HEAD & NECK MUCOSAL MELANOMA GUIDELINE

Executive Summary

April 2020

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

MELANOMA FOCUS

www.melanomafocus.com

Authors

Guideline Development Group members

Prof Kevin Harrington	Chairman, Professor in Biological Cancer Therapies	The Institute of Cancer Research
Dr Derfel ap Dafydd	Consultant Radiologist	The Royal Marsden NHS Foundation Trust
Dr Izhar Bagwan	Consultant Histopathologist	Royal Surrey County Hospital NHS Foundation Trust
Mrs Donna Begg	Clinical Nurse Specialist	University Hospitals Birmingham
Dr Paul Craig (Resigned November 2018)	Dermatopathologist	Gloucestershire Hospitals NHS Foundation Trust
Mr Cyrus Kerawala	Consultant Maxillofacial/Head and Neck Surgeon	The Royal Marsden NHS Foundation Trust
Mrs Emma King	Consultant Otorhinolaryngology, Head and Neck surgeon	Poole Hospital NHS Foundation Trust and Uni-versity of Southampton
Ken Lingley	Carer representative	Suffolk
Dr Pablo Nenclares	Rapporteur Research Fellow	The Institute of Cancer Research
Professor Vinidh Paleri	Consultant Head and Neck Surgeon	The Royal Marsden NHS Foundation Trust
Gillian Paterson	Patient representative	Suffolk
Dr Miranda Payne	Consultant Medical Oncologist	Oxford University Hospitals NHS Foundation Trust
Dr Oliver Pearce (Resigned January 2019)	Consultant Radiologist	The Royal Bournemouth and Christchurch NHS Foundation Trust
Mr Priyamal Silva	Consultant Otolaryngologist/ Head and Neck Surgeon	Oxford University Hospitals NHS Foundation Trust
Dr Neil Steven	Consultant Medical Oncologist	University of Birmingham University Hospitals Birmingham NHS Foundation Trust
Dr Kent Yip	Consultant Clinical Oncologist	East Suffolk and North Essex NHS Foundation Trust

Co-optees

Dr Richard Roope	RCGP & CRUK Clinical Champion for Cancer	The Whiteley Surgery, Fareham, Hampshire
Prof Paul Speight	Professor Emeritus Pathology	University of Sheffield

Support

Mrs Nancy Turnbull	Project Manager	London

Observers

Mr Simon Rodwell	Chief Executive	Melanoma Focus
Susanna Daniels	Project Manager	Melanoma Focus

Contents

1 How to use this guideline 4

2 Introduction 5

3 Recommendations 6

4 Photographs 14

5 Care Pathway 14

6 Implementing the guideline 15

7 Research recommendations 16

8 Review and updates 16

9 Abbreviations 17

1 HOW TO USE THIS DOCUMENT

This document is the Executive Summary, containing the recommendations and care pathway. It focuses on the management of patients with Head and Neck Mucosal Melanoma (HNMM) and is, therefore, more accessible for practising clinicians than the Full Guideline. In general, unless stated specifically, the recommendations hold true for all of the respective sub-sites within the head and neck region (sino-nasal, oral cavity and laryngo-pharyngeal) and are not repeated separately for each sub-site. In particular, the general recommendations on patient-focused care, management guided by multidisciplinary team meetings, and the treatment of patients with metastatic disease are identical irrespective of the sub-site of origin within the head and neck region.

The Full Guideline supporting this document contains the background information, methodology, evidence reviews and the Guideline Development Group (GDG) discussion. The Appendices with the evidence tables, search strategies and other background information are also available as a separate document.
All documents are available to download from the Melanoma Focus website:
https://melanomafocus.com/activities/mucosal-guidelines/

The abbreviations used in the document are detailed at the end of the document in Abbreviations.

2 INTRODUCTION

Mucosal melanomas mainly occur within the upper aero-digestive tract and paranasal sinuses, the conjunctiva, the anorectal region, vagina and vulva, and penis. This guideline relates to mucosal melanomas in the head and neck region, specifically dealing with sinonasal, oral cavity, laryngeal and pharyngeal mucosal melanomas. It does not address the management of patients with mucosal melanomas affecting the anorectal region or urogenital tract, which have been addressed in detail in a previous guidance document (https://melanomafocus.com/activities/mucosal-guidelines/mucosal-melanoma-resources/). Melanomas of the uveal tract have also been excluded from the analyses in this guideline but are covered in the previous guideline: https://melanomafocus.com/activities/um-guidelines-resources/.

This guidance specifically relates to mucosal melanomas arising in the upper aerodigestive tract. The term 'mucosal' was used in our systematic searches. In contrast to mucosal melanomas of ano-uro-genital (AUG) origin, HNMM is rarely confused with cutaneous melanoma. The only anatomical sites at which confusion might arise are at the vermilion border of the lips, at the commissures of the lips where the buccal mucosa abuts the skin, and at the nostrils. In most circumstances, the nature of the melanoma (mucosal versus cutaneous) is readily evident, based on clinical, radiological, pathological and, occasionally, molecular features.

The recommendations are supported by systematic reviews of the best available evidence. Details of the methods used, evidence reviews and the GDG discussions are available in a separate document together with a further document containing the appendices and supporting tables. All documentation is available from the Melanoma Focus website: **melanomafocus.com**

3 RECOMMENDATIONS

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

Patient focused care

1. Information should be available throughout the patient pathway in an individualised manner and provided as needed.
2. Cancer centres should name a specific oncologist or surgeon within the specialist melanoma team who is responsible for communication between the cancer centre teams caring for the patient, and between the cancer centre and primary and secondary care. Provision should also be made for a deputy when this person is away.
3. Standard care available to all patients throughout the UK should include:
   - A named cancer nurse specialist and consultant, together with contact details
   - Contact details of a designated keyworker, who is usually the cancer 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
   - Easy access to out-patient review
   - Easy and prompt access to cross-sectional imaging during follow-up and if symptoms or signs develop
   - Early access to palliative support networks.
4. Offer the patient and/or carer an opportunity to discuss prognosis.
5. Offer early referral to services, for example enhanced supportive care, palliative care support services and support groups.

Multi-disciplinary teams

6. The specialist MDT that deals with melanomas and the head and neck MDT should be linked. Prior to treatment the following should take place:
   - The patient's management should be discussed at both the specialist melanoma and the head and neck MDT meetings.
   - The diagnostic pathology specimen (i.e. tissue with conventional and immunohistochemical stains, plus any associated molecular pathology reports) should be reviewed by the melanoma pathologist.
   - The management plan should represent a consensus between the melanoma MDT and the specialist head and neck team. The outcome of the MDT discussion should be shared with the patient and carer and should be communicated to other health professionals involved in the patient's care (e.g. general practitioner).
   - Following the melanoma MDT discussion, a named consultant responsible for the patient's care ('the responsible melanoma MDT consultant') should communicate directly with other consultants who are involved (e.g. surgeons/oncologists from the head and neck MDT) about all aspects of the patient's management.
   - This communication should be entered into the patient notes by 'the responsible melanoma MDT consultant' and copied to the patient's general practitioner so that all communication can be audited.
7. Staging should be confirmed and documented at the MDT, entered in the patient's notes and copied to the patient's general practitioner.
8. Head and neck specialist follow-up may be devolved locally in accordance with the guidance in the Follow-up section below.

9. Patients with proven metastatic disease should be referred directly to the specialist melanoma MDT and copied to the patient's G.P.

Recognition, referral and diagnosis

10. Patients with persistence or recurrence of any of the following symptoms or signs lasting approximately 3 weeks or more* should be referred to a head and neck clinic via the urgent cancer referral pathway (e.g. two-week wait pathway):
    - unilateral nosebleeds
    - unilateral nasal blockage or obstruction (not responding to topical steroids)
    - a non-healing mouth ulcer
    - persistent hoarseness
    - cervical lymphadenopathy

    *as per NICE guidance NG12 https://www.nice.org.uk/guidance/ng12

11. Patients with persistence or recurrence of any of the following symptoms or signs lasting approximately 3 weeks or more* should be referred to a head and neck clinic via the urgent cancer referral pathway (e.g. two-week wait pathway):
    - pigmented lesion of the mouth, particularly palate or gingivae
    - rapidly progressing and/or bleeding non-pigmented lesion

    *as per NICE guidance NG12 https://www.nice.org.uk/guidance/ng12

12. Ideally, where practical, imaging should precede biopsy (see recommendations 22 and 23 for details of staging investigations).
    - Especially if malignancy is strongly suspected.
    - Depending on clinical presentation, tumour location, route of referral and local infrastructure, post-biopsy imaging may be considered appropriate in certain cases.

13. Imaging evaluation of the primary tumour should include contrast-enhanced cross-sectional imaging (either CT or MRI) of the primary site.
    - Depending on local availability, dual modality assessment of the primary tumour with both CT and MRI should be considered, especially in cases with potential orbital involvement, or intra-cranial or perineural spread.

14. A representative diagnostic biopsy should be performed. The diagnosis can be reached by thorough histopathological examination of a scalpel biopsy and/or surgical excision specimens. An adequate biopsy should incorporate adjacent clinically normal mucosa and extend into the submucosal tissues.
    - For lesions where there is a high degree of suspicion that it may be malignant, an incisional biopsy rather than an excisional biopsy is preferred to allow for subsequent appropriate surgical management.
    - A pre-biopsy photography might be useful to aid further surgical management.

15. Patients who present with a head/neck lesion and palpable neck node(s) should have pathological confirmation ideally by FNA or core biopsy of the suspicious node(s) or, if this fails to secure a diagnosis, by open biopsy.

16. The following histological features of the primary should be included in all reports (refer to ICCR dataset https://www.iccr-cancer.org/datasets/published-datasets/head-neck) :
    - macroscopic size of the biopsy
    - vertical tumour depth wherever possible
    - presence/absence of ulceration
    - cytomorphological subtype (i.e. spindle, epithelioid, plasmacytoid, rhabdoid, undifferentiated or mixed)
    - presence/absence of perineural and/or lymphatic invasion

- presence/absence of tumour-infiltrating lymphocytes
- involvement of surrounding structures
- confirmation of the diagnosis of melanoma with immunostaining with a melanocytic marker
- involvement (or not) of surgical resection margins with either invasive melanoma or melanoma in situ: this may often require immunostaining with a melanocytic marker where there are surgery-induced artefacts.

Additional features such as presence/absence of pigmentation, presence/absence of necrosis, could also be noted. PD-L1 staining is not routinely done, but could be requested in the context of clinical trials.

17. The anatomical site specialist pathologist should seek a second opinion on the pathology should there be any doubt about the diagnosis.

18. In cases where a suspected mucosal melanoma proves to be cutaneous in origin, the reader is directed to the NICE guidelines for Cutaneous Melanoma https://www.nice.org.uk/guidance/ng14.

Staging and molecular tests

19. Clinicians should use the most recent UICC TNM (UICC and AJCC are equivalent) staging methods for primary HNMM (see separate Appendix A.4.1.1 for sites). At the time of writing, staging is being performed using TNM8 (2018).

20. Refer to recommendation 16 with regard to pathological reporting.

21. Local staging should include:
    - Examination/inspection to include:
      - Palpation of cervical nodes
      - Flexible nasendoscopy (FNE)
    - CT of the neck (including orbits, skull base and sinuses)
    - Depending on local availability, MRI of the primary site may be considered (instead of or in addition to CT)
    - Orthopantomogram if required to plan surgery or in anticipation of post-operative radiotherapy
    - Ultrasound +/- FNA or core biopsy for neck nodes.

22. Systemic staging should include:
    - contrast-enhanced CT of the thorax, abdomen, and pelvis
    - contrast-enhanced MRI of the brain.

23. If surgery is being considered, a PET-CT scan should be performed pre-operatively to exclude synchronous metastatic disease.

24. Molecular analysis for mutations in *BRAF* and *C-KIT* should be performed routinely at the time of first diagnosis according to local and national genomic guidelines and pathways because these may offer patients therapeutic options in both the adjuvant and metastatic settings.

25. Others genes that are known to be mutated in mucosal melanoma may also form part of a molecular diagnostic panel. In the future, mutations in genes other than *BRAF* and *C-KIT* may be of clinical relevance or allow entry into clinical trials.

Surgery

26. Patients with HNMM should be seen by surgeons who practise in an MDT with an appropriate skill mix.

27. Surgery should be performed with the aim of achieving clear margins. However, there is a role for palliative surgery for control of symptoms.

28. Contraindications to surgery include:
    - unacceptable morbidity; where the treatment-related morbidity is likely to have a negative impact on survival or quality of life
    - evidence of intracerebral disease
    - multiple metastases/widespread disseminated disease.

29. Skull base involvement should be managed with the aid of a specialist skull base team.

30. The least morbid surgery with the potential to achieve clear margins should be offered.

31. Where possible, surgical management should comprise trans-nasal endoscopic excision for sinonasal MM.

32. Oral cavity and laryngo-pharyngeal MM should be managed by surgical procedures appropriate for cancers of the CUADT of the same site (ref NICE guideline https://www.nice.org.uk/guidance/ng36).

33. Organ-preserving surgical techniques should be used where possible.

Sentinel Lymph Node Biopsy and Elective Neck Dissection

34. The role of SLNB is to identify patients with occult nodal metastases to render them eligible for adjuvant therapy (standard of care or clinical trial entry)*.

35. Consider SLNB for patients with accessible sinonasal or oral cavity MM where positivity will influence adjuvant therapy or clinical trial entry.

36. In the event of a positive lymph node on SLNB, completion neck dissection is not recommended.

37. Elective neck dissection should not be performed routinely.

38. If SLNB is not technically feasible, an elective selective neck dissection of appropriate levels depending on the primary site should be considered only if this will influence the decision for adjuvant treatment.

*See recommendation 19 or Section 7.2 on Staging as the majority of patients are Stage III+ and hence already currently eligible for adjuvant therapy without SLNB.

Adjuvant Systemic Treatment

39. Adjuvant therapies using ICI should be offered and, where the appropriate mutation is present, *BRAF*-targeted therapies.

Post-operative Adjuvant Radiation Therapy

40. There is insufficient evidence to recommend the routine use of adjuvant radiotherapy in all patients following curative resection.

41. Adjuvant radiotherapy may be considered after discussion within an MDT for patients with specific features that denote a particularly high risk of local recurrence, such as: T4 sinonasal tumours, close and positive margins and multifocal primary lesions.

42. Discussions regarding the use of adjuvant therapies should take into account the likely treatment-related toxicities.

43. Photon radiotherapy with IMRT technique, with or without image guidance, should be the standard of care for delivering post-operative radiotherapy.

44. Proton beam and carbon ion therapy should only be used in research protocols.

45. The recommended dose-fractionation schedule in the post-operative setting should be 60 Gy in 30 fractions or a biologically equivalent regimen.

46. The recommended dose fractionation schedule in the post-operative setting with positive margins or in the primary setting with macroscopic disease should be 65 Gy in 30 fractions or a bio-logically equivalent regimen.

47. When necessary, dose-fractionation schedules should be modified to avoid exceeding normal tissue dose-constraints, even if this leads to relative under-dosing in the target volume.

48. In the post-operative setting, more hypofractionated schedules could be considered for older patients or patients with poorer performance status.

49. Moderately hypofractionated schedules (between 2.5 and 3 Gy per fraction) should be considered for radical radiotherapy in the primary setting.

50. The optimal radiation dose-fractionation regimen should be determined by a clinical oncologist on a patient-by-patient basis. In this regard, several clinical parameters should be considered, including: treatment goal (curative or palliative intent); tumour location; proximity to critical normal tissue structures; natural history of the disease and its prognosis; and the need to complete radiotherapy in a timely matter for potential enrolment in a clinical trial of systemic therapy.

Rehabilitation

51. Patients should be referred to a specialist centre for ocular, nasal & facial and dental prosthetic rehabilitation as appropriate.

52. Where possible, consider primary prosthetic rehabilitation at the time of definitive resection.

53. In patients at risk of thyroid, adrenal or pituitary dysfunction, early involvement of specialist endocrine services is recommended.

54. As appropriate, refer to NICE pathway for rehabilitation in the Cancer of the upper aerodigestive tract guideline https://pathways.nice.org.uk/pathways/upper-aerodigestive-tract-cancer#path=view%3A/pathways/upper-aerodigestive-tract-cancer/further-treatment-rehabilitation-and-follow-up-of-upper-aerodigestive-tract-cancer.xml&content=view-node%3Anodes-rehabilitation.

55. Patients should be referred to specialist psychological services to support them in the pre- and post-operative periods. Some patients may require ongoing psychological support.

Follow-up

56. Patients who have any concerns should have rapid access to clinical review between appointments or after discharge. Patients should be followed up for evidence of local, regional and systemic relapse.

57. Clinicians may want to discuss with patients the advantages and disadvantages of surveillance imaging as set out in NG14 1.9.16 https://www.nice.org.uk/guidance/ng14/resources/follow up-with-regular-ct-scans-yes-or-no-pdf-250598416.

58. Routine surveillance imaging with PET-CT is not advised.

59. Following potentially curative treatment or treatment for relapse, all patients should be followed up as follows:

    Year 1
    - 6-8 weekly clinical examination to identify loco-regional disease (see recommendation 60)
    - 3 monthly imaging to identify systemic disease (see recommendation 61)
    - 6-monthly brain imaging

    Years 2-3
    - 3-monthly clinical examination to identify loco-regional disease (see recommendation 60)
    - 6-monthly imaging to identify systemic disease (see recommendation 61)
    - 6-monthly brain imaging

    Years 4-5
    - 6-monthly clinical examination to identify loco-regional disease (see recommendation 60)
    - 12-monthly imaging to identify systemic disease (see recommendation 61)
    - 12-monthly brain imaging

    > 5 years
    - consider either annual review or patient discharge with open rapid access.

60. The clinical examination should include:
    - examination of the upper aero-digestive tract mucosa supplemented by flexible nasendoscopic examination of the nose, paranasal sinuses, and larynx and pharynx
    - palpation of the neck
    - ultrasound may have a role in assessing suspicious lymph nodes, especially to facilitate fine aspiration cytology.

61. Imaging should include:
    - cross-sectional imaging of upper aero-digestive tract, neck, chest, abdomen and pelvis
    - cross-sectional imaging of the brain (MRI is preferable).*

    *Centres using MRI may wish to image the sinuses at the same time.

Radical Radiotherapy for Unresectable Disease

62. Radical radiotherapy for unresectable head and neck mucosal melanoma is rarely indicated.

63. The recommended dose fractionation schedule in the primary treatment setting should be 65 Gy in 30 fractions or a biologically equivalent regimen.

64. Moderate hypofractionated schedules (between 2.5 and 3 Gy per fraction) should be considered.

65. There is a role for palliative radiotherapy alone or in combination with systemic treatment, such as immunotherapy.

Loco-regional residual/recurrent disease

66. For local or regional recurrence, diagnosis and staging should include: (see chapters 6 and 7)
    - examination/inspection to include:
        - palpation of cervical nodes
        - flexible nasendoscopy (FNE)
    - CT of the neck (including orbits, skull base and sinuses)
    - depending on local availability, MRI of the primary site may be considered (instead of or in addition to CT)
    - orthopantomogram if required
    - ultrasound +/- FNA or core biopsy for neck nodes if local relapse
    - CT or PET/CT scan whole body.

67. Systemic treatment should be the treatment of choice for local and loco-regional recurrence in the majority of cases (see Adjuvant systemic therapy recommendations).

68. Salvage surgery is rarely indicated.

69. A decision to offer salvage surgery should be made on a case-by-case basis by a specialist MDT. Factors to consider would include:
    - long disease-free interval
    - likelihood of achieving complete excision
    - acceptable morbidity
    - suitability for systemic therapy.

70. Radiotherapy as definitive treatment for local and loco-regional recurrence is rarely indicated.

71. A decision to offer radiotherapy should be made on a case-by-case basis by a specialist MDT. Factors to consider would include:
    - whether or not the patient has had prior radiotherapy
    - the use of concurrent systemic treatment
    - for patients who have had prior adjuvant radiation, re-irradiation could be considered preferably in the context of a clinical trial
    - if systemic therapy is not an option.

Systemic treatment for advanced disease

72. Consider entry to clinical trials for all patients as an option at each line of systemic therapy and after currently available treatments are exhausted.

73. Offer combination immunotherapy (anti-PD-1 and anti-CTLA-4) for patients with advanced HNMM judged by the clinician as sufficiently fit and willing to accept high risk of immune-related adverse events.

74. Offer *BRAF* or *C-KIT* targeted agents for patients with appropriate mutations first-line if urgent symptomatic benefit is desired, or on failure of immune therapy.

75. Consider nivolumab or pembrolizumab monotherapy as treatment for advanced HNMM if the patient is insufficiently fit for combination immunotherapy or does not wish to risk the greater toxicity risk associated with combination immunotherapy.

76. Consider chemotherapy if immunotherapy and targeted therapy are not options or have been exhausted.

Palliative Care

77. Decisions regarding management of palliative care should be made in discussion with the community team and the patient's GP.

78. Refer to United Kingdom National Multidisciplinary Guidelines chapter on Palliative and supportive care in head and neck cancer and the Scottish Palliative Care Guidelines (updated March 2019) for guidance on symptom control.

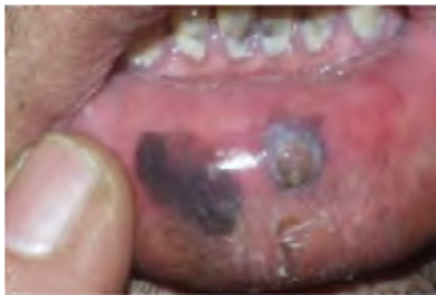
79. Refer to NICE Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (NG36) for guidance on specific symptom management, including palliation of breathing difficulties.

80. Refer to NICE guidance for palliative care for skin metastases, such as:
    - Electrochemotherapy for metastases in the skin from tumours of non-skin origin and mela-noma (IPG446)
    - Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410)

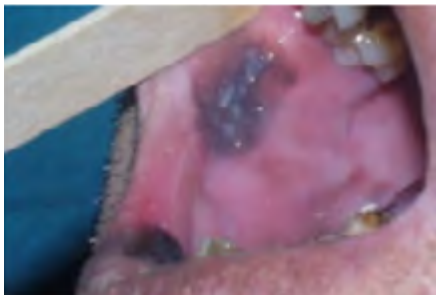
81. Refer to NICE End-of-life-care quality standard (QS13) for general guidance on palliative care.

82. Refer to NICE Care of dying adults in the last days of life, guideline [NG31] for general guidance on end-of-life care.

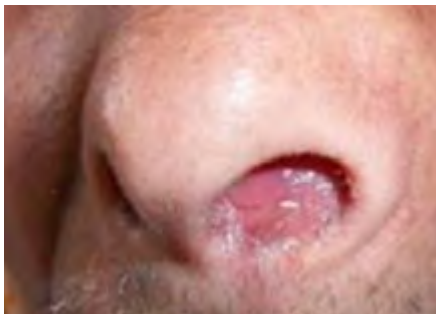
4 PHOTOGRAPHS



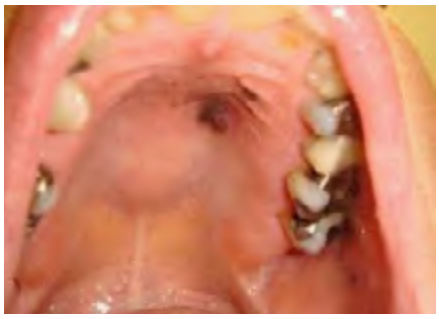
1



2



3



4

Figures 1 & 2: Mucosal melanoma: pigmented lesions of the internal face of the lower lip and the cheek
From Disky et al https://escholarship.org/uc/item/37t8g7bf

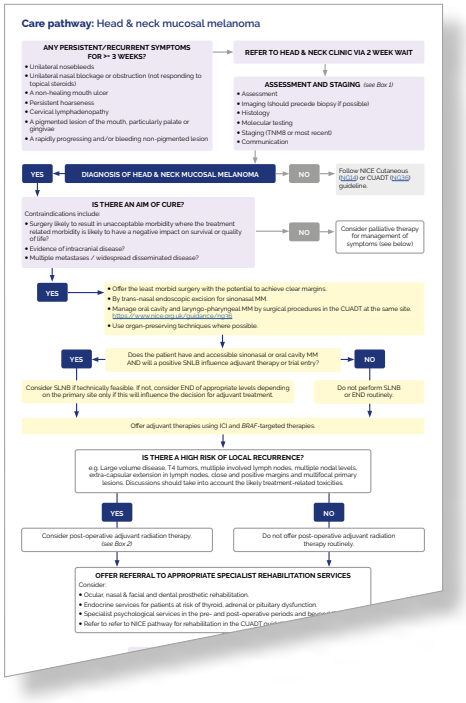
Figure 3: Sino-nasal mucosal melanoma
From https://www.semanticscholar.org/paper/Head-and-Neck-Primary-Mucosal-Melanoma%3A-Report-of-Belhoucha-Essaadi/a879166b284a3f7920fd8b9b3b28c2d73b9a50a4

Figure 4: Oral mucosal melanoma
From Tacastacas et al, https://www.sciencedirect.com/science/article/abs/pii/S0190962214012651

5 CARE PATHWAY

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

CARE PATHWAY: HEAD & NECK MUCOSAL MELANOMA



6 IMPLEMENTING THE GUIDELINE

6.1 Potential organisational and financial barriers to applying the recommendations

The recommendations listed in this guideline represent a distillation of a relatively sparse body of literature, supplemented by the expert opinion of a diverse group composed of medical and allied healthcare professionals and patient representatives with experience of HNMM. In many instances, the literature does not provide specific guidance on HNMM and many inferences have had to be drawn from consideration of data relating to patients with cutaneous melanoma or mucosal melanomas at non-HNMM sites.

With this in mind, the GDG has attempted to recognise that practices might vary across the UK and has tried to provide guidance that will be broadly applicable across the great majority of centres treating patients with HNMM. Nonetheless there may well be components of this guideline that are at odds with local practices in terms of referral pathways, staging investigations, pathological assessment, surgical, radiotherapeutic and drug treatments, and follow-up. In addition, we recognise that there may be organisational barriers (for example, absence of specific post-holders or infrastructure within a given organisation) and financial barriers to the adoption of some of the recommendations that we have made in this document. In this regard, we ask that local teams evaluate their approaches in light of the evidence considered and reviewed here and also take into account the consensus views of the GDG.

We hope that in some instances this guideline may provide an impetus to revising local practices, in terms of changes in clinical approaches but also through discussion with fund-holders and management structures, to enable investment in services and their reconfiguration to bring them into line with the recommendations made here.

We also recognise that challenges may be made to any set of recommendations based on a paucity of level I and II evidence derived from randomised trials and/or meta-analyses and relying, to a large part, on inference, interpretation and opinion. We understand that there may be centres which choose to practise in ways that differ from the recommendations of the GDG. In such instances, it would be reasonable to expect that they will be willing to explain to their patients the reasons for their different approaches and to base these discussions on the evidence available.

.

6.2 Audit criteria

- A member of the treating MDT is named in the case-notes as the designated keyworker and this person's contact details are given to the patients.
- There is a record in the case-notes of the following: discussion of management at both the anatomical site and the specialist melanoma MDT meetings, communication between the responsible melanoma consultant and other relevant consultants involved in the patient's management, especially the surgeon from the anatomical site MDT, and the patient's general practitioner.
- Whether the patient has been referred via the 2-week wait pathway.
- Imaging has preceded biopsy or the reason for the exception has been documented.
- A contrast-enhanced CT of the thorax, abdomen, and pelvis took place at presentation.
- UICC TNM staging has been documented.
- Molecular testing (*BRAF* and *C-KIT*) takes place as soon as is practical, ideally at the time of first diagnosis.
- For sinonasal MM, surgical management has comprised endo-nasal endoscopic excision if technically feasible.
- Adjuvant radiation therapy was only used for specific high-risk features after MDT discussion and the reasons for recommending radiotherapy were clearly documented.
- In the relatively uncommon event that adjuvant radiotherapy was prescribed, that account was taken of the QUANTEC guidance in avoiding excessive radiation dose to organs-at-risk.
- Patients were referred for appropriate rehabilitation following primary treatment.
- There is a follow-up appointment documented every 6-8 weeks for the first year and every 3 months for the following 2 years, with a record kept of the results of the follow-up scans.

7 RESEARCH RECOMMENDATIONS

1. Development of a prospective, centralised national or international database to collate information on upper aerodigestive tract melanoma may facilitate research and thereby improve outcomes.

2. A National registry of patients with HNMM should include data on short- and long-term outcomes of each line of systemic therapy.

3. Mucosal melanoma should not be an exclusion criterion in larger melanoma trials. Specific stratification or dedicated trials in patients with HNMM should be encouraged.

4. Collaborative research studies of proton beam therapy and carbon ion therapy are needed to improve consistency within and among institutions and for accurate determination of dose thresholds and dose-volume effects.

5. The development of a trials dataset with specific relevance to patients with HNMM, for: (i) development of trials testing standard and novel therapies specifically for this patient group; (ii) inclusion of this patient group in trials of treatments for melanoma; and (iii) reporting trials so treatments and outcomes for patients with HNMM are transparent.

8 REVIEW & UPDATES

This guideline was published 1/4/2020 and a full copy of the Guideline and Appendices is available on the Melanoma Focus website. Melanoma Focus will take administrative responsibility and the chairman, or a person designated by the chairman, will take clinical responsibility for maintaining the guideline. GDG members will be asked to notify the chairman immediately should new evidence make any aspect of the guideline unsafe. Annually, the chairman or designated representative will write to the GDG members and the consultees, who comprise many of the leaders in the field, asking if there has been any new evidence that would change the recommendations. At three-year intervals there will be a full search of the literature published since the date of the last search to identify any new evidence that would change a recommendation. This will be reviewed by the chairman, or designate, and experts from the each of the clinical area subgroups (Surgery, Radiotherapy, Systemic Therapy and Investigations) will meet to review the evidence and agree changes. The re-drafted sections of the Guideline will be sent to the full GDG for agreement before publication. Only if there are several sections that need updating will the full GDG meet. Updates of the guideline should follow the methodology detailed in Melanoma Focus Guideline Development Methodology, which also contains further details of the update methods.

8 ABBREVIATIONS

AJCC	American Joint Committee on Cancer
CIT	Carbon ion therapy
CLND	Complete Lymph Node Dissection
CNS	Cancer Clinical Nurse Specialist
CPI	Checkpoint Inhibitors
CT	Computed Tomography
CUADT	Cancer pf the Upper Aerodigestive Tract (NICE Guideline NG36 https://www.nice.org.uk/guidance/ng36)
DFS	Disease-Free Survival
DM	Distant Metastases
DMFS	Distant Metastasis-Free Survival
DSS	Disease-Specific Survival
EUA	Examination Under Anaesthetic
FNA	Fine Needle Aspiration
GDG	Guideline Development Group
HNMM	Head And Neck Mucosal Melanoma
HR	Hazard Ratio
ICCR	International Collaboration on Cancer Reporting
ICI	Immune Checkpoint Inhibitors
IMRT	Intensity Modulated Radiotherapy
IrAE	Immune-Related Adverse Events
LC	Local Control
LRC	Loco-Regional Control
LRFS	Loco-regional Failure-Free Survival
LRPF	Loco-regional Progression-Free
MDT	Multi-Disciplinary Team
MDTM	Multi-Disciplinary Team Meeting
MRI or **MR**	Magnetic Resonance Imaging
MM	Mucosal Melanoma
MVA	Multivariate Analysis
NGS	Next-Generation Sequencing
NICE	National Institute for Health And Care Excellence
NPV	Negative Predictive Value
ORN	Osteoradionecosis
OS	Overall Survival
PBT	Proton Beam Therapy
PET	Positron Emission Tomography
PNS	Paranasal Sinus
PORT	Post-Operative Radiotherapy
PPV	Positive Predictive Value
QUANTEC	Quantitative Analyses Of Normal Tissue Effects In The Clinic
RC	Regional Control
RT	Radiotherapy
SACT	Systemic Anti-Cancer Therapy
SIGN	Scottish Intercollegiate Guidelines Network
SLNB	Sentinel Lymph Node Biopsy
SN	Sinonasal
SN	Sensitivity
SP	Specificity
SX	Surgery - (+ve): positive; (-ve): negative
TNM	Tumour, Node, Metastasis – is used in the staging system
US	Ultrasound