patients with R0 margins, those who underwent APR had better 5-year survival rates (30%) than those who underwent WLE (19%) although again this difference was not deemed statistically significant (p=0.513). Two studies offered details on resection status based on surgical procedure undertaken.\(^{(34,63)}\) However, only one study offered further details on survival status. \(^{(34)}\) In those patients in whom R0 resection status was achieved (76% who underwent APR and 26% who underwent WLE), median OS was longer in those who had WLE (38 months) compared to those who had undergone APR (17 months, p=0.011). In multivariable Cox hazard regression analysis, resection status was a significant prognostic factor for survival. The chances of survival for those patients with tumour positive post-surgical margins (R+) were significantly diminished compared to those in whom R0 margins were achieved (HR 0.53 [95% CI 0.37-0.77] p<0.001), when controlling for sex, age, tumour size, tumour stage and type of surgery.

### 6.3.1.5 Morbidity and patient-centred quality of life outcomes

No studies reported data on these outcomes.

### 6.3.2 Vulvovaginal melanoma – Narrative summary

Fourteen studies were identified that compared the effectiveness of radical surgery such as vulvectomy or vaginectomy with LE for vulvovaginal melanoma. Eleven studies were non-randomised observational cohort studies, two of which described the same population. \(^{(50,52,54–61,64)}\) Three case series that included data to allow a comparison between surgery types were also included. \(^{(49,51,53)}\) Sub-group analysis was not possible due to the diversity of the populations in the included studies.

### 6.3.2.1 Survival and recurrence

Eight studies (n=316) provided evidence on overall survival, \(^{(49–55,60)}\) and four (n=168) provided evidence on local recurrence, \(^{(51,54,57,59)}\) that could be meta-analysed and assessed using GRADE. Meta-analysis of eight studies provided low quality evidence that suggested there was NO difference in the overall survival for radical surgery, such as vulvectomy or vaginectomy, compared with local excision (RR 1.05 [95% CI 0.9-1.22]). Similarly there was also no clinically important difference between the two surgical procedures for the rates of local recurrence (RR 1.20 [95% CI 0.73-1.97]). This evidence is summarised in Table 8. Forest plots are available in Appendix A1.2 and GRADE tables in Appendix A1.4 in the supplementary appendix.

Of the three studies that explored the effect of surgical procedure in multivariable cox regression analysis, one (59) reported that there was no statistically significant difference in corrected survival between patients undergoing LE or radical vulvectomy. A sub-group analysis of only those with stage I disease found that those patients who have undergone LE were at greater risk of recurrence than those who (58) underwent radical vulvectomy with inguinal lymph node dissection (RR 5.930 [95% CI 1.663-21.15] p=0.006), when controlling for DNA non-diploid and angioinvasion (however, no further information on other confounders were controlled for). A third study (60) found that surgical procedure was not a statistically significant prognostic factor for worsened disease-specific survival in multivariable analysis, when controlling for older age, advanced stage, positive lymph nodes, ethnicity and radiation.
Two studies that did not provide any raw data on survival but some narrative data describe that the extent of initial surgery did not appear to affect overall survival \( (p=0.53) \) (61), and that there was no significant difference in PFS between the two surgical approaches \( (p=0.573) \). (64)

Two studies reported data for duration of overall survival and one study provided results for the duration of DFS (see Table 9). These data were reported as medians with no associated variance data (no meta-analysis or GRADE ratings provided).

### 6.3.2 Resection rate and margins

Only one study on vulval-vaginal melanoma (64) provided details about the surgical margins. Of those patients who underwent a WLE with specified margins of ≤2cm, 14% had microscopically positive margins post-surgery compared to 10% with positive post-surgical margins in the radical excision group \( (p=0.173) \). The authors concluded that there was no statistically significant correlation between survival and positive margins.

### 6.3.2 Morbidity and patient-centred quality of life outcomes

No studies reported data on these outcomes.

### 6.3.3 Urogenital melanoma – Narrative summary

Two case series with very small numbers of participants were identified that compared the effectiveness of radical surgery with local excision for urogenital melanoma. One study (47) compared radical expiration (including traditional pelvic exenteration or radical urethrectomy with bladder preservation) with partial urethrectomy for women with urethral melanoma. The second study (48) compared WLE with partial penectomy and radical penectomy in men with genitourinary melanoma. As both of these studies were case-series the evidence is at very high risk of bias.

#### 6.3.3.1 Survival and recurrence

In women with urethral melanoma (n=11) (47), 25% survived after radical surgery compared to 14% in those with partial urethrectomy. However, the single survivor in the radical group was only followed-up for 2 months, whilst the range of follow up for all 11 patients was 2-53 months. The recurrence rate was 50% in the radical surgery group and 57% in the partial surgery group. No multivariable analysis controlling for possible confounding factors was undertaken.

In men with genitourinary melanoma (n=16) (48), of those with mucosal melanoma (n=6; excluding those with melanoma of the scrotum and shaft), there was 40% survival in the partial penectomy group (3/5), and 100% in the group who had WLE (1/1). Recurrence rates were 20% in the partial penectomy group, and 0% in those who underwent WLE. No multivariable analysis controlling for possible confounding factors was undertaken.

#### 6.3.3.2 Morbidity and patient-centred quality of life outcomes

No studies reported data on these outcomes.
6.3.3.3 Resection rate and margins

2 No evidence on appropriateness of different surgical margins was identified.
### 6.3.4 Anorectal melanoma – Clinical evidence summary tables

#### Table 3: Clinical evidence summary: Overall survival radical surgery compared to local surgery for patients with anorectal melanoma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of patients (studies) Follow up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival: Total population</td>
<td>895 (23 studies)</td>
<td>⊕⊕⊕⊕ VERY LOW</td>
<td>RR 0.8 (0.6 to 1.07)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>167 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33 fewer per 1000 (from 67 fewer to 12 more)</td>
</tr>
<tr>
<td>Overall survival: MARGINS – R0 margins</td>
<td>447 (12 studies)</td>
<td>⊕⊕⊕⊕ VERY LOW</td>
<td>RR 0.87 (0.6 to 1.28)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>167 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22 fewer per 1000 (from 67 fewer to 47 more)</td>
</tr>
<tr>
<td>Overall survival: STAGE – Stage I only</td>
<td>52 (3 studies)</td>
<td>⊕⊕⊕⊕ VERY LOW</td>
<td>RR 0.65 (0.23 to 1.83)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>563 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>197 fewer per 1000 (from 434 fewer to 467 more)</td>
</tr>
<tr>
<td>Overall survival: STAGE – Stage I &amp; II (no distant metastases)</td>
<td>272 (6 studies)</td>
<td>⊕⊕⊕⊕ VERY LOW</td>
<td>RR 0.86 (0.5 to 1.48)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>261 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37 fewer per 1000 (from 131 fewer to 125 more)</td>
</tr>
</tbody>
</table>

1. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias
2. Downgraded by 1 increment as the confidence interval crosses one default line of minimally important difference
3. Downgraded by 2 increments as the confidence interval crosses both default lines of minimally important difference
4. Downgraded by 1 increments due to heterogeneity I-squared > 50%

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By Nancy Turnbull
### Table 4: Clinical evidence summary: Disease-free survival radical surgery compared to local surgery for patients with anorectal melanoma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of patients (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>229 (7 studies)</td>
<td>☹☹☹☹ VERY LOW(^1,2) due to risk of bias, imprecision</td>
<td>RR 1.08 (0.61 to 1.91)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Disease-free survival: MARGINS – R0 margins</td>
<td>152 (5 studies)</td>
<td>☹☹☹☹ VERY LOW(^1,2) due to risk of bias, imprecision</td>
<td>RR 0.86 (0.39 to 1.92)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Disease-free survival: STAGE – Stage I only</td>
<td>no evidence available</td>
<td>-</td>
<td>-</td>
<td>Moderate</td>
</tr>
<tr>
<td>Disease-free survival: STAGE – Stage I &amp; II (no distant metastases)</td>
<td>32 (2 studies)</td>
<td>☹☹☹☹ VERY LOW(^1,2) due to risk of bias, imprecision</td>
<td>RR 0.52 (0.12 to 2.26)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

1 Downgraded by 2 increments as the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the confidence interval crosses both default lines of minimally important difference
### Table 5: Clinical evidence summary: Local recurrence radical surgery compared to local surgery for patients with anorectal melanoma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of patients (studies) Follow up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk with LE</th>
<th>Risk difference with APR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>638 (19 studies)</td>
<td>✖️ ✖️ ✖️ ✖️ VERY LOW¹,²,³ due to risk of bias, inconsistency, imprecision</td>
<td>RR 0.71 (0.44 to 1.14)</td>
<td>Moderate</td>
<td></td>
<td>500 per 1000</td>
</tr>
<tr>
<td>Local recurrence: MARGINS – R0 margins</td>
<td>272 (9 studies)</td>
<td>✖️ ✖️ ✖️ ✖️ VERY LOW¹,²,³ due to risk of bias, inconsistency, imprecision</td>
<td>RR 0.49 (0.23 to 1.04)</td>
<td>Moderate</td>
<td></td>
<td>625 per 1000</td>
</tr>
<tr>
<td>Local recurrence: STAGE – Stage I only</td>
<td>52 (3 studies)</td>
<td>✖️ ✖️ ✖️ ✖️ VERY LOW¹,³,⁴ due to risk of bias, inconsistency, imprecision</td>
<td>RR 0.29 (0.02 to 3.72)</td>
<td>Moderate</td>
<td></td>
<td>750 per 1000</td>
</tr>
<tr>
<td>Local recurrence: STAGE – Stage I &amp; II (no distant metastases)</td>
<td>106 (5 studies)</td>
<td>✖️ ✖️ ✖️ ✖️ VERY LOW¹,³,⁴ due to risk of bias, inconsistency, imprecision</td>
<td>RR 0.79 (0.32 to 1.94)</td>
<td>Moderate</td>
<td></td>
<td>647 per 1000</td>
</tr>
</tbody>
</table>

1 Downgraded by 2 increments as the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment as the confidence interval crosses one default line of minimally important difference
3 Downgraded by 2 increments due to heterogeneity I²-squared > 75%
4 Downgraded by 2 increments as the confidence interval crosses both default lines of minimally important difference
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Radical surgery</th>
<th>Local excision</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniuk 1993</td>
<td>Mean</td>
<td>29 months</td>
<td>22 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>11-72</td>
<td>6-82</td>
<td></td>
</tr>
<tr>
<td>Belli 2009</td>
<td>Median</td>
<td>17 months</td>
<td>17 months</td>
<td>(p=0.91)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>15-31</td>
<td>12-49</td>
<td></td>
</tr>
<tr>
<td>Che 2011</td>
<td>Median</td>
<td>22 months</td>
<td>21 months</td>
<td>(p=0.645)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Choi 2011</td>
<td>Mean</td>
<td>66.1 months</td>
<td>11.2 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>9-103</td>
<td>7-13</td>
<td></td>
</tr>
<tr>
<td>Hicks 2014</td>
<td>Median</td>
<td>11.5 months</td>
<td>13.5 months</td>
<td>(p=0.75)</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>3.2-15.3</td>
<td>1.5-57.3</td>
<td></td>
</tr>
<tr>
<td>Iddings 2010</td>
<td>Median</td>
<td>16 months</td>
<td>18 months</td>
<td>(p=0.775)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Knowles 2016</td>
<td>Unclear</td>
<td>216 days</td>
<td>479 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Moozar 2003</td>
<td>Median</td>
<td>12 months</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5-51</td>
<td>3-39</td>
<td></td>
</tr>
<tr>
<td>Nilsson 2010</td>
<td>Median</td>
<td>17 months</td>
<td>38 months</td>
<td>(p=0.011)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Perez 2013</td>
<td>Median</td>
<td>27 months</td>
<td>19 months</td>
<td>(p=0.2)</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>10-51</td>
<td>13-30</td>
<td></td>
</tr>
<tr>
<td>Ross 1990</td>
<td>Median</td>
<td>19.5 months</td>
<td>18.9 months</td>
<td>(p=not)</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td>significant</td>
</tr>
<tr>
<td>Slingluff 1990</td>
<td>Mean</td>
<td>34.0 months</td>
<td>33.4 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>12.1</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Wang 2013</td>
<td>Median</td>
<td>22 months</td>
<td>32 months</td>
<td>(p=0.279)</td>
</tr>
</tbody>
</table>

Table 6: Duration of overall survival: radical surgery compared to local surgery for patients with anorectal melanoma
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Radical surgery</th>
<th>Local excision</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang 2010</td>
<td>Median</td>
<td>25 months</td>
<td>13 months</td>
<td>p=0.281</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.28</td>
<td>18.62</td>
<td></td>
</tr>
<tr>
<td>Zhou 2010</td>
<td>Median</td>
<td>32.3 months</td>
<td>35.9 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

1

2

**Table 7**: Duration of disease-free survival: radical surgery compared to local surgery for patients with anorectal melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Radical surgery</th>
<th>Local excision</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniuk 1993</td>
<td>Mean</td>
<td>19 months</td>
<td>14 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5-45</td>
<td>1-53</td>
<td></td>
</tr>
<tr>
<td>Belli 2009 4</td>
<td>Median</td>
<td>7 months</td>
<td>9 months</td>
<td>p=0.97</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>6-15</td>
<td>5-18</td>
<td></td>
</tr>
<tr>
<td>Hicks 2014</td>
<td>Median</td>
<td>2.5 months</td>
<td>13.2 months</td>
<td>p=0.7</td>
</tr>
<tr>
<td></td>
<td>IQR</td>
<td>2.0-10.8</td>
<td>6.1-33.3</td>
<td></td>
</tr>
<tr>
<td>Perez 2013</td>
<td>Median</td>
<td>18 months</td>
<td>8 months</td>
<td>p=0.36</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ross 1990</td>
<td>Median</td>
<td>10 months</td>
<td>5 months</td>
<td>p=0.7</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Slingluff 1990</td>
<td>Mean</td>
<td>23.2 months</td>
<td>16.0 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>12.1</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>Wang 2013</td>
<td>Median</td>
<td>16 months</td>
<td>8 months</td>
<td>p=0.022</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
6.3.5 Vulvovaginal melanoma – Clinical evidence summary tables

Table 8: Clinical evidence summary: radical surgery compared to local surgery for patients with vulvovaginal melanoma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of patients (studies) Follow up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>316 (8 studies)</td>
<td>☩ ☩ ☩ ☩ VERY LOW due to risk of bias</td>
<td>RR 1.05 (0.9 to 1.22)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25 more per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(from 50 fewer to 110 more)</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>168 (4 studies)</td>
<td>☩ ☩ ☩ ☩ VERY LOW due to risk of bias, indirectness, imprecision</td>
<td>RR 1.2 (0.73 to 1.97)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>307 per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61 more per 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(from 83 fewer to 298 more)</td>
</tr>
</tbody>
</table>

1 Downgraded 2 increments as the majority of the evidence was at very high risk of bias
2 Downgraded 1 increment as the majority of the evidence is from an indirect population
3 Downgraded by 2 increments as the confidence interval crosses both default lines of minimally important difference

Table 9: Duration of survival: radical surgery compared to local surgery for patients with vulvovaginal melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>Radical surgery</th>
<th>Local excision</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang 2013</td>
<td>Median</td>
<td>18.2 months</td>
<td>60.6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Belli 2009</td>
<td>Median</td>
<td>39.5 months</td>
<td>38.8 months</td>
<td>p=0.842</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miner 2004</td>
<td>Median</td>
<td>12 months</td>
<td>10 months</td>
<td>p=0.53</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
6.4 Economic evidence

No health economic evidence was identified.

6.5 Meta-analysis evidence statements

6.5.1 Anorectal melanoma

The evidence for the outcomes of OS and DFS was of low quality, and while suggesting that local surgery may be more beneficial, the effects were not at clinically relevant levels. The confidence intervals all crossed the line of ‘no effect’, suggesting that there may in fact be NO difference in survival based on the type of surgery undertaken. There are multiple confounders that need to be taken into account when considering this evidence, such as stage of disease, thickness or depth of the tumour and the location of the tumour. However, sub-group analysis did not provide any clearer indication for one surgery or another. Similarly, the evidence for local recurrence was also of low quality, and whilst the data suggest that radical surgery may be better, the imprecision around the effect estimates indicates that there is no confidence in these results.

6.5.2 Vulvovaginal melanoma

Low quality evidence showed no clinically important difference for overall survival between radical surgery and local excision. Low quality evidence suggested that those patients who underwent local surgery were less likely to experience local recurrence. However, the confidence intervals surrounding this effect are wide, and cross the line of ‘no effect’, suggesting that there is little confidence in this result.

6.5.3 Urogenital melanoma

Insufficient evidence was identified for a meta-analysis to be carried out.

6.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations for Anorectal Mucosal Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>16. Surgery for anorectal melanoma should be performed in centres regularly performing complex anorectal surgery and regularly managing complex melanoma within a specialist melanoma MDT.</td>
</tr>
<tr>
<td>17. The aim of surgical management should be to achieve an R0 (microscopically clear &gt; 1 mm) margin in the least radical fashion (i.e. with local excision).</td>
</tr>
<tr>
<td>18. In the event of R1 margins, repeat local excision or radical resection should be performed to obtain an R0 margin.</td>
</tr>
<tr>
<td>19. Resectability should be assessed by investigations outlined in the Staging</td>
</tr>
<tr>
<td>Investigations section above.</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
</tbody>
</table>

20. Lymphadendectomy should only be performed when there is evidence of metastatic regional nodal disease. In the presence of isolated meso-rectal nodes, a low anterior resection or APR should be considered.

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

22. Sentinel lymph node biopsy is not routinely recommended at present outside the context of clinical trials.

<table>
<thead>
<tr>
<th>Relative values of different outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>The committee considered survival outcomes to be of critical importance (OS, DFS, and RFS). Quality of life and patient reported outcomes were also considered critical. Important outcomes were morbidity and negative resection rate. In the absence of protocol-specified outcomes being reported, rate of local recurrence was also collected as an important outcome. No patient-specific outcomes or quality of life evidence was identified.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of the clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the evidence identified is of very low quality. A major contributor to this quality rating is the nature of the research design for included studies. All the evidence is at very high risk of bias due to the non-randomised, observational nature of cohorts and the case-series designs. Many of the comparison surgery groups differed at baseline for multiple factors irrespective of surgical procedure, e.g. disease stage, tumour size and depth. Similarly patients groups were managed differently alongside their surgical procedure, e.g. the use of differing adjuvant therapies. All of these factors are likely to have confounded the relationship between the surgical procedure undertaken and the critical patient outcomes. While some studies conducted multivariable analysis, in an attempt to control for possible confounding factors, very few of them included the surgical procedure type in this analysis. Therefore, the evidence included in the meta-analyses in the raw unadjusted data is at very high risk of bias.</td>
</tr>
</tbody>
</table>

The quality of the evidence is further affected by the presence of heterogeneity or inconsistency within the results. This may be due to the widely varying durations of follow-up times within the analyses as well as in the comparative populations, which vary in their level of the previously-identified confounders (stage of disease, tumour size, adjuvant therapy etc.). Where possible, this heterogeneity is explored in sub-group analysis; however, only a very few of the papers provided results in such a way allowing for sub-group analysis. Therefore, heterogeneity is considered by analysing the data using a ‘random-effects’ model, which accounts for the variations between studies and calculates a more conservative ratio that with a ‘fixed-effects’ model technique, and the level of variation is noted in the inconsistency rating in the GRADE evaluation.

Some of the evidence is drawn from populations that include a small number of patients with later stage disease, noted by the presence of distant metastases. These patients were outside the scope of this review which for surgery for the primary. However as the numbers within individual studies were low (noted in the clinical evidence tables), these studies were included but rated down for indirectness when appropriate.

Imprecision of the ‘pooled effect estimate’ was also taken into account when appraising the evidence included in the meta-analysis. In the majority of cases, the evidence is rated down, as the confidence intervals surrounding the point estimate cross at least one line of the default measures for minimally important difference (for dichotomous outcomes 0.75 and 1.25).
| Trade-off between clinical benefits and harms | There is no evidence that suggests there is a benefit in terms of local recurrence or overall survival following radical resection for anorectal melanoma. Although the poorly described in anorectal melanoma, the morbidity associated with radical resection in other colorectal pathologies is well documented. In light of this, the Committee recommends that conservative surgical strategies be employed, with the aim of gaining an R0 margin with the minimum morbidity. The pre-operative assessment of resectability should include pelvic MRI, EUA and proctoscopy. The Committee agreed that, in addition to its limited availability, endoscopic ultrasound is unlikely to alter surgical decision-making and so is not recommended in anorectal melanoma. A wide local excision should be the primary operative strategy in patients with anorectal melanoma. Wide local excision should only be forgone if technically unfeasible or if it would result in unacceptable compromise of anorectal function. Salvage surgery, in the form of repeat wide local excision or an abdominoperineal resection, may be performed in the event of microscopically involved margins (R1) on examination of the pathological specimen or local recurrence. If further surgery is not feasible or is declined by the patient after an initial resection, the following treatment strategies should be discussed with patients in the context of the associated risks and potential benefits:
- Watchful waiting with further treatment only in the event of recurrent disease;
- Adjuvant radiotherapy to the primary site with the aim of reducing the risk of local recurrence;
- Systemic therapies.
There is no evidence to suggest that removal of clinically evident regional nodal disease improves survival in anorectal melanoma. Patients with metastatic nodal disease at presentation are recognised to have poorer outcomes than those who are node negative. However, the Committee recognised that the progression of regional nodes has the potential to lead to fungation causing considerable morbidity and potentially interfering with the delivery of other treatment modalities. In light of this, it is recommended that clinically evident regional nodes are resected to gain local control of disease. As well as allowing assessment of the extent of the primary tumour, pelvic MRI will allow nodal disease within the mesorectum and bilateral groins to be detected prior to surgery. If involved nodes are present in the mesorectum, a more radical initial surgical strategy, in the form of an abdomino-perineal resection, may be justified. Radical resection may be appropriate in the following specific circumstances:
- Where wide local excision would result in compromised anorectal function.
- Where involved nodes are present in the mesorectum and there is no evidence of metastatic disease elsewhere.
- Where an R0 resection cannot be achieved without proctectomy.
- For salvage surgery following positive pathological margins or local recurrence.
The Committee recommends that prior to any radical resection, PET-CT and MRI of the brain should be performed to exclude low volume metastatic disease. In the absence of low volume metastatic disease, radical resection for local control may be justified. In the presence of low volume metastatic disease, surgery should only be performed in the presence of intractable local symptoms. De-functioning colostomy may be considered in the presence of metastatic disease without intractable local symptoms with the aim of avoiding obstructive complications and maintaining quality of life. |

| Trade-off between net clinical effects and costs | No cost-effectiveness evidence was identified |
### Vulvo-Vaginal Mucosal Melanoma

**Recommendations**

| 62. | 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. |
| 63. | Vulval melanomas less than 4 cm in size should be treated with wide local excision with an R0 (microscopically clear > 1mm) margin. |
| 64. | Vulval melanomas greater than 4 cm in size should be treated with radical excision in the form of anterior or posterior vulvectomy with an R0 (microscopically clear > 1mm) margin. |
| 65. | The aim of surgical management of vaginal melanomas should be to achieve an R0 (microscopically clear > 1 mm) margin in the least radical fashion. |
| 66. | Resectability should be assessed by investigations outlined in the Staging Investigations section above. |
| 67. | Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease. |
| 68. | If radical resection (e.g. an exenteration) is being considered, PET-CT and MR of the brain should be performed pre-operatively to exclude low volume metastatic disease. |
| 69. | Sentinel lymph node biopsy is not routinely recommended at present outside the context of clinical trials. |

**Relative values of different outcomes**

- The committee considered survival outcomes to be of critical importance (OS, DFS, and RFS). Quality of life and patient reported outcomes were also considered critical.
- Important outcomes were morbidity and negative resection rate. In the absence of protocol-specified outcomes being reported, rate of local recurrence was also collected as an important outcome. No patient-specific outcomes or quality of life evidence was identified.

**Quality of the clinical evidence**

- All of the evidence identified is of very low quality. A major contributor to this quality rating is the nature of the research design for included studies. All the evidence is at very high risk of bias due to the non-randomised, observational nature of cohorts and the case-series designs. Many of the comparison surgery groups differed at baseline for multiple factors irrespective of surgical procedure, e.g. disease stage, tumour size and depth. Similarly patients groups were managed differently alongside their surgical procedure, e.g. the use of differing adjuvant therapies. All of these factors are likely to have confounded the relationship between the surgical procedure undertaken and the critical patient outcomes. While some studies conducted multivariable analysis, in an attempt to control for possible confounding factors, very few of them included the surgical procedure type in this analysis. Therefore, the evidence included in the meta-analyses in the raw unadjusted data is at very high risk of bias.
The quality of the evidence is further affected by the presence of heterogeneity or inconsistency within the results. This may be due to the widely varying durations of follow-up times within the analyses as well as in the comparative populations, which vary in their level of the previously-identified confounders (stage of disease, tumour size, adjuvant therapy etc.). Where possible, this heterogeneity is explored in sub-group analysis; however, only a very few of the papers provided results in such a way allowing for sub-group analysis. Therefore, heterogeneity is considered by analysing the data using a ‘random-effects’ model, which accounts for the variations between studies and calculates a more conservative ratio that with a ‘fixed-effects’ model technique, and the level of variation is noted in the inconsistency rating in the GRADE evaluation.

Some of the evidence is drawn from populations that include a small number of patients with later stage disease, noted by the presence of distant metastases. However as the numbers within individual studies were low (noted in the clinical evidence tables), these studies were included but rated down for indirectness when appropriate.

Imprecision of the ‘pooled effect estimate’ was also taken into account when appraising the evidence included in the meta-analysis. In the majority of cases, the evidence is rated down, as the confidence intervals surrounding the point estimate cross at least one line of the default measures for minimally important difference (for dichotomous outcomes 0.75 and 1.25).

---

**Trade-off between clinical benefits and harms**

There is no consensus on mapping biopsies prior to definitive surgery but some surgeons consider mapping biopsies prior to radical surgery or suspected multifocal disease.

In vulval melanoma, tumours less than 4 cm in size should be considered potentially curative. In such patients, radical excision or wide local excision to achieve clear margins should be conceded.

Patients with metastatic nodal disease at presentation are recognised to have poorer outcomes to obtain clear margins with anterior or posterior vulvectomy dependent on patient and tumour factors may be justified. Tumours greater than 4 cm in size or multifocal tumours are unlikely to be potentially curative. In such patients, a wide local excision should be performed to gain local control of disease.

In vaginal melanoma, the local disease extent should be clarified pre-operatively with pelvic MRI and examination under anaesthetic with mapping biopsies to evaluate any skip lesions. There is no evidence that suggests there is a benefit in terms of local recurrence or overall survival following radical resection for vaginal melanoma. In light of this, the Committee recommends that conservative surgical strategies be employed, with the aim of gaining an R0 margin with the minimum morbidity.

Salvage surgery, in the form of a more extensive resection, may be performed in the event of microscopically involved margins (R1) on examination of the pathological specimen or local recurrence. If further surgery is not feasible or is declined by the patient after an initial resection, the following treatment strategies should be discussed with patients in the context of the associated risks and potential benefits:

- Watchful waiting with further treatment only in the event of recurrent disease;
- Adjuvant radiotherapy to the primary site with the aim of reducing the risk of local recurrence;
- Systemic therapies

If R0 margins are unlikely to be achieved with a conservative surgical resection, other available treatment options should be discussed with the patient. The Committee recommends that prior to any radical resection (i.e. exenterative surgery), PET-CT and MRI for the brain should be performed to exclude low volume metastatic disease. In the absence of low volume metastatic disease, radical resection for local control may be justified. In the presence of low volume metastatic disease, surgery should only be
performed in the presence of intractable local symptoms. Clitorectomy should only be performed in the presence of direct involvement of the clitoris. If the urethra is involved but the clitoris is not, all efforts should be made to preserve the clitoris and reconstruct the urethra following resection.

There is no evidence to suggest that removal of clinically evident regional nodal disease improves survival in vulvo-vaginal melanoma. However, the Committee recognised that the progression in involved regional nodes has the potential for considerable morbidity and may negatively affect quality of life. Loss of disease control in inguinal and pelvic nodes also has the potential to interfere with the delivery of other treatment modalities. In light of this, it is recommended that proven metastatic regional nodes are resected to gain local control of disease.

The Committee agreed that sentinel node biopsy has no role in the management of vulvo-vaginal melanoma. The Committee recommends that patients with vulvo-vaginal melanoma undergo regular surveillance, with lymphadenectomy only performed in the presence of proven metastatic regional nodes.

| Trade-off between net clinical effects and costs | No cost-effectiveness evidence was identified. |

### Penile Mucosal Melanoma

**Recommendations**

104. **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.

105. **The aim of surgical management** should be to achieve an R0 (microscopically clear > 1 mm) margin in the least radical fashion.

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

107. **In the event of R1 margins, repeat local excision** or radical resection should be performed to obtain an R0 margin.

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

109. **Sentinel lymph node biopsy** is not routinely recommended at present outside the context of clinical trials.

| Relative values of different outcomes | The committee considered survival outcomes to be of critical importance (OS, DFS, and RFS). Quality of life and patient reported outcomes were also considered critical. Important outcomes were morbidity and negative resection rate. In the absence of protocol-specified outcomes being reported, rate of local recurrence was also collected as an important outcome. No patient-specific outcomes or quality of life evidence was |
Quality of the clinical evidence

All of the evidence identified is of very low quality. A major contributor to this quality rating is the nature of the research design for included studies. All the evidence is at very high risk of bias due to the non-randomised, observational nature of cohorts and the case-series designs. Many of the comparison surgery groups differed at baseline for multiple factors irrespective of surgical procedure, e.g. disease stage, tumour size and depth. Similarly patients groups were managed differently alongside their surgical procedure, e.g. the use of differing adjuvant therapies. All of these factors are likely to have confounded the relationship between the surgical procedure undertaken and the critical patient outcomes. While some studies conducted multivariable analysis, in an attempt to control for possible confounding factors, very few of them included the surgical procedure type in this analysis. Therefore, the evidence included in the meta-analyses in the raw unadjusted data is at very high risk of bias.

The quality of the evidence is further affected by the presence of heterogeneity or inconsistency within the results. This may be due to the widely varying durations of follow-up times within the analyses as well as in the comparative populations, which vary in their level of the previously-identified confounders (stage of disease, tumour size, adjuvant therapy etc.). Where possible, this heterogeneity is explored in sub-group analysis; however, only a very few of the papers provided results in such a way allowing for sub-group analysis. Therefore, heterogeneity is considered by analysing the data using a ‘random-effects’ model, which accounts for the variations between studies and calculates a more conservative ratio than with a ‘fixed-effects’ model technique, and the level of variation is noted in the inconsistency rating in the GRADE evaluation.

Some of the evidence is drawn from populations that include a small number of patients with later stage disease, noted by the presence of distant metastases. However as the numbers within individual studies were low (noted in the clinical evidence tables), these studies were included but rated down for indirectness when appropriate.

Imprecision of the ‘pooled effect estimate’ was also taken into account when appraising the evidence included in the meta-analysis. In the majority of cases, the evidence is rated down, as the confidence intervals surrounding the point estimate cross at least one line of the default measures for minimally important difference (for dichotomous outcomes 0.75 and 1.25).

Trade-off between clinical benefits and harms

There is no evidence that suggests there is a benefit in terms of local recurrence or overall survival following radical resection for penile melanoma. In light of this, the Committee recommends that conservative surgical strategies be employed, with the aim of gaining an R0 margin with the minimum morbidity.

The Committee agreed that the following evidence suggests that limited resection for penile mucosal melanoma would be logical and safe. Limited resections have now replaced radical resections in the management of penile squamous cell carcinoma (SCC), with acceptable local recurrence rates with close margins (including < 5 mm). Similarly, close margins over vital structures in the management of cutaneous melanoma of the head and neck, are acceptable clinical practice. SCC also tends to be more locally aggressive than mucosal melanoma.

Penile MRI with an artificial erection is routinely used in planning limited surgical resections for SCC and allows accurate assessment of the local extent of disease. Although there is no evidence related to the use of MRI in penile melanoma, the Committee agreed that it would be logical to utilise this modality in the same fashion.

The extent of resection will be dependent on the anatomical location of disease. The Committee recommends the following approaches according to anatomical location and the involved structures:
- Lesions limited to the foreskin – circumcision.
- Small lesions limited to the glans – wide local excision with split skin graft reconstruction.
- Larger lesions limited to the glans – glansectomy with split skin graft reconstruction.
- Lesions involving the corpus cavernosum – partial/total penectomy.
- Lesions involving the anterior urethra – distal urethrectomy.
- Lesions involving the posterior urethra – panurethrectomy.

Salvage surgery, in the form of a more extensive resection, may be performed in the event of microscopically involved margins (R1) on examination of the pathological specimen or local recurrence. If further surgery is not feasible or is declined by the patient after an initial resection, the following treatment strategies should be discussed with patients in the context of the associated risks and potential benefits:
- Watchful waiting with further treatment only in the event of recurrent disease;
- Adjuvant radiotherapy to the primary site with the aim of reducing the risk of local recurrence;
- Systemic therapy.

There is no evidence to suggest that removal of clinically evident regional nodal disease bearing metastatic melanoma improves survival in penile mucosal melanoma. However, the Committee recognised that progression in involved regional nodes has the potential for considerable morbidity and may negatively affect quality of life. Loss of disease control in inguinal and pelvic nodes also has the potential to interfere with the delivery of other treatment modalities. In light of this, it is recommended that proven metastatic regional nodes are resected to gain local control of disease. There is no evidence to support the routine use of sentinel node biopsy in penile mucosal melanoma. However, some recommendations may be made based on the likely sites of relapse in mucosal melanoma. From the limited evidence available, it is recognised that patients with in-situ melanomas and T1 tumours are at low risk of regional nodal relapse. In contrast, patients with T4 tumours are at high risk of visceral relapse, which often occurs without preceding regional nodal relapse. Patients with T2 or T3 tumours are at high risk of regional nodal relapse. In contrast to anorectal or vulvovaginal tumours, the lymphatic drainage from penile lesions is well characterised and sentinel node biopsy has an established role in the management of T2/3 tumours of other penile pathologies. However, it is evident that the rates of visceral metastasis are higher in mucosal melanoma than cutaneous melanoma and, as such, it is not clear that sentinel node biopsy and completion lymphadenectomy has any impact on the survival of this group. The Committee agreed that sentinel node biopsy has no role in the management of patients with in-situ, T1 or T4 tumours. The majority of patients should undergo regular surveillance, with lymphadenectomy only performed in the presence of clinically evident disease. Sentinel node biopsy may be discussed with selected patients with T2 and T3 tumours at institutional discretion, though it should be made clear that the role of this technique in this pathology remains to be defined.

Radical resection may be appropriate in specific circumstances. The Committee recommends that prior to any radical resection, PET-CT and MRI of the brain should be performed to exclude low volume metastatic disease. In the absence of low volume metastatic disease, radical resection for local control may be justified. In the presence of low volume metastatic disease, surgery should only be performed in the presence of intractable local symptoms.

**Trade-off between net clinical effects and costs**

No cost-effectiveness evidence was identified.
7 Lymph Nodes

7.1 Introduction

Confirming or refuting the presence of loco-regional lymph node involvement is crucial in deciding the most appropriate intervention in patients with mucosal melanoma. Patients who present with lymph node involvement are recognised to have poorer outcomes. Although there is insufficient evidence to suggest that surgical excision of involved lymph nodes in itself prolongs survival, if left unchecked, loco-regional lymph nodes may progress causing distressing symptoms, such as fungation, or interrupt the delivery of systemic therapies. As such, there is a clear rationale for identifying macroscopic loco-regional nodal disease at presentation.

The identification of microscopic loco-regional lymph node involvement is more controversial. Whilst sentinel lymph node biopsy has a well-established role in the management of cutaneous melanoma, it is uncertain whether this is transferrable to mucosal disease. Due to their anatomical location, the lymphatic drainage of mucosal melanomas may be less uniform than in cutaneous disease. In addition, sentinel node biopsy and lymphadenectomy are not without the risk of complications. The potential morbidity of such intervention is of particular importance given the poor prognosis of mucosal melanoma. Hence, the key question is whether the identification of microscopic loco-regional nodal disease impacts on outcome in patients with mucosal melanoma and whether the potential morbidity of these investigations is justified.

7.2 Review question: What is the most accurate technique to diagnose lymph node involvement?

Table 10: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>AUG melanoma patients stage I-III who have undergone curative surgical treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)</td>
<td>• Sentinel lymph node biopsy • PET • CE-CT • CE-MRI • MRI</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Clinical examination and ultrasound</td>
</tr>
<tr>
<td>Outcomes</td>
<td>• Diagnostic accuracy • Sensitivity • Specificity • Likelihood ratio • Positive and negative predictive value</td>
</tr>
<tr>
<td>Study design</td>
<td>Systematic reviews, randomised controlled trials and non-randomised observational studies</td>
</tr>
</tbody>
</table>

7.3 Clinical evidence

We searched for randomised trials and non-randomised observational studies regarding techniques for identifying regional lymph node metastases in patients undergoing potentially curative treatment of Stage I-III anorectal, vulvovaginal and penile mucosal melanomas. No randomised...
controlled trials were identified. Forty papers were identified. Nine observational cohort studies were identified as matching the review protocol and are summarised in the study evidence tables in A1.3. The reasons for excluding the other 31 studies are given in appendix A1.5 in the supplementary appendix.

Seven studies were related to the identification of regional lymph nodes metastases in vulvovaginal melanoma. All of the identified studies related to the use of sentinel node biopsy in the diagnosis of regional lymph nodes. No studies regarding the use of PET, CE-CT, CE-MRI or MRI in vulvovaginal melanoma were identified. The number of patients with vulvovaginal melanoma undergoing sentinel node biopsy in these studies was small ranging from 1 to 12 (1-7). Lymphoscintigraphy was reliably able to identify draining nodes in each of these studies (65–71). However, the patterns of drainage were noted to vary, with unilateral and bilateral drainage reported, as well as drainage to the superficial inguinal and deep pelvic basins (65–69). Where reported, sentinel node biopsy was associated with low rates of peri-operative morbidity (65,69,71). The rates of positive sentinel node biopsy in these series were low, ranging from 0-50% (65–69,71). On completion lymphadenectomy, the presence of further positive nodes was rare ranging from 16.7-33.3% of patients (67,69). False negatives following sentinel node biopsy in this pathology were noted, ranging from 33.3-50.0% of patients (66,71). In one study, improved survival was noted in patients with negative sentinel nodes compared with those with positive sentinel nodes (67).

One study was related to the identification of regional lymph nodes metastases in anorectal melanoma (72). This study examined sentinel node biopsy, and included 33 patients. Lymphoscintigraphy was able to identify drainage in all patients, although the pattern of drainage again varied, with unilateral drainage in 16 patients and bilateral drainage in 17 patients. Positive sentinel nodes were identified in 15 patients, who proceeded to completion lymphadenectomy. No information on the presence of further nodes on completion lymphadenectomy was given. Patients with negative sentinel nodes were noted to have improved survival compared with those with positive sentinel nodes. No studies regarding the use of PET, CE-CT, CE-MRI or MRI in anorectal melanoma were identified.

One study included patients with either vulvovaginal (19/26) or anorectal (7/26) melanoma (73). Sentinel node biopsy was performed in 9 patients, with a positive node identified in 4 patients. Completion lymphadenectomy was performed in 2 of these patients, with no further nodal disease identified. No difference in survival was noted in patients undergoing sentinel node biopsy compared with those who had no nodal staging.

No studies were identified with regard to penile melanoma. However, the use of sentinel node biopsy in penile SCC is an accepted part of clinical practice and the drainage to regional lymph nodes had been well characterised in this pathology.

**Conclusions**

With regard to vulvovaginal and anorectal melanoma, although there is some evidence to suggest that patients with positive sentinel nodes have poorer outcomes, there is insufficient evidence to suggest that sentinel biopsy in itself has any impact on survival outcomes. The pattern of drainage in both pathologies is noted to vary considerably, with the rates of positive sentinel nodes and further nodes on completion lymphadenectomy particularly low in vulvovaginal melanoma. As such, there is insufficient evidence to support the routine use of sentinel lymph node biopsy in patients with vulvovaginal or anorectal melanoma.
Sentinel lymph node biopsy has a defined role in the management of penile SCC as outlined in the Surgery chapter. Although no studies were identified regarding its use in penile melanoma, as the patterns of lymph node drainage appear more uniform in penile malignancy, the Committee believe it is reasonable for sentinel node biopsy to be used with the same rationale in patients with penile melanoma.

Patients presenting with vulvovaginal and anorectal melanoma will undergo clinical examination of the groins and pelvic MRI as part of their diagnostic work up. This will allow clinically evident inguinal lymphadenopathy to be detected at presentation. As described in the Surgery chapter, patients with clinically evident regional lymph node involvement should then undergo lymphadenectomy. Those patients without clinically evident regional lymph node involvement should receive treatment for their primary lesion and enter surveillance as appropriate.

7.4 Economic evidence

No economic studies were found

7.5 Evidence statements

Clinical

- There is insufficient evidence to support the routine use of sentinel node biopsy for vulvovaginal melanoma.
- There is insufficient evidence to support the routine use of sentinel node biopsy for anorectal melanoma.

7.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>All AUG Mucosal Melanomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td>22. Sentinel lymph node biopsy is not routinely recommended at present outside the context of clinical trials.</td>
</tr>
<tr>
<td><strong>Quality of the clinical evidence</strong></td>
</tr>
<tr>
<td>- Agreed that lymph node assessment would be considered at follow-up and staging in two ways, 1. Anatomical sites, 2. Melanoma</td>
</tr>
<tr>
<td>- Vulvo-vaginal – scene still playing out – not clear about biopsy. Going straight into metastatic is common.</td>
</tr>
<tr>
<td>- Higher incidence in ano-rectal, may reflect late presentation</td>
</tr>
<tr>
<td>- Penile – sentinel node biopsy more common as it is standard as drainage is much more constant. However incidence of lymph node involvement is also low. Is this procedure done because the lymph nodes are more accessible? Under pressure from colleagues. Going straight into metastatic is very rare. High risk of local nerve involvement.</td>
</tr>
</tbody>
</table>

The Committee agreed that sentinel node biopsy has no role in the management of...
anorectal melanoma. The patterns of regional relapse in anorectal melanoma appear to differ from other colorectal pathologies, with lesions above the dentate line retaining the potential to spread to the inguinal nodes. In addition, the rates of haematogenous dissemination in anorectal melanoma are higher than in other mucosal melanomas. The Committee recommends that patients with anorectal melanoma undergo regular surveillance, with lymphadenectomy only performed in the presence of proven metastatic regional nodes.

- There is no evidence to support the routine use of sentinel node biopsy in penile mucosal melanoma. However, some recommendations may be made based on the likely sites of relapse in mucosal melanoma. From the limited evidence available, it is recognised that patients with in-situ melanomas and T1 invasive melanomas are at low risk of regional nodal relapse. In contrast, patients with T4 tumours are at high risk of visceral relapse, which often occurs without preceding regional nodal relapse. Patients with T2 or T3 melanomas are at high risk of regional nodal relapse. In contrast to anorectal or vulvovaginal tumours, the lymphatic drainage from penile tumours is well characterised and sentinel node biopsy has an established role in the management of T2/3 tumours of other penile pathologies. It is evident that the rates of visceral metastasis are higher in mucosal melanoma than cutaneous melanoma and, as such, it is not clear that sentinel node biopsy and completion lymphadenectomy has any impact on the survival of this group.

<table>
<thead>
<tr>
<th>Other considerations</th>
<th>•</th>
</tr>
</thead>
</table>

1
2
8 Adjuvant Systemic Therapy

8.1 Introduction

Surgical excision with curative intent is the treatment of choice for AUG mucosal melanoma. However, most patients with this diagnosis are at high risk of inoperable local recurrence and/or distant metastatic disease, in which case treatment is no longer curative. Features of the primary tumour and involvement of regional lymph node metastases can help identify patients at greatest risk of disease recurrence. It is essential to establish whether adjuvant systemic treatment, after excision of mucosal melanoma, can reduce the subsequent risk of developing incurable disease and whether the absolute survival benefit justifies the potential toxicity of treatment.

8.2 Review question: What is the effectiveness of adjuvant systemic therapy for stage I-III AUG melanoma in people who have undergone curative resection?

Table 11: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>AUG melanoma patients stage I-III who have undergone curative surgical treatment.</th>
</tr>
</thead>
</table>
| Intervention(s) | • Chemotherapy  
|              | • Immunotherapy (interferon, interleukin-2, pembrolizumab, nivolumab, ipilimumab)  
|              | • Combinations of the above. |
| Comparison | Observation (no systemic therapy) |
| Outcomes | Overall survival (OS)  
|          | Progression-free survival  
|          | Local control  
|          | Health-related quality of life  
|          | Treatment-related morbidity  
|          | Treatment-related mortality |
| Study design | Randomised Controlled trial, Observational studies, Case Series GT 1. |

8.3 Clinical evidence

A systematic review of the literature was performed. All papers in which patients with a diagnosis of AUG mucosal melanoma received systemic treatment were identified. Of 65 papers, 11 included patients receiving systemic treatment with adjuvant (curative) intent, after surgical excision of AUG mucosal melanoma. Case reports or retrospective case series, in which n=1 for a particular systemic regimen, were excluded. Therefore, three papers were included in the final review.

Janco et al (74) published a retrospective case series of 50 patients who had undergone surgery for primary vulval or vaginal melanoma over a 20-year period at a single centre. No patient with vaginal melanoma received adjuvant systemic therapy. Ten patients out of 33 operated on for vulval melanoma received adjuvant systemic therapy, of whom three represented a single example of a particular systemic regime (one patient received temozolomide, one received Granulocyte macrophage colony-stimulating factor (GM-CSF) plus radiotherapy and one received carboplatin/...
paclitaxel/bevacizumab). Three patients received GM-CSF alone and four patients received Interferon α-2b (IFN α-2b). Doses and schedules for the systemic regimes were not specified. Selection criteria for offering adjuvant systemic therapy are not described. This study demonstrated no evidence that the use of systemic adjuvant therapy in AUG mucosal melanoma is associated with an improvement in overall survival (OS). The median OS in the 23 patients, who were managed by surgery alone, was 5.7 years compared to 1.8 years for the ten patients who also received adjuvant systemic therapy. Median relapse free survival was 3.0 years versus 1.5 years. Neither of these results was statistically significant (p=0.33 and 0.56).

This is a retrospective review of practice from a single centre. It is a small study identified in the systematic review of the literature in which patients with AUG mucosal melanoma were treated with adjuvant systemic therapy although only two regimens were administered to more than one patient. Patients were not randomised and were offered adjuvant systemic therapy based on unspecified criteria. There will be inevitable bias in selection of patients who receive adjuvant systemic therapy. The use of adjuvant systemic therapy was not associated with an improvement in OS. The adjuvant therapies included within this review pre-date the introduction of currently established systemic treatments for metastatic cutaneous melanoma - neither GM-CSF nor IFN α-2b form part of current treatment guidelines for the management of cutaneous melanoma nor have they been recommended by NICE.

Xia et al (64) published a retrospective case series of 44 women who had received treatment for primary melanoma of the vagina at a single centre over a nine year period. It aimed to include only patients with Stage I disease (confined to the vagina) under the International Federation of Gynecology and Obstetrics staging system (version 2009), with follow-up data for six months or more. Of these over three quarters (77.8%) had T4 tumours (>4 mm). 21 patients included in the series also underwent lymphadenectomy of whom six had metastatic disease identified in the lymph nodes and therefore would not be classified as having Stage I disease. 41 patients underwent excision of their primary vaginal melanoma of whom five had surgical margins which, on histological examination, were positive for melanoma.

Of the 41 patients who could be considered for post-operative systemic treatment with adjuvant intent, 30 women received adjuvant IFN α-2b at a dose of 3 million units twice a week for an unknown duration and 19 patients received adjuvant chemotherapy (regimens not specified but including dacarbazine and cisplatin) with an unknown number of women receiving both treatments. Eight women receiving chemotherapy also received radiotherapy, and an additional five women received radiotherapy. It is unclear how many of these five women also received interferon α-2b. Selection criteria for adjuvant systemic therapy was not defined (‘on the basis of post-operative pathologic reports’).

Use of adjuvant therapy was not associated with an improvement in overall survival (median 20.2 versus 39.5 months, p=0.212) although PFS between WLE followed by adjuvant therapy versus WLE only was statistically different (p=0.019). Toxicity data is not included. After a median follow-up of 18.9 months (range 6.0-94.3 months) 30 patients (68.2%) had recurrent disease of whom 21 had died of their disease (47.7%).

This is a retrospective review of practice from a single centre. It is the second largest study identified in the systematic review of the literature in which patients with AUG mucosal melanoma were treated with adjuvant systemic therapy. Patients were not randomised and were offered adjuvant systemic therapy based on unspecified criteria. There is a high probability of bias in the selection of patients for the different adjuvant systemic treatment modalities. The use of adjuvant systemic therapy was not associated with an improvement in OS. The adjuvant therapies included within this
review pre-date the introduction of currently established systemic treatments for metastatic cutaneous melanoma, are not included in current guidelines for the management of cutaneous melanoma nor have they been recommended by NICE.

Lian et al (75) report the only randomised, controlled trial of patients receiving adjuvant systemic therapy for mucosal melanoma identified in the systematic literature search. 189 patients, of whom 103 had a diagnosis of AUG mucosal melanoma, who had undergone complete resection of Stage II or III disease were randomised into three treatment arms (1:1:1). The patients in the first arm received no systemic adjuvant therapy but were randomised to observation. The patients in the second arm received IFN α-2b 15x10^6 U/m^2/d iv D1-5 each week for four weeks, followed by 9x10^6 U s/c three times a week for 48 weeks. The patients in the third arm received temozolomide 200 mg/m^2/D1-5 plus cisplatin 75 mg/m^2 iv divided into three days, repeated every three weeks for six cycles. The three arms were not stratified but patient characteristics were well-balanced.

At a median follow-up of 26.8 months, the median relapse free survival was 5.4 months in the observation arm, 9.4 months in the arm treated with IFN α-2b and 20.8 months in the arm who received chemotherapy. This improvement in RFS in patients receiving adjuvant systemic therapy compared to observation was statistically significant (p<0.001 for IFN α-2b and for chemotherapy). The estimated median OS in the observation arm was 21.2 months (95% CI, 15.8-26.6 months), 40.4 months for patients who had received IFN α-2b (95% CI, 32.5-48.3 months) and 48.7 months for patients who had received chemotherapy (95% CI, 41.8-55.6 months), suggesting that adjuvant systemic therapy was associated with improved OS (p<0.001 for IFN α-2b and for chemotherapy).

This non-stratified Phase II trial represents the only randomised data identified in the systematic literature review exploring the benefit of adjuvant systemic therapy after resection of AUG mucosal melanoma, and includes the greatest number of patients with the diagnosis. Extrapolation of these regimen-specific results is difficult within the current clinical environment. A trial favouring adjuvant chemotherapy over immunotherapy in the treatment of melanoma is discordant with oncological principles of systemic adjuvant therapy. The chemotherapy regimen of temozolomide plus cisplatin has no proven survival benefit in the palliative treatment of metastatic mucosal melanoma, and the evidence from this trial was considered insufficient to recommend it as an adjuvant therapy for mucosal melanoma following resection with curative intent.

In summary, this randomized study does support a potential role for systemic adjuvant therapy for AUG mucosal melanoma following resection with curative intent, However both regimens included in the study pre-date the introduction of currently established systemic treatments with proven survival benefit in metastatic cutaneous melanoma, and do not form part of current clinical guidelines for the management of cutaneous melanoma nor have they been recommended by NICE.

Evidence from these studies is summarised in the in study evidence tables in Appendix A3.2, and excluded studies list in Appendix A3.3 in the supplementary appendix.

8.4 Economic evidence

No Economic evidence was found.

8.5 Evidence statements

- Available evidence for adjuvant systemic treatment of AUG mucosal melanoma is of ‘Very Low Quality’, and there is no good evidence base to support its use. In particular, there is no literature at all in AUG mucosal melanoma, on the use of therapies recently approved for the treatment of
metastatic cutaneous melanoma, such as the anti-CTLa4 antibody ipilimumab, or the antiPD1 inhibitors, Pembrolizumab and Nivolumab.

• There is evidence in cutaneous melanoma, which demonstrates a benefit in overall survival for the use of adjuvant ipilimumab 10 mg/kg after complete resection of high risk (Stage III) cutaneous melanoma. A prospective, randomised placebo controlled trial including over 950 patients with resected Stage III cutaneous melanoma evaluated ipilimumab 10 mg/kg q21 for four doses, followed by a maintenance dose every three months for three years versus observation alone. At a median follow-up of 5.3 years, the five-year overall survival was 10% higher in the patients receiving ipilimumab with a similar increase in the recurrence free survival. However 41.6% patients in the ipilimumab group experienced serious toxicity (Grade 3 or 4) compared with only 2.7% on the placebo arm and there were five deaths due to immune-related adverse events (1.1%) (76). This regimen is not included in the guidelines for the management of cutaneous melanoma nor has it been recommended by NICE.

8.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>All AUG Mucosal Melanomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td>23. Do not routinely offer systemic adjuvant therapy.</td>
</tr>
<tr>
<td>24. If emerging data in cutaneous melanoma supports the use of immunotherapy agents in the adjuvant setting, in particular if less toxic regimens such as single agent anti-PD1 antibodies show a survival benefit, then consideration should be given for its use in mucosal melanoma.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Linking evidence to recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is currently no adjuvant treatment for cutaneous melanoma recommended by NICE or in routine use within the UK. The question of adjuvant therapy following excision of high-risk cutaneous melanoma was not addressed in the cutaneous melanoma NICE guidance. Despite prospective randomised placebo controlled evidence demonstrating a survival benefit in cutaneous melanoma with the use of high dose ipilimumab, concern remains regarding the significant toxicity and treatment-related deaths observed with this regime, particularly in an adjuvant population which inevitably includes some patients already cured of their melanoma. In addition, there is evidence to suggest metastatic mucosal melanoma demonstrates lower response rates to ipilimumab than metastatic cutaneous melanoma (see Chapter 9), and, therefore, clinical efficacy in the adjuvant population would be anticipated to be similarly reduced. It is not recommended that these data are extrapolated to AUG mucosal melanoma. Given the greater efficacy of anti-PD1 inhibitors compared to ipilimumab in metastatic melanoma and their improved toxicity profile, it is anticipated that emerging data on the use of anti-PD1 monotherapy in the adjuvant treatment of high risk cutaneous melanoma could inform decision making regarding the adjuvant treatment of AUG mucosal melanoma. The single randomised non-stratified trial suggesting that adjuvant systemic therapy after high-risk mucosal melanoma prolongs overall survival includes treatment regimens, which pre-date the introduction of currently established systemic treatments for metastatic cutaneous melanoma and do not form part of current clinical guidelines.</td>
</tr>
</tbody>
</table>
for the management of cutaneous melanoma.

| Quality of the clinical evidence | • Single randomized trial of adjuvant systemic therapy in patients following resection of mucosal melanoma, including patients with AUG mucosal melanoma  
|                                | • Literature frequently reports ‘mucosal melanoma’ rather than differentiating AUG from Head and Neck mucosal melanoma  
|                                | • Some abstracts/posters only  
|                                | • Literature base pre-dates recent new therapies which have a proven OS benefit in metastatic disease e.g. ipilimumab, pembrolizumab, nivolumab  |
| Trade-off between clinical benefits and harms | • See earlier comment under ‘Linking evidence to recommendations’  |
Radiotherapy

9.1 Introduction

The use of radiotherapy is well established as an adjuvant therapy or as treatment of primary melanoma in many tumour sites. In cutaneous melanoma there is evidence to support improved local control and DFS for the use of RT after nodal dissection, albeit with high rates of toxicity. In ano-genital melanoma, surgical excision is the primary therapy, but may often be associated with morbidity, given the sensitive anatomical locations. Radiotherapy may therefore be useful in improving local control, quality of life through avoidance of surgery and improved overall survival. This may be particularly relevant in the setting of incomplete resection where further surgery is not possible.

9.2 Review question: What is the clinical and cost effectiveness of adjuvant radiotherapy for Stage I-III AUG melanoma in people who have undergone curative resection?

Table 12: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>AUG melanoma patients Stage I-3 who have undergone curative surgical treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention(s)</td>
<td>Adjuvant radiotherapy only</td>
</tr>
<tr>
<td></td>
<td>External beam radiotherapy (brachytherapy and stereotactic radiotherapy)</td>
</tr>
<tr>
<td>Comparison(s)</td>
<td>Observation (no radiotherapy)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Overall survival (OS)</td>
</tr>
<tr>
<td></td>
<td>Stage at recurrence</td>
</tr>
<tr>
<td></td>
<td>Time to recurrence</td>
</tr>
<tr>
<td></td>
<td>Patient preferences</td>
</tr>
<tr>
<td></td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
</tr>
<tr>
<td></td>
<td>Costs</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Change of management</td>
</tr>
<tr>
<td>Study design</td>
<td>Case reports excluded, Other studies included</td>
</tr>
<tr>
<td>Considerations</td>
<td>• Type of melanoma: (anorectal, urogenital, vulvovaginal)</td>
</tr>
<tr>
<td></td>
<td>• Stage (1, 2, 3)</td>
</tr>
<tr>
<td></td>
<td>• R1 and R0 resection (presence or absence of positive resection margin)</td>
</tr>
<tr>
<td></td>
<td>• Technique/dose/target</td>
</tr>
<tr>
<td></td>
<td>• Node +ve or node –ve</td>
</tr>
</tbody>
</table>

9.3 Clinical evidence

We searched for randomised trials and non-randomised observational studies comparing the effectiveness of adjuvant radiotherapy compared to no radiotherapy for people with anorectal, urogenital or vulvovaginal melanoma. No randomised controlled trials were identified. Twelve retrospective reviews were identified. Five ano-rectal studies were included (37,77–80) from same
institution with overlapping data, were included in the review. Seven vulvo-vaginal studies were included in the review. (53,81–86) No studies were found for penile melanoma. Most were single institution case series. No papers directly addressed the use of adjuvant radiotherapy. There was little detail on RT schedules and indications.

Included studies are grouped by strata and summarised in Table 13 below. See also the study evidence tables in Appendix 4.2, and excluded studies list in Appendix 4.3 in the supplementary appendix.

**Table 13: Summary of studies included in the review**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and comparison</th>
<th>Population</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ano-rectal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ballo 2002</td>
<td>Sphincter sparing surgery + LND in patients with involved LN followed by adjuvant RT 30 gy in 5 fractions twice weekly. 9 patients received adjuvant systemic therapy</td>
<td>Anal rectal melanoma treated with sphincter sparing surgery at MD Anderson. Median age 55yrs (33–89) 17 female 6 male</td>
<td>5yrs OS 31% 5yrs DSS 36% 5yrs DFS 37% 5yrs Distant metastasis free survival 35% Actuarial 5yr local control rate 74% and Actuarial nodal control rate 84%</td>
<td>(Over lap of authors from Kelly 2011) Risk of bias: high non randomised</td>
</tr>
<tr>
<td>Homsi 2007</td>
<td>5 APR +Inguinal LND (+RT in 1, +interferon in 1 and both in another) 6 had WLE (+Inguinal LND in 1, +RT and interferon in 2)</td>
<td>Retrospective case series w. Anal/rectal melanoma pathology 12 cases 142 cases anal malignancy - 12(8%) melanoma</td>
<td>Relapse data available for 8/11 patients Median time to relapse 6.5months (4-31months) 5/11 (45%) died within 12 months</td>
<td>Risk of bias: high non randomised</td>
</tr>
<tr>
<td>Kelly 2011</td>
<td>Sphincter sparing surgery + RT</td>
<td>Retrospective case series – Patients with anorectal melanoma managed by sphincter sparing surgery and adjuvant radiotherapy. - - 54 cases</td>
<td>At time of final analysis 39 (72%) had experienced disease relapse and 42 (78%) had died Median OS 29 months DSS at 2yrs was 60% OS at 2yrs was 59% DSS at 5yrs was 32% OS at 5yrs was 30%</td>
<td>(Over lap of authors from Ballo 2002) Risk of bias: high non randomised</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Kirchoff 2016</td>
<td>Retrospective analysis - 227 patients -82 anorectal melanoma</td>
<td>Median overall survival 38.7 months 5yrs OS 32.8% Melanoma specific 5yr survival 37.5%</td>
<td>Adjuvant RT led to worse OS at all sites. (median OS 33.3 months with RT vs 44.0 months without RT) $P=0.007$</td>
<td>Risk of bias: high non randomised</td>
</tr>
<tr>
<td>Ramakrishnan 2008</td>
<td>Retrospective case series - Any stage anal rectal melanoma. 63 patients 18/63 treated by surgery +/-RT</td>
<td>Median OS in 18 patients treated was 9.5 months Median OS in 5 WLE only 12months vs 3 WLE +RT 34 months Median DFS 5 WLE only 8 months vs 3 WLE +RT 28 months 4/5 patients developed local recurrence following WLE alone BUT 50% had LN or distant mets simultaneously None of the three patients who received adjuvant RT following WLE developed local or nodal recurrence</td>
<td>Risk of bias: High</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal Ditto</td>
<td>Retrospective database review - Primary surgical treatment for genital (female melanoma) - 67(68%) vulva, 31 (32%) vaginal</td>
<td>Vaginal localization and number mitoses associated with worse DFS on multivariate No factors associated with 5year OS (including adjuvant therapy)</td>
<td>Risk of bias: High</td>
<td></td>
</tr>
</tbody>
</table>

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By Nancy Turnbull
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and comparison</th>
<th>Population</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frumovitz 2010</td>
<td>Adjuvant radiotherapy 20 patients received adjuvant RT – 10 patients treated with a hypofractionated schedule 30gy in 5fractions over 2.5 weeks to vagina and paravaginal tissues or distal pelvis including the vaginal and distal iliac or inguinal LN.</td>
<td>Retrospective review 37 cases - Clinical and pathological Stage I vaginal melanoma</td>
<td>Median OS 29.4months (WLE/radical Sx +Adj RT) Vs 16.1months (WLE/radical Sx no RT) (P=0.46)</td>
<td>Risk of bias: High</td>
</tr>
<tr>
<td>Gupta 2002</td>
<td>Primary melanomas of the vagina FU 3-276 months available in 23pts 1 cases Ant exenteration +LND +RT ( stage IVB recurrence at 12months, DOD 16 months) 2 cases WLE +RT +chemo 2 cases WLE +RT 2 cases WLE+LND+RT 2 case WLE alone (one went on to have salvage vaginectomy +RT 1 case RT alone 1 Case CT+RT alone (Brain mets RT to brain) 1 case had pall RT to brain alone</td>
<td>7 cases underwent Ant exenteration +/- CT +RT – 4 patients died in 3-33months, 1 is alive with disease at 24 months, 2 are alive without disease at 24 and 108 months 9 cases underwent WLE +/-LND +/- RT/CT , 5 patients died at 10-83 months, 3 are alive with disease at 6-276 months, 1 is alive without disease at 17 months</td>
<td>Risk of bias: High</td>
<td></td>
</tr>
<tr>
<td>Irvin, 2001</td>
<td>Treatment for invasive vulval melanoma</td>
<td>6/14 treated with curative intent relapsed, media time 7.5 months</td>
<td>No mention of adjuvant RT in paper</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and comparison</td>
<td>Population</td>
<td>Outcomes</td>
<td>Comments</td>
</tr>
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<td>-----------------------------------------------------------------------------</td>
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<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Kirschner, 2013</td>
<td>Surgery &amp; radiotherapy</td>
<td>Vaginal melanoma included in registry identified by ICD code - 43% surgery alone (radical 52, partial 40, excision biopsy 38, other 11) 15% RT alone 26.4% surgery +RT 41.8% received RT, (surg+RT in 26.3%, nearly all adjuvant) 65.5% EBRT 27 pts brachytherapy For LN+ 56.7% got RT</td>
<td>Adjuvant RT did not offer a SS OS advantage compared to surgery alone. (but no data in database on local control to know whether this is better)</td>
<td>Risk of bias: high - non randomised</td>
</tr>
<tr>
<td>Petru, 1998</td>
<td>Radiotherapy 50Gray or 64-60 gy if lower vagina to include inguinal area</td>
<td>Vaginal only - 9/14 received RT, 3 as adjuvant, 6 after biopsy</td>
<td>For the 3 5 year survivors, all had tumours &lt;3cm and received 50Gy RT</td>
<td>Risk of bias: high - non randomised</td>
</tr>
<tr>
<td>Vaysse, 2013</td>
<td>Primary vaginal melanoma treated with curative intent - 9/46 local adjuvant therapy</td>
<td></td>
<td>In advanced disease adjuvant RT associated with worse OS and met-free survival</td>
<td>Risk of bias: high - non randomised</td>
</tr>
</tbody>
</table>

9.3.1 Anorectal melanoma – Narrative summary

Five papers (37,77–80) were identified for inclusion of which two had overlapping data. All were single institution retrospective case series. There were no studies which that directly compared the use of adjuvant RT with no RT after surgery, nor were details of RT indications, schedules and toxicities well documented.

In Kelly, 2011 (79), which overlapped with Ballo, 2002(77), 54 patients with anorectal melanoma were treated by sphincter sparing surgery and adjuvant radiotherapy between 1989 and 2008. At time of final analysis (median FU was 36 months), 39 (72%) had experienced disease relapse and 42
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(78%) had died. Median overall survival (OS) was 29 months with 59% OS at 2 years and 30% at 5 years. Side effects of RT were well documented. As there are no criteria for the use of RT and no comparator, no conclusions can be drawn about the effect of adjuvant RT on OS. There were similar results in Ballo 2004 (87). In the paper by Ramakrishnan 2008,(37) a single centre retrospective database review with a slightly younger population (Median Age 53yrs), only 3/63 received adjuvant RT following a WLE. All achieved local control and there was an acceptable level of toxicity for RT. In Homsi, 2007 (78) 12 cases from 1987-2004 were reviewed. No conclusions on the effect of adjuvant RT can be drawn. In the study by Kirchoff, 2015 (80) a conference abstract reporting on a single centre retrospective database review of all mucosal melanomas, it was reported that adjuvant RT led to worse OS. However, there was no statistical analysis provided.

In conclusion, there was limited poor quality evidence. There are some data to suggest a reduction in OS with adjuvant RT but this may be due to high risk case selection. There is no documentation of the margin status as an indication for RT. No data on the effects on Quality of Life of RT although side effects are documented in several studies.

9.3.2 Vulvo-vaginal melanoma – Narrative summary

Seven studies were identified for inclusion (53,81–86). With the exception of Kirschner (from SEER database), Petru (three centres in Austria) and Vaysse (12 centres in France) (84–86), all studies were single institution retrospective case series with cases included from for 30-50 years ago in some.

The paper by Ditto, 2016 (81) was a retrospective database review of 98 pts, between 1969-2013, which used univariate and multivariate analysis of localization, mitosis number mitosis, positive margins, advanced stage, for OS and 5 year DFS. No factors were associated with 5 year OS, including adjuvant therapy. There was no comment on RT use.

Frumovitz, 2010 (82) was a retrospective review of 37 cases, between 1980-2009, all with Stage I vaginal melanoma. The outcomes of patients who received adjuvant RT were compared with those who did not. The median OS was 29.4 months from patients receiving WLE or radical surgery and adjuvant RT compared to 16.1 months OS for patients receiving WLE or radical surgery and no RT (p=0.46). Gupta, 2002 (83) provided a single centre retrospective study of 26 cases 1972-2001. A range of interventions including surgery +/- RT were documented but there was no statistical analysis or outcomes, therefore, no conclusions about RT benefit. Kirschner, 2013 (84) used the SEER database 1998-2008 to review 201 cases from 17 registries: 43% surgery alone (radical 52, partial 40, excision biopsy 38, other 11), 15% RT alone and 41.8% received RT, (surg+RT in 26.3%, nearly all adjuvant). Adjuvant RT did not offer an OS advantage compared to surgery alone. However, there were however no data on local control.

Petru, 1998 (85) conducted a retrospective institutional review from 3 centres examining 14 cases from 1982-1996. 9/14 received RT, three as adjuvant after WLE, six after biopsy only. It was reported that the three 5 year survivors, all had tumours <3cm and received 50Gy RT. There was no statistical analysis. Vaysse, 2013 (86) provided a retrospective multicenter database review of 46 patients of which 9/46 had local adjuvant therapy reported that with advanced disease, adjuvant RT was associated with worse OS.
In conclusion, there was limited poor quality evidence. In some studies, there was a trend towards improved OS with adjuvant RT but this effect may be due to case selection. There are no data on local control, quality of life, or margin status as an indication for RT.

9.3.3 Penile Melanoma

No evidence was found

9.4 Economic evidence

No economic evidence was found

9.5 Evidence statements

Clinical

- The are no data to support the use of adjuvant RT routinely in any anatomical site
- For vulvo-vaginal melanoma, at best, a trend towards improved OS with adjuvant RT is seen
- It is not clear how postoperative margin status influences outcome from adjuvant RT, although it is reasonable to assume that in the case of close or positive margins, RT may result in improved local control if further surgery is not possible or will be associated with morbidity
- For ano-rectal melanoma there is some data to suggest reduction in OS with adjuvant RT but these results are confounded by case selection bias

9.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>All AUG Mucosal Melanomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>25. The routine use of adjuvant radiotherapy following curative resection in AUG melanoma is not recommended outside of the context of clinical studies.</td>
<td></td>
</tr>
<tr>
<td>26. If resection with curative intent only achieves an R1 margin, and radical resection is deemed inappropriate, due to associated morbidity or clinical assessment, then consideration should be given to adjuvant radiotherapy.</td>
<td></td>
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<tr>
<td>27. Regional lymph nodes should not be included routinely in the target volume.</td>
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<tr>
<td>28. If external beam radiotherapy is planned in the adjuvant setting a dose should be a radical dose equivalent (e.g. at least equivalent to 45Gy/25#).</td>
<td></td>
</tr>
<tr>
<td><strong>Quality of the clinical evidence</strong></td>
<td>There is limited evidence regarding the role of adjuvant radiotherapy following curative resection in patients with stage I-III melanomas of the anorectal and vulvo-vaginal mucosae and no evidence regarding the role of this modality in penile melanoma. The evidence that is available is of poor quality and insufficient to prove the benefit of adjuvant radiotherapy in AUG melanoma in terms of local disease control, time to the onset metastatic disease or overall survival. It is recognised that adjuvant radiotherapy would be delivered over several weeks which may cause considerable inconvenience to the patient, and may be associated with side effects, both of which may adversely affect quality of life. As such, in the absence of sufficient evidence to support its benefit, The Committee does not recommend the routine use of adjuvant radiotherapy following curative resection in this setting.</td>
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<tr>
<td><strong>Trade-off between clinical benefits and harms</strong></td>
<td>In the event of positive microscopic margins (R1) following curative resection, further surgery to obtain an R0 margin is recommended. However, if further surgery is not feasible or is declined by the patient, adjuvant radiotherapy to the primary site with the aim of securing local disease control may be considered alongside other treatment options such as watchful waiting or a trial of systemic therapy. For further guidance on the management of R1 margins, please refer to the Surgical Chapter. When given, the aim of adjuvant radiotherapy should be to secure disease control at the primary site. It is not recommended that regional nodal basins are included within the treatment field. If there is evidence of metastatic regional nodal disease in the absence of further metastatic disease, patients should undergo lymphadenectomy, as outlined in the Surgical Chapter. There is no role for the prophylactic irradiation of regional nodal basins.</td>
</tr>
</tbody>
</table>
10 Follow-up

10.1 Introduction

Patients with AUG mucosal melanoma who have undergone surgery to the primary site require careful follow up because AUG mucosal melanomas have a high rate of locoregional and/or systemic relapse. The reason that AUG mucosal melanomas have a high rate of relapse is not entirely understood but they tend to be thick tumours and they also have a difference molecular profile from cutaneous melanomas and therefore different biology.

The main principle of follow up for these patients therefore relates to the early detection of locoregional or systemic relapse. The detection of early locoregional relapse is important because it allows surgery to be an option in order to attempt to gain local control. Effective systemic therapies are now available for AUG mucosal melanomas in particular, the same immunotherapies with immune checkpoint inhibitors as are used in cutaneous melanoma. There is evidence that patients with advanced disease and good prognostic features have better outcomes with immunotherapy and therefore early detection of metastases gives the patient a better chance of response to systemic therapy.

There are no randomised or nonrandomised data of follow up in the modern era of immunotherapy and targeted treatment to guide recommendations. The data generated during the era when there were no effective treatments for systemic disease are therefore of limited utility for risk:benefit assessments of the type and frequency of follow up. The data does however have utility in informing us of the pattern, frequency and timing of relapse.

The recommendations for follow up in these guidelines are divided into two: firstly, recommendations for the detection of locoregional recurrence and secondly, the detection of distant relapse. For the detection of locoregional relapse, the recommendations are based on the schedules commonly used for the follow up of patients with common tumours at the 3 anatomical sites relevant to this document, ie anorectum, gynaecological tract and penis. For the detection of distant relapse, the recommendations are based clinical trial follow up protocols and those schedules commonly used in specialist centres for the follow up of patients with high risk cutaneous melanoma.

10.2 Review question: What is the optimal method and frequency of follow-up for patients who have undergone potentially curative surgical treatment for Stage I-III?

Table 14: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>AUG melanoma patients stage I-III who have undergone curative surgical treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To diagnose loco-regional and systemic relapse/recurrence early</td>
</tr>
<tr>
<td>Strata</td>
<td>Type of melanoma: 1) anorectal</td>
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<tr>
<td>Intervention/Investigations and comparators</td>
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<td>-------------------------------------------</td>
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<tr>
<td>2) urogenital</td>
<td></td>
</tr>
<tr>
<td>3) vulvovaginal</td>
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<tr>
<td>Blood tests (FBC, UEs, LDH, LFTs)</td>
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</tr>
<tr>
<td>Radiological testing (US, CT TAP, MRI brain, MRI pelvis, PET-CT)</td>
<td></td>
</tr>
<tr>
<td>Clinical examination (anaesthesia, colposcopy, proctoscopy, speculum examination).</td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
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<tr>
<td>e Twice-yearly interventions for assessment of local site and distant metastases</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (OS)</td>
</tr>
<tr>
<td>Stage at recurrence</td>
</tr>
<tr>
<td>Time to recurrence</td>
</tr>
<tr>
<td>Patient preferences</td>
</tr>
<tr>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>Costs</td>
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<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Change of management</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (I-III)</td>
</tr>
<tr>
<td>Symptomatic vs. asymptomatic</td>
</tr>
<tr>
<td>High-risk vs. low-risk follow-up (high risk defined as survived radical surgery with positive nodes).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients should be assessed at 3 months post initial surgery with clinical examination, full assessment of local area as for the 6-monthly follow up assessment and a base-line CT TAP and if necessary MRI of the region.</td>
</tr>
<tr>
<td>New symptoms must be investigated urgently and fully with imaging if necessary.</td>
</tr>
</tbody>
</table>

**10.3 Clinical evidence**

Three papers were identified as matching the review protocol (82,88,89) These are detailed in Appendix A5.2 in the supplementary appendix.

**10.3.1 Quality of papers**

AUG mucosal melanoma are rare and biological aggressive cancers with poor 5-year overall survival. We cannot find any evidence in the literature of a patient who presented with metastatic disease who has survived for five years or longer, no matter how aggressively they were treated. Most published work tends to come from specialist centres, which have retrospectively reviewed highly selected cases retrospectively. Consequently, these studies suffer from multiple biases. Their results are not necessarily applicable to different centres in different countries. Conclusions written can be misleading or incorrect and may be contradicted with more robust data collected in the future. Institutions who do not find a positive benefit will be more likely to be refused publication. This positive publication bias may encourage, incorrectly, more surveillance to be performed without improving patient survival. Therefore patients may come to hospital to have a test that may not help
them, and at a cost to themselves and the NHS. Attempting to analyse these disparate groups using NICE methodology is therefore very challenging. Consequently, patients and doctors’ opinions regarding the published work vary widely.

All three papers were retrospective case series. The largest cohort of 116 patients was published by our German colleagues (88). This cohort included non-AUG mucosal melanoma: 55/116 patients had penile, vulval or vaginal mucosal melanomas. 20/116 cases melanomas were gastrointestinal (GI) in origin that included both upper and lower GI primary tumour sites. The remaining 41/116 patients had non-AUG mucosal melanomas.

Similarly, a cases series published from Boston that again was not specific to AUG sites. 15/19 melanomas arose in anal, rectal or vaginal sites (89). The remaining 4/19 patients had melanomas of sinonasal origin.

The largest site-specific publication is from MD Anderson. 37/37 patients had clinical stage I mucosal melanoma of the vagina (64).

10.3.2 Outcome measures

Stage and time to recurrence including methods of detection of recurrence

What methods of follow up intervention were described in these papers?

Follow-up was not always standardised in the largest cohort (88). In general, follow-up was carried according to standards in cutaneous melanoma: during the first 5 years after diagnosis, follow-up examinations were carried out every 3 months, thereafter every 6 months. Examinations consisted of a clinical examination of the original location and blood tests (FBC, LFTs, Creatinine and LDH). Upper abdominal US, CXR and whole-body CTs were performed every 6-12 months in selected patients. How these patients were selected to undergo imaging is not clear. Further, how patients were selected for CXR or alternatively US abdomen is not clear. If symptoms were suggestive of metastatic recurrence then a CT of the brain, neck, chest, abdomen and pelvis was completed. The follow-up time range was 8-297 months.

The follow up strategies from Boston were not stated (89). The frequency of clinical appointments and blood tests were not indicated. The patients were imaged frequently with both CT and PET-CT studies. The commonest imaging techniques employed were CT examinations followed by PET-CT studies. 100 CT studies of the chest, abdomen and pelvis were completed with a mean 5.3 studies per patient (range 0-13). 69 PET-CT studies were performed with a mean 3.6 studies per patient (range 0-9).

Follow-up in the vaginal melanoma series was possibly more standardised (89). Typical follow-up included clinical examinations every 3 months for the first year, every 4 months for the second year, every 6 months for the third to the 5th years, and then annually. A chest radiograph was organised annually. Other imaging was ordered as clinically indicated.
10.3.2.2 When and how was local recurrence identified?

In the 37 vaginal melanoma cases, 89% of patients developed recurrence (64). The median vaginal tumour size and range was 3.0 cm and 0.4 cm – 5.0 cm, respectively. During a median follow-up period of 17.4 months, 22% were local (vaginal or vulval), 63% distal and 15% combined local and distal. As no locally directed imaging was routinely used in the follow up, it is presumed that the local recurrence was detected by either the patient or physician. It is not known from the paper whether these recurrences were symptomatic or not.

In the Boston series 5/7 vaginal melanomas developed local recurrence, median time and range to recurrence was 11 months and 5-33 months, respectively. (89). The median vaginal tumour size and range was 2.75 cm and 1.1 cm – 3.5 cm, respectively. 6/7 vaginal primary tumours were initially staged locally with MRI but no mention is made as to whether MRI was employed in surveillance was made. In the same publication, 3/4 rectal tumours developed recurrence, median time to recurrence 3 months, range 2-30 months. The median rectal tumour size and range was 3.8 cm and 3.0 cm – 4.0 cm respectively. The method of local recurrence detection, - whether with this was by proctoscopy, sigmoidoscopy or imaging-, is not stated. Further, it is unclear whether the local recurrence was symptomatic or asymptomatic.

None of the 4 patients with anal mucosal melanomas developed local recurrence (89). The median anal tumour size and range was 1.35 cm and 0.4 cm – 2.0 cm, respectively.

In a case series that included 55/116 patients with AUG mucosal melanoma, there were 2 patients with Tis/T1 penile mucosal melanoma and 6 patients with Tis/T1 vulval mucosal melanoma (88). Site- specific Tis/T1 tumour location was confirmed by e-mail correspondence with the authors. Tumour depth measured up to 1 mm using the 7th AJCC/TNM 2009 classification system. The exact follow-up period of these 8 patients is not stated but the authors describe no local, regional nodal metastatic or distal metastatic disease detection at follow-up. They conclude that surveillance should be concentrated on detecting local recurrence and local nodal metastatic disease. They advocated a whole-body staging CT study only in the unlikely event of new nodal metastatic disease.

10.3.2.3 When and how was local regional nodal metastatic disease identified?

In the 37 vaginal melanoma cases, 89% developed recurrence (64). During a median follow up period of 17.4 months, 22% were local (vaginal or vulval), 63% distal and 15% combined local and distal. As no locally directed nodal imaging was routinely used in the follow up, it is assumed that local or regional nodal recurrence was either detected by patient or physician. It is not known whether these recurrences were symptomatic or not.

In the 15/19 cases that were AUG mucosal melanoma in origin (vaginal, anal and rectal) the time range for new nodal metastatic disease was 3-18 months (89). Both PET-CT and CECT were frequently utilised in the follow up of these patients. It is not clear whether recurrence was detected in asymptomatic or symptomatic patients. The method of nodal metastatic disease detection is not stated. We do not know what proportion of the recurrences was detected clinically or by imaging.

10.3.2.4 When and how was distal metastatic disease identified?

In the 37 vaginal melanoma cases, 89% developed recurrence (64). During a median follow-up period of 17.4 months, 22% were local (vaginal or vulval), 63% distal and 15% combined local and distal.
distal. An annual CXR was completed in the follow-up. Patients were reviewed regularly in clinic at 3- and 6-monthly time intervals in the first 5 years. Additional imaging was requested when clinically needed. It is not known what proportion of metastatic disease was detected in an asymptomatic patient on CXR or with additional imaging that was requested when there was clinical concern of new metastatic disease.

In a case series of 116 patients that included non-AUG mucosal melanoma patients, the mean time interval from regional nodal metastases to distant metastases was 10.2 months +/- 8.5 months (88) mean time straight to metastatic disease detection in this same cohort containing non-AUG patient was 21 months (+/-21.5 months). A CXR and CT whole-body including the brain, neck, chest, abdomen and pelvis were performed in selected patients. It is not clear how patients were selected for imaging studies. It is not clear whether metastatic disease was detected in clinically symptomatic patients or whether distal metastatic disease was detected in the well asymptomatic patient.

The lungs, liver and peritoneum are the commonest sites of metastases (88,89). Less common sites include the CNS, bone, skin, subcutaneous tissue and GIT metastases (88,89).

10.3.3 Overall survival

In 19 patients, 4 of whom had non-AUG mucosal melanoma, the median follow-up was 16 months (89). During this time, 9/19 died, 7/19 were alive but the disease status not known; and 3/19 patients were lost to follow-up.

In the 37 site specific vaginal cases, 2-year overall survival and 5-year overall survival was 46.4% and 20% respectively (64).

- Patient preferences - None stated
- Health-related quality of life - None stated
- Adverse events including false positive and false negative imaging studies - None stated
- Costs - None stated
- Radiation - None stated
- Change in management - None stated

10.4 Economic evidence

No economic evidence was identified

10.5 Evidence statements

Clinical
- Mucosal melanomas have a high relapse rate
- Relapse is commonest in the first 3 years following diagnosis
• Immune checkpoint inhibitor therapy is the preferred first line therapy at systemic relapse*
• Immune checkpoint inhibitor therapy is more effective when low volume disease is present/the LDH is normal and patients have a good performance status *
* Refer to evidence in Chapter 11

10.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Ano-Rectal Mucosal Melanoma</th>
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<tbody>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td>29. In patients with further treatment options for local recurrence, the follow-up schedule for local relapse following potentially curative treatment should be with a 3 monthly clinical examination for the first three years including:</td>
</tr>
<tr>
<td>• External inspection/examination</td>
</tr>
<tr>
<td>• Palpation of inguinal lymph nodes</td>
</tr>
<tr>
<td>• Digital examination</td>
</tr>
<tr>
<td>• Proctoscopy and sigmoidoscopy.</td>
</tr>
<tr>
<td>30. During the first three years following potentially curative treatment the follow-up schedule for systemic relapse should be with:</td>
</tr>
<tr>
<td>• 3 monthly clinical examination according to that used for other malignant tumours at the primary site</td>
</tr>
<tr>
<td>• Baseline CT 2-3 months post-surgery</td>
</tr>
<tr>
<td>• 6-monthly CT thorax, abdomen and pelvis</td>
</tr>
<tr>
<td>• 6 monthly CT or MR of brain should be discussed with the patient</td>
</tr>
<tr>
<td>31. From years 3-5 the follow-up schedule for systemic relapse should include</td>
</tr>
<tr>
<td>• 6-monthly clinical examination according to that used for other malignant tumours at the primary site</td>
</tr>
<tr>
<td>• 12-monthly CT thorax, abdomen and pelvis;</td>
</tr>
<tr>
<td>• CT or MR of brain should be discussed with the patient.</td>
</tr>
<tr>
<td>32. From years 6-10 patients should be given an annual appointment or open rapid access if available.</td>
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<tr>
<td>33. Patients should be discharged at year 10 follow-up.</td>
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<thead>
<tr>
<th>Vulval-vaginal mucosal melanoma</th>
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<tbody>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td>34. In patients with further treatment options for local recurrence, the follow-up schedule for local relapse following potentially curative treatment should be with a 3 monthly clinical examination for the first three years</td>
</tr>
</tbody>
</table>
including:
- External inspection/examination
- Palpation of inguinal lymph nodes
- EUA including speculum examination
- Cystoscopy, if indicated clinically, e.g. urethral involvement.

35. During the first three years following potentially curative treatment the follow-up schedule for systemic relapse should be with:
- 3 monthly clinical examination according to that used for other malignant tumours at the primary site
- Baseline CT 2-3 months post-surgery
- 6-monthly CT thorax, abdomen and pelvis
- 6 monthly CT or MR of brain should be discussed with the patient

36. From years 3-5 the follow-up schedule for systemic relapse should include:
- 6-monthly clinical examination according to that used for other malignant tumours at the primary site
- 12-monthly CT thorax, abdomen and pelvis;
- CT or MR of brain should be discussed with the patient.

37. From years 6-10 patients should be given an annual appointment or open rapid access if available.

38. Patients should be discharged at year 10 follow-up.

Penile Mucosal Melanoma

Recommendations

120. In patients with further treatment options for local recurrence, the follow-up schedule for local relapse following potentially curative treatment should be with a 3 monthly clinical examination for the first three years including:
- External inspection/examination
- Palpation of inguinal lymph nodes
- Cystourethroscopy, if urethral involvement or lesion close to the perimeatal area.

121. During the first three years following potentially curative treatment the follow-up schedule for systemic relapse should be with:
- 3 monthly clinical examination according to that used for other malignant tumours at the primary site
- Baseline CT 2-3 months post-surgery
- 6-monthly CT thorax, abdomen and pelvis
- 6 monthly CT or MR of brain should be discussed with the patient
122. From years 3-5 the follow-up schedule for systemic relapse should include:
   - 6-monthly clinical examination according to that used for other malignant tumours at the primary site
   - 12-monthly CT thorax, abdomen and pelvis;
   - CT or MR of brain should be discussed with the patient.

123. From years 6-10 patients should be given an annual appointment or open rapid access if available.

124. Patients should be discharged at year 10 follow-up.

### Quality of the clinical evidence

Evidence from the literature is of low quality with single centres producing audits of current practice. There are no internationally agreed standards. Three papers selected from recognised cancer centres, two from the same centre in Tubingen.

### Modalities clinical benefits and harms

<table>
<thead>
<tr>
<th>Modality</th>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>Ultrasound is quick, cheap and readily accessible. It has particular utility for the identification of inguinal lymph node involvement and guiding fine needle aspiration.</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>CT can assess the whole body including the brain and is readily accessible, cheap and very convenient to the patient. A CT study can be completed in just a few minutes and patients tolerate this whole body staging very well.</td>
<td></td>
</tr>
<tr>
<td>PET-CT</td>
<td>PET-CT is a longer procedure than CT, results in a higher dose of radiation to the patient and is about 10 times more expensive than a CT examination. PET-CT has an important role in the initial staging of selected patients prior to radical surgery. Its high negative predictive value for excluding distal disease has the potential to detect difficult to detect metastatic disease prior to radical surgery with curative intent.</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>MRI typically may help with detection of local recurrence but can also be used to examine the nodes, brain, abdomen, pelvis and bones. However, MRI is less accurate than CT in detecting metastatic spread to the lungs, which is the most common organ that AUG melanoma spreads to. Some patients find MRI time consuming, claustrophobic and very noisy. The prognosis of AUG mucosal melanomas is poor once it has spread to either local nodes or distant sites although there is emerging data demonstrating the activity of immunotherapy disease for both visceral and CNS disease. Therefore, it is important that the timing and investigations of follow up schedules are discussed with the patient.</td>
<td>In the absence robust data on the optimal follow up schedule and imaging modalities, these guidelines are based on consensus and the principle that there may be an advantage to early diagnosis of systemic relapse in view of emerging data on immunotherapy.</td>
</tr>
</tbody>
</table>
11 Management of metastatic disease

11.1 Introduction

Mucosal melanomas generally carry a worse prognosis than those arising from cutaneous sites. Often the primary tumours are thick and locally advanced at diagnosis, and a large proportion of patients develop metastatic disease. Once tumour dissemination occurs, the outlook for these patients is very poor. Options for the systemic treatment of cutaneous melanoma have improved dramatically in the last decade with successes seen in both targeted treatments, e.g. BRAF inhibitors and in immunotherapy, e.g. CTLA4 and PD1 checkpoint inhibitors. These novel systemic options have demonstrated an unprecedented improvement in progression free and overall survival in patients with melanoma with some patients achieving long terms (>5-year) survival. Due to the rarity of mucosal melanoma, and because of the unique biology and clinical challenges of mucosal melanoma arising from each anatomic location, our understanding of these malignancies and their optimal management remains uncertain. Patients with mucosal melanoma were enrolled in a proportion of the trials of systemic treatment for cutaneous melanoma but there are few studies specifically aimed at patients with metastatic mucosal melanoma. It is important to understand the true success and potential toxicities of novel agents in mucosal melanomas to aid patient decision-making.

11.2 Review question: What is the effectiveness of systemic therapy for stage IV and unresectable stage III disease?

Table 15: PICO characteristics of review question

<table>
<thead>
<tr>
<th>Population</th>
<th>AUG melanoma patients stage III (unresectable) and stage IV (metastatic or advanced melanoma/mucosal melanoma).</th>
</tr>
</thead>
</table>
| Intervention(s) | Targeted immunotherapy (palliative treatment)  
• Chemotherapy (bio-chemotherapy)  
• Immunotherapy (interferon ± interleukin-2, pembrolizumab, nivolumab, ipilimumab)  
• KIT or CKIT targeted treatment (imatinib, dasatinib)  
• Combinations of the above. |
| Comparison(s) | Observation (no systemic therapy) |
| Outcomes | Overall survival (OS)  
Progression-free survival  
Local control  
Health-related quality of life  
Treatment-related morbidity  
Treatment-related mortality |
| Study design | Randomised Controlled trial, Observational studies, Case Series GT 2 |
11.3  Clinical evidence

We searched for randomised trials and non-randomised observational studies comparing the effectiveness of systemic treatment compared to no systemic treatment for people with Stage IV or unresectable Stage III anorectal, urogenital or vulvovaginal mucosal melanoma. Single case reports and review articles were excluded. No randomised controlled trials specifically for patients with mucosal melanoma were identified.

11.3.1 Immunotherapy

Ipiilimumab

Following a positive phase 3 trial in metastatic melanoma many countries gained access to 2nd line Ipiilimumab via Extended Access Programmes (EAPs). Retrospective reviews of patients within EAPS provide some data on the efficacy of ipilimumab in unresectable and metastatic mucosal melanoma. However, many reports contain little detail about the number of patients with mucosal melanoma who accessed the drug, and those papers that give details about the number of patients with mucosal melanoma do not stratify between anatomical sites. Furthermore, whilst details of inclusion of patients with mucosal melanoma may be described, often little detail is given on the outcome of this specific subgroup.

Overall data was included from 5 EAPs (90–94) 1 phase 2 study of ipilimumab (95) and 1 3 centre review of practice (96) (n=165 patients total). These were all non-randomized, second line reports. Data from 2 of the EAPs (93,94) were only available in abstract form.

In all studies the overall survival for patients with mucosal melanoma was less than 12 months. Some groups felt the patients with mucosal melanoma had worse outlook and worse response than those with cutaneous melanoma, although there was a lack of consistency between reports with the larger report form the Italian EAP suggesting no difference in outcome and response between cutaneous and mucosal melanoma. The studies are summarized in Table 16

Table 16: Included studies of ipilimumab in unresectable Stage III or Stage IV mucosal melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>N mucosal (total number patients in study)</th>
<th>Type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander</td>
<td>8 (104)</td>
<td>Australia EAP 2nd line ipilimumab</td>
<td>Cutaneous MM median OS 11.7mo; Mucosal MM OS 5.8mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cutaneous MM median PFS 3 mo, mucosal MM median PFS 2.7mo</td>
</tr>
<tr>
<td>Del Vecchio</td>
<td>71 (855)</td>
<td>Italy EAP 2nd line ipilimumab</td>
<td>Mucosal melanoma: Immune-related best overall RR 12%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disease control rate 36%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median OS 6.4 MO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median PFS 4.3MO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Similar results to the overall population.</td>
</tr>
<tr>
<td>Name</td>
<td>Number (Reference)</td>
<td>Location/Program</td>
<td>Result</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Jung</td>
<td>27 (104)</td>
<td>Korean patient programme</td>
<td>Overall: Median PFS 2.73 months (95% CI 2.67-2.85) Overall response rate (ORR=CR+PR) 8.6% Disease control rate (DCR=CR+PR+stable disease) 29.8% Mucosal melanoma results not statistically different.</td>
</tr>
<tr>
<td>Rapoport (abstract only)</td>
<td>42 (119)</td>
<td>S. Africa EAP</td>
<td>Overall Survival 8.9 mo</td>
</tr>
<tr>
<td>Postow</td>
<td>33</td>
<td>USA 3 centre analysis</td>
<td>Median OS 6.4mo</td>
</tr>
<tr>
<td>Shaw (abstract only)</td>
<td>4 (27)</td>
<td>UK EAP</td>
<td>No responses seen in 4 patients with mucosal melanoma.</td>
</tr>
<tr>
<td>Zimmer</td>
<td>7 (103)</td>
<td>Phase 2 2nd line</td>
<td>Overall Survival 9.6 months ORR 17%</td>
</tr>
</tbody>
</table>

**Pembrolizumab**

One report was identified describing efficacy of the PD1 inhibitor pembrolizumab in patients with metastatic mucosal melanoma. At the time of writing data this is currently only available in abstract form (97) This abstract details subgroup analysis of KEYNOTE 1, 2 and 6 studies of pembrolizumab. It should be noted that differing doses and schedules of pembrolizumab were used in these studies. Overall 84 patients with mucosal melanoma were included in the trials: 5% of the total study population. Overall response rate to pembrolizumab was 19% (95% CI 12–29%) in patients with mucosal melanoma, Disease control rate 31% (95% CI 22–42%), Progression free survival 2.8 months (95% CI 2.7–2.8) and overall survival 11.3 months (95% CI 7.7–16.6). This compares to results in the overall population of 33% overall response rate, 47% disease control rate, 4.2 months PFS and 23.5 month OS.

**Nivolumab and Combination Nivolumab and Ipilimumab.**

Data on nivolumab and combination nivolumab and ipilimumab treatments were available from 1 study (98) This reported pooled data on patients with mucosal melanoma from 6 studies including 4 phase 3 trials. Overall 86 patients with mucosal melanoma had been treated with single agent nivolumab, and 35 patients with nivolumab and ipilimumab combination treatment.
Patients treated with Nivolumab monotherapy had a median PFS of 3.0 months (95% CI 2.2-5.4) compared to a PFS of 6.3 months (95% CI 5.1-7.5) for patients with cutaneous melanoma. The Objective Response rate to nivolumab was 23.3% (95% CI 14.8-33.6%) in patients with mucosal melanoma versus 40.9% (95% CI 8.9-16.7) in patients with cutaneous melanoma.

For the Nivolumab and ipilimumab combination the median PFS was 5.9 months (95% CI 2.8-not reached) for mucosal melanoma patients and median PFS of 11.7 months (95% CI 8.9-16.7) in cutaneous melanoma. Objective response rate was 37.1% (95% CI 21.5-55.1%) in mucosal melanoma and 60.4% (95% CI 54.9-65.8) in cutaneous melanoma.

Importantly toxicity did not appear to be worse in patients with mucosal melanoma.

**PD1 inhibitors**

Further evidence for the use of single agent PD1 inhibitors mainly in the second line setting comes from a USA multicentre retrospective review of patients with acral or mucosal melanoma who received varying doses and schedules of nivolumab or pembrolizumab as single agents (99). Thirty-five patients with mucosal melanoma were included in the report (n=12 anorectal, n=14 vulvovaginal, n=9 head and neck). The authors report an ORR of 23%, median PFS of 3.9 months and median OS of 12.4 months in the mucosal melanoma subgroup. These results are numerically similar to the results observed in trials of single agent PD1 inhibitors in clinical trials.

**11.3.2 Chemotherapy/Biochemotherapy.**

Three reports of multiple treatments including chemotherapy and biochemotherapy were included. (87,100,101) were all descriptive retrospective reviews, 2 from USA centres (87,100) (N=18 and n=61, one abstract only) and one larger series from China (46) (n=263, abstract only available). These reports mostly included patients prior to the availability of immunotherapy treatment options. Activity was reported in mucosal melanoma with chemotherapy and biochemotherapy but little in-depth data is given to draw any firm conclusions about response rates and specific therapies. Other reports of chemotherapy in mucosal melanoma suggest some activity with carboplatin paclitaxel (102) in the pretreated population; however, there is little data specific to the AUG mucosal melanoma group, which means that robust evidence based recommendations are not possible.

**11.3.3 CKIT inhibitors**

Mutations and/or amplifications of the CKIT gene have been identified in up to 25% of mucosal melanomas. (103)

A number of small phase 2 trials and case series have studied the use of agents targeting CKIT in mucosal melanoma. (104–109) Many of these studies are specific to melanomas harbouring CKIT mutations and/or amplifications and as such are not specific to mucosal melanomas, as CKIT mutations are also found in acral melanomas and melanomas arising in chronically sun-damaged skin. A number of drugs are available that target CKIT including imatinib, sunitinib, dasatenib and sorafenib. These have been studied in varying doses and schedules. Responses to these drugs have been reported in AUG melanomas harbouring CKIT mutations but the numbers too small to draw firm conclusions about efficacy, drug choice, dose, schedule or biomarkers. Indeed some CKIT mutations, particular those in exon 11 and 13 appear to have a higher response to CKIT targeting. (104,109)
CKIT targeting agents are not currently licensed or funded in the UK for use specifically in CKIT mutated mucosal melanomas. Data from ongoing studies, e.g. the PLX3397 KIT in Acral and mucosal Melanoma (PIANO) trial, are awaited.

11.3.4 BRAF inhibitors

The use and efficacy of BRAF inhibitors +/- MEK inhibitors in unresectable Stage III and Stage IV malignant melanoma is well established and are recommended by NICE in England and Wales. BRAF mutations are less common in mucosal melanomas but have been reported in non-cutaneous melanomas particularly in patients of Asian descent. A single site retrospective review of patients treated with BRAF inhibition in Korea demonstrated similar efficacy of BRAF inhibitors in patients with mucosal melanoma harbouring BRAF mutations compared with the effects seen in cutaneous BRAF mutated malignant melanoma. (110)

11.4 Economic evidence

No Economic evidence was found.

11.5 Evidence statements

- There is evidence supporting the use of immunotherapy in patients with mucosal melanoma from a small number of studies. Evidence supports the use of PD1 inhibitors, as monotherapy or in combination with ipilimumab. There are also some retrospective data to support the use of 2nd line ipilimumab. The data suggests that these treatments may not be as effective as in cutaneous melanoma. Importantly, there are no mucosal melanoma-specific randomised studies, and these conclusion are based on ‘all comers’ rather than AUG-specific mucosal melanoma data. Randomised prospective trial data supports the use of antiPD1 agents although the data is not yet mature and OS benefit is not yet known.

- There is insufficient evidence to recommend the use of chemotherapy or biochemotherapy in unresectable Stage III or Stage IV mucosal melanoma.

- A small number of phase 2 trials and case reports report promising responses using CKIT inhibitors in CKIT-mutated mucosal melanoma.

- There is evidence to support the use of BRAF and MEK inhibitors in BRAF-mutated mucosal melanoma. Evidence can also be extrapolated from the use of BRAF and MEK inhibitors in BRAF mutated malignant melanomas from other anatomical sites.

11.6 Recommendations and link to evidence

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>ALL AUG Mucosal Melanomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staging</td>
<td>Investigations</td>
</tr>
<tr>
<td>34. Local staging’ should be as for common tumours at the anatomical site (vulva, vagina, anus, rectum, and penis). At presentation there should also</td>
<td></td>
</tr>
</tbody>
</table>
be staging investigations looking for systemic disease and these are generic for all anatomical sites.

Treatment

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

36. Use single agent anti-PD1 antibodies in suitable patients with unresectable Stage III or Stage IV tumours.

37. Consider combination immunotherapy in selected fit patients.

38. 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.

39. BRAF + MEK inhibitors should be offered as a treatment option to patients with BRAF mutated unresectable Stage III or Stage IV A UG melanoma.

40. In patients with targetable mutations, immunotherapy is the preferred first line option unless the patient has a poor performance status and/or very bulky disease.

41. Even if a targetable CKIT mutation is identified, the patient needs to be carefully counselled that it is most likely this test will not change their management. Funding for a CKIT inhibitor would have to be sought on and would not be guaranteed. The presence of a CKIT mutation may facilitate entry into clinical trials.

42. There is insufficient evidence to recommend the routine use chemotherapy or bio-chemotherapy in the treatment of metastatic disease.

43. Palliative radiotherapy can be considered alongside immunotherapy without interruption of the immunotherapy. There is currently no data to suggest increased rates of toxicity but this is the subject of ongoing research.

Follow-up

44. If there is metastatic disease, follow-up should include CT thorax, abdomen and pelvis and MR or CT of brain. Other palliative options for skin metastases that could be considered include:

45. Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446) Electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma (IPG446)
## 46. Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410)  [https://www.nice.org.uk/guidance/ta410](https://www.nice.org.uk/guidance/ta410)

### Linking Evidence to recommendations

- Randomised prospective trial data supports the use of anti-PD1 agents although the data are not yet mature and OS benefit is not yet known.
- The data demonstrates lower response rates from immunotherapy in mucosal melanoma.
- Therefore, the significant toxicity of combination immunotherapy needs to be carefully discussed with patients as the younger, fitter patients may prefer this.
- There is insufficient evidence to support the use of either chemotherapy or biochemotherapy in the treatment of metastatic disease.

### Quality of the clinical evidence

- No specific randomised trials of mucosal melanoma.
- Quality of evidence:
  - Evidence for ‘mucosal melanoma’ rather than any specific split into AUG and head and neck.
  - Evidence for immunotherapy mainly from retrospective reviews of EAPs of ipilimumab and/or subgroup analysis of trials.
  - Evidence for CKIT inhibitors often small numbers, phase 2 or case reports. Often combined CKIT- mutated melanoma including acral melanomas.
  - Some abstracts/posters only.

### Trade-off between clinical benefits and harms

Subgroup analysis of randomised controlled trials demonstrate an improved response rate and 1-year survival rate benefit in patients with mucosal melanoma treated with combination immunotherapy compared to single agent PD1 inhibitor. However, the data remains immature. Concern also remains about the significant increased toxicity observed with combination immunotherapy. It is recommended that the risks and benefits of combination immunotherapy are discussed with the patient taking into account individual co-morbidities and preferences.

### Other considerations

Treatment with immunotherapy and BRAF/MEK inhibitors has been recommended in NICE guidance for the treatment of metastatic cutaneous melanoma.

Any future recommendations regarding the use of BRAF- inhibitors and immunotherapy should be considered when deciding on treatment for patients with mucosal melanomas.
12 Care Pathways
12.1 Anorectal mucosal melanoma

Possible AR melanoma?
(See Box 1)

Refer to colorectal surgeon or dermatologist with an interest in pigmented lesions via the urgent cancer referral pathway for patients with symptoms or signs (Refer to Box 1)

Perform excision biopsy or punch biopsy to make diagnosis.

If clinically suspicious/palpable lymph nodes refer for an ultrasound and FNA of the suspicious node

Staging Investigations
- Local staging should be as for common tumours at the anatomical site (anus, rectum) and include:
  - External inspection/examination
  - Palpation of inguinal lymph nodes
  - Digital examination
  - Examination Under Anaesthetic (EUA), Proctoscopy + flexible +/- sigmoidoscopy
  - MR pelvis.
- 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.
- If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered a PET-CT scan should be performed.
- Carry out BRAF, NRAS and KRAS mutational testing
- Assess resectability by investigations detailed above.

Resectable with no inguinal lymph nodes
- WLE aiming for R0 margin
- Post-operative margins
- R0
- Enter surveillance
- Repeat WLE or consider low anterior resection/APR if appropriate

Resectable with regional lymph nodes
- WLE aiming for R0 margins + lymphadenectomy
- Post-operative margins
- R1 – suitable for further surgery

Resectable with mesorectal lymph nodes
- Perform PET-CT and MRI of the brain to exclude low volume metastatic disease.
- Low anterior resection or APR

Irresectable or metastatic disease
- Consideration of systemic therapies (see recommendations for metastatic disease). Surgery only for palliation.

Consider adjuvant radiation
- External beam radiotherapy with a radical dose equivalent [e.g. at least equivalent to 450Gy/25f]
- Regional lymph nodes should not be included routinely in the target volume
12.2 Vulval-vaginal mucosal melanoma

Box 1

Signs and symptoms of possible ano-rectal mucosal melanoma

- Bleeding
- Pain
- Mass or swelling
- Palpable lymph nodes associated with anal symptoms (e.g. in the groin)
- Tenesmus
- Pigmented lesions
- Atypical haemorrhoids
- Polyps
- Unexplained lumps

Follow-up

0-3 Years post-surgery
- 2-3 months post-surgery: baseline CT
- 3 monthly clinical examination:
  - External inspection/examination
  - Palpation of inguinal lymph nodes
  - Digital examination
  - Proctoscopy and sigmoidoscopy
- 6 monthly CT thorax, abdomen and pelvis
  - CT or Mri of brain should be discussed with the patient

3-5 Years post-surgery
- 6 monthly clinical examination according to that used for other malignant tumours at the primary site
- 12 monthly CT thorax, abdomen and pelvis
- CT or Mri of brain should be discussed with the patient

6-10 Years post-surgery
- Annual appointment or open rapid access if needed

10 Years post-surgery
- Discharge
Possible Vulvo-vaginal melanoma?
(See Box 1)

- Refer to joint gynaecology/dermatology clinic or gynaecological oncology team via the urgent cancer referral pathway (e.g. the two 2 week wait pathway)
- Consider ultrasound and FNA or core biopsy of lymph nodes, if patient presents with vulva/vaginal lesions and loco-regional lymphadenopathy.

Perform excision biopsy or punch biopsy to make diagnosis.

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
  - Biopsy including speculum examination
  - Cystoscopy, if indicated clinically e.g. urethral involvement.
- 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 MR or CT of brain.
- If major surgery (i.e. surgery involving more than WLE and/or lymph node dissection) is being considered a PET-CT scan should be performed.
- Carry out BRAF, NRAS and KIT mutational testing.
- Assess resectability by investigations detailed above.

Vulval melanomas < 4 cm in size
- Radical excision in the form of anterior or posterior vulvectomy aiming for an R0 margin

Vulval melanomas > 4 cm in size
- WLE aiming for R0 margin + lymphadenectomy

Resectable with metastatic nodal disease
- Perform PET-CT and MRI of the brain to exclude low-volume metastatic disease.
- Radical resection

No
- Perform Lymphadenectomy

Metastatic regional nodal disease?
- Yes
- Consideration of systemic therapies (see recommendations for metastatic disease). Surgery only for palliation.

R0
- R0 - suitable for further surgery
- Enter surveillance

R1 - unsuitable for further surgery
- Repeat WLE
- Consider adjuvant radiation
- External beam radiotherapy with a radical dose equivalent (e.g. at least equivalent to 450 Gy/25 F).
- Regional lymph nodes should not be included routinely in the target volume.
Box 1

**Signs and symptoms of possible vulvo-vaginal mucosal melanoma**

- Melanocytic pigmentation
- Persistent itching
- Lump or an ulcer
- Bleeding
- Difficulty in passing urine/urethral obstruction
- Lump in the groin
- Irregularly-edged pigmented lesion (black or dark brown, red, white or patchy coloured.
- Vulval/vaginal lesion(s) with ulceration or contact bleeding
- Groin lymph node(s) enlargement
- Obstruction of urethral meatus
- Distant metastasis

Follow-up

**0-3 Years post-surgery**

- 2-3 months post-surgery: baseline CT
- 3 monthly clinical examination:
  - External inspection/examination
  - Palpation of inguinal lymph nodes
  - Digital examination
  - Proctoscopy and sigmoidoscopy
- 6-monthly CT thorax, abdomen and pelvis

CT or MR of brain should be discussed with the patient

**3-5 Years post-surgery**

- 6-monthly clinical examination according to that used for other malignant tumours at the primary site
- 12-monthly CT thorax, abdomen and pelvis
- CT or MR of brain should be discussed with the patient

**6-10 Years post-surgery**

- Annual appointment or open rapid access if available

**10 Years post-surgery**

- Discharge
12.3 Penile mucosal melanoma

Staging Investigations:
- Local staging should be as for common tumours at the anatomical site (squamoid cell carcinoma of the penis) should include:
  - External inspection/examination
  - Palpation of inguinal lymph nodes
  - Penile MR with a pharmacologically induced artificial erection should be utilised in surgical planning. Staging should be performed as per penile squamous cell carcinoma.
  - Cysto-urethroscopy, if urethral involvement or lesion close to the perineal area
- 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 MR or CT of brain.
- If radical penile surgery is being considered, PET-CT and MR of the brain should be performed pre-operatively to exclude low volume metastatic disease.
- Carry out BRAF, NRAS and CKIT mutations testing
- Assess resectability by investigations detailed above.

**Possible Penile melanoma?**
(See Box 1)

Refer to a dermatologist or urologist via the urgent cancer referral pathway (e.g. the 2-week wait pathway)

Perform excision biopsy or punch biopsy to make diagnosis.

Consider ultrasound and FNA or core biopsy of lymph nodes, if patient presents with a penile lesion and palpable inguinal lymph nodes

Resectable with no locoregional lymph nodes
- WLE aiming for R0 margin
- Post-operative margins
  - R0
  - Enter surveillance

Resectable with regional lymph nodes
- WLE aiming for R0 margin + radical lymphadenectomy
- Repeat WLE or consider glansectomy/distal urethrectomy
- Consider adjuvant radiation
- External beam radiotherapy with a radical dose equivalent (e.g. at least equivalent to 45Gy/25#).
  - Regional lymph nodes should not be included routinely in the target volume

Resectable with metastatic nodal disease
- Perform PET-CT and MRI of the brain to exclude low volume metastatic disease.
- Radical resection for primary
  - R1 - suitable for further surgery
  - Consider adjuvant radiation

Irresectable or metastatic disease
- Consideration of systemic therapies (see recommendations for metastatic disease). Surgery only for palliation.
  - R1 - unsuitable for further surgery

Cont...
Box 1

Signs and symptoms of possible penile mucosal melanoma

- Bleeding from penile lesion
- Urethral discharge/bleeding
- Presence of mole/lump on penis
- Pigmented lesion on glans 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

Follow-up

0-3 Years post-surgery
- 2-3 months post-surgery: baseline CT
- 3 monthly clinical examination
  - External examination
  - Palpation of inguinal lymph nodes
  - Cystoscopy if urethral involvement
- 6-monthly CT thorax, abdomen and pelvis
  C7 or MR of brain should be discussed with the patient

3-5 Years post-surgery
- 6-monthly clinical examination according to that used for other malignant tumours at the primary site
- 12-monthly CT thorax, abdomen and pelvis
  - C7 or MR of brain should be discussed with the patient

6-10 Years post-surgery
- Annual appointment or open rapid access if available

10 Years post-surgery
- Discharge
13 Using and implementing the guideline

13.1 Potential organisational and financial barriers to applying the recommendation

The main potential organisational barrier to these guidelines relates to where, the specialist melanoma team, which deals with advanced local or metastatic melanoma and the anatomical site specialist surgical team, are located. It is therefore imperative that within a tertiary centre, the surgical teams caring for ano-rectal, gynaecological and penile cancers and the team caring for those with advanced local or metastatic melanoma prospectively define the communication pathways between them. The communication pathway must also include clear procedures, for communicating with secondary and primary care colleagues.

There will be geographic challenges to closer working between the teams responsible for patients with AUG melanoma but this does not change the imperative of close communication between the relevant MDTs. Lead cancer clinicians within tertiary centres must take responsibility for ensuring that these pathways are robust, 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, it is likely to be very small.

13.2 Audit criteria

- A member of the MDT is named in the case-notes as the designated keyworker.
- There is a record in the case-notes of the discussion of management, between the named consultant responsible for the patients care and other consultants involved in the care and that this has been copied to the patient’s general practitioner.
- Staging investigations included BRAF, NRAS and CKIT mutations testing
- Systemic adjuvant therapy was not offered (7% of cases)
- There is a follow-up appointment documented every 3 months for the first 3 years.
- Patients are discharged after 10 years of symptom free survival
14 Review and updates

The guideline was published **** 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 designate 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 Guideline Development Methodology (Link), which also contains further details of the update methods.
15 Research recommendations

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

1. 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 surgery treatment radical or otherwise to obtain on-going and dynamic data on surgical practice and outcomes.

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

3. 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.

4. There are good data from prospective studies in patients with cutaneous 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.

5. 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.

6. The use of the SACT database will form an important part of any audit of systemic therapy and rolling prospective audits of this database should be put in place.

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)
16 References


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<tr>
<td>APR</td>
<td>Abdominoperineal resection</td>
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<td>AUG</td>
<td>Ano-uro-genital</td>
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<td>CLND</td>
<td>Complete lymph node dissection</td>
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<tr>
<td>CNS</td>
<td>Clinical Nurse Specialist</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>EUA</td>
<td>Examination under anaesthetic</td>
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<td>GDG</td>
<td>Guideline Development Group</td>
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<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>MDT</td>
<td>Multi-disciplinary team</td>
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<tr>
<td>MR</td>
<td>Magnetic resonance imaging</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>PIANO</td>
<td>PLX3397 KIT in Acral aNd mucOsal Melanoma</td>
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<td>PFS</td>
<td>Progression free survival</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SNBx</td>
<td>Sentinel Node Biopsy</td>
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<td>WLE</td>
<td>Wide Local Excision</td>
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