Head and Neck Mucosal Melanoma Guideline

MELANOMA FOCUS

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

Guideline Group

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Methodology

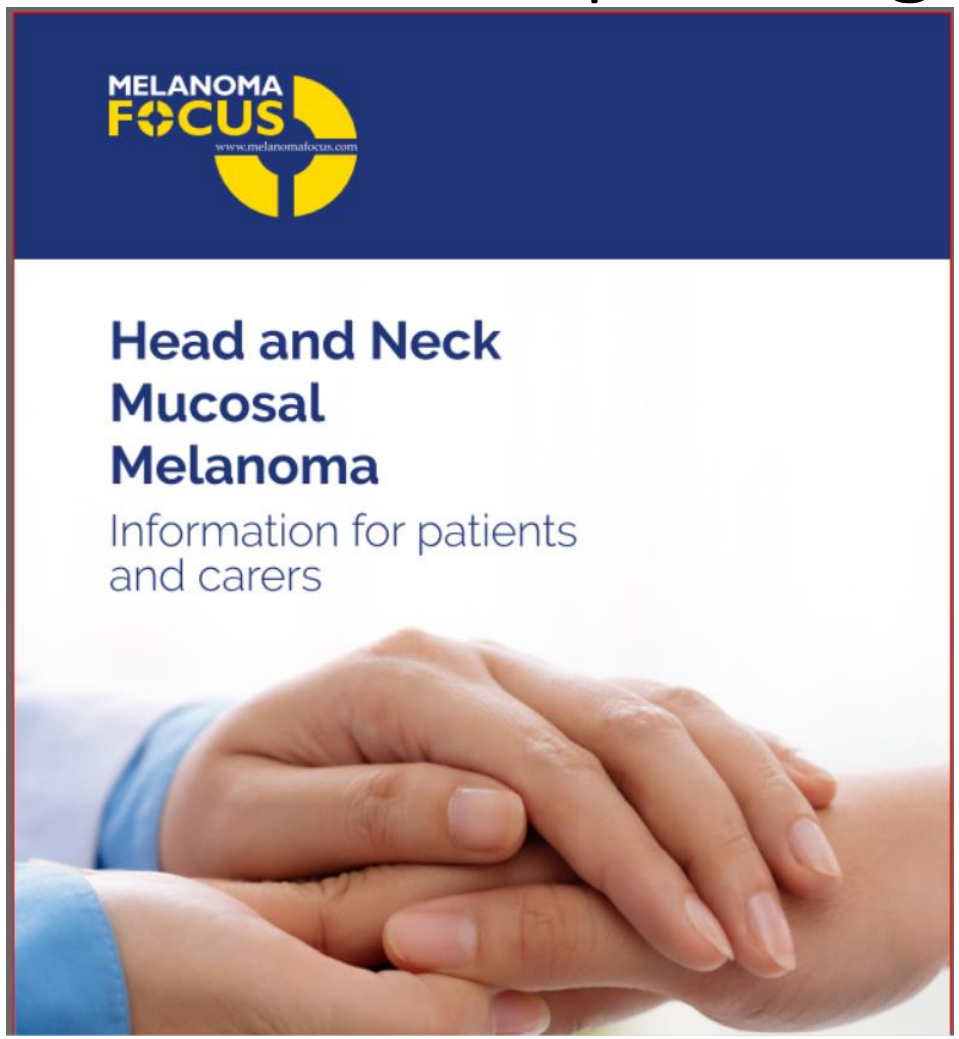
- About 2 years to develop – published April 2020
- Evidence based, transparent with a wide consultation
- Based on AGREE2
- NICE Accredited
- Details of methods are on the Melanoma Focus Website

Patient-focused care

Patients should expect:

- good individualised information throughout their treatment including signs and symptoms of recurrence*
- a designated keyworker (e.g cancer clinical nurse specialist) with contact details
- easy access to outpatient review and prompt access to cross-sectional imaging during follow-up and if symptoms or signs develop.
- the opportunity to discuss prognosis
- the opportunity of early access to palliative support networks and support groups

Patient information accompanies guideline



Multi-disciplinary teams

- 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 discussed at both meetings and a consensus reached
  - The diagnostic pathology specimen reviewed by the melanoma pathologist.
  - A named consultant should responsible for communication between MDT's.
  - The outcome of the MDT discussion and staging communicated the patient and carer and to other health professionals involved in the patient's care (e.g. general practitioner).
  - 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.
- Patients with proven metastatic disease should be referred directly to the specialist melanoma MDT.

Recognition, referral and diagnosis

- 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.
- 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

Illustrations

Figure 1

Figure 2

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

Oral MM taken from Tacastacas et al
https://www.sciencedirect.com/science/article/abs/pii/S0190962214012651

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

Imaging

- Ideally, where practical, imaging should precede biopsy.
  - 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.
- 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.
- If surgery is being considered, a PET-CT scan should be performed pre-operatively to exclude synchronous metastatic disease.

Biopsy

- 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.
- 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.
- The following histological features of the primary should be included in all reports (refer to ICCR dataset http://www.iccr-cancer.org/datasets/published-datasets/head-neck)
- The anatomical site specialist pathologist should seek a second opinion on the pathology should there be any doubt about the diagnosis.

Staging

- Use most recent UICC TNM staging methods for primary HNMM
- 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.
- Systemic staging should include:
  - contrast-enhanced CT of the thorax, abdomen, and pelvis
  - contrast-enhanced MRI of the brain.

Molecular Tests

- 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.
- 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 - Considerations

- Patients with HNMM should be seen by surgeons who practise in an MDT with an appropriate skill mix.
- 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
- Surgery should be performed with the aim of achieving clear margins. However, there is a role for palliative surgery for control of symptoms.

Surgery

- The least morbid surgery with the potential to achieve clear margins should be offered.
- Organ-preserving surgical techniques should be used where possible.
- Where possible, surgical management should comprise trans-nasal endoscopic excision for sinonasal MM.
- 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).
- Skull base involvement should be managed with the aid of a specialist skull base team.

Sentinel lymph node biopsy and elective neck dissection

- Bear in mind that majority of HNMM patients are Stage III+ and hence already currently eligible for adjuvant therapy without SLNB.
- Consider SLNB only if accessible and positivity will influence adjuvant therapy or clinical trial entry.
- Consider an elective selective neck dissection of appropriate levels depending on the primary site <u>only</u> if SLNB not technically feasible is not AND <u>only</u> if it will influence the decision for adjuvant treatment.
- In the event of a positive lymph node on SLNB, completion neck dissection is not recommended.

Adjuvant therapy

- Adjuvant therapies using ICI should be offered and, where the appropriate mutation is present, *BRAF*-targeted therapies.
- Adjuvant radiotherapy may be considered, taking account of likely treatment related toxicities, 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.
- Photon radiotherapy with IMRT technique, with or without image guidance, should be the standard of care for delivering post-operative radiotherapy.

Radiation therapy dose and fractionation

- The recommended dose-fractionation schedule in the post-operative setting should be 60 Gy in 30 fractions or a biologically equivalent regimen.
- 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 biologically equivalent regimen.
- 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.
- In the post-operative setting, more hypofractionated schedules could be considered for elderly patients or patients with poorer performance status.
- Moderately hypofractionated schedules (between 2.5 and 3 Gy per fraction) should be considered for radical radiotherapy in the primary setting.
- 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

- Patients should be referred to a specialist centre for ocular, nasal & facial and dental prosthetic rehabilitation as appropriate.
- Where possible, consider primary prosthetic rehabilitation at the time of definitive resection.
- In patients at risk of thyroid, adrenal or pituitary dysfunction, early involvement of specialist endocrine services is recommended.
- 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.
- 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 examination and imaging

- 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.
- 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

Routine surveillance imaging with PET-CT is not advised.

Follow-up schedule

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 (ee recommendation 61)
- 12-monthly brain imaging

> 5 years

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

Radical radiotherapy for unresectable disease

- Radical radiotherapy for unresectable head and neck mucosal melanoma is rarely indicated.
- The recommended dose fractionation schedule in the primary treatment setting should be 65 Gy in 30 fractions or a biologically equivalent regimen.
- Moderate hypofractionated schedules (between 2.5 and 3 Gy per fraction) should be considered.
- There is a role for palliative radiotherapy alone or in combination with systemic treatment, such as immunotherapy.

Loco-regional residual/recurrent disease

- For local or regional recurrence, follow diagnosis and staging of primary disease
- Systemic treatment should be the treatment of choice for local and loco-regional recurrence in the majority of cases as per adjuvant treatment.
- Salvage surgery is rarely indicated.
- 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
- Radiotherapy as definitive treatment for local and loco-regional recurrence is rarely indicated.
  - 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

- Consider entry to clinical trials for all patients as an option at each line of systemic therapy and after currently available treatments are exhausted.
- 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.
- 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.
- 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.
- Consider chemotherapy if immunotherapy and targeted therapy are not options or have been exhausted.

Palliative Care

- Decisions regarding management of palliative care should be made in discussion with the community team and the patient's GP.
- 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.
- 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.
- 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 melanoma (IPG446)
  - Talimogene laherparepvec for treating unresectable metastatic melanoma (TA410)
- Refer to NICE End-of-life-care quality standard (QS13) for general guidance on palliative care.
- Refer to NICE Care of dying adults in the last days of life NICE guideline [NG31] for general guidance on end-of-life care.

Research recommendations

- Development of a prospective, centralised national or international database to collate information on upper aerodigestive tract melanoma may facilitate research and thereby improve outcomes.
- A national registry of patients with HNMM should include data on short- and long-term outcomes of each line of systemic therapy.
- Mucosal melanoma should not be an exclusion criterion in larger melanoma trials. Specific stratification or dedicated trials in patients with HNMM should be encouraged.
- 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.
- 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.

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.