Head and Neck Mucosal Melanoma: UK National Guidelines

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Abstract

The United Kingdom (UK) head and neck mucosal melanoma (HNMM) guideline development group (GDG) used an evidence-based systematic approach to make recommendations in key areas of uncertainty in the field, including accurate diagnosis and staging; the appropriate treatment pathway including surgery, adjuvant radiation and new systemic treatments, such as targeted agents and immunotherapy; and the surveillance of patients following treatment. The guidelines were sent for international peer-review and have been accredited by the National Institute for Health and Care Excellence (NICE). A summary of key recommendations is presented. The full documents are available on the Melanoma Focus website (https://melanomafocus.com/activities/mucosal-guidelines/mucosal-melanoma-resources/).

1. Introduction

1.1. Aim of the guideline

The aim of these guidelines is to optimise patient care by providing recommendations based on the best available scientific evidence. These guidelines should assist the planning of patient care and provide an indication of management, as well as facilitating patient counselling and informed decision-making. Where adequate evidence was lacking, the guideline development group (GDG) reached an expert consensus. The Group recognises, however, that each patient is an individual. These guidelines should, therefore, neither be prescriptive nor dictate clinical care; however, where care significantly differs from the guidelines, such variance should be justifiable. Our review also identifies gaps in current evidence, thereby defining scope for further research and audit. The GDG reviewed the evidence, where available, for the key areas of uncertainty in the field, which include: (1) the appropriate imaging evaluation and cytogenetics/genetic analysis for diagnosis and prognostication; (2) the recommended primary and adjuvant treatment in clinically localized diseased; (3) the management of loco-regional and distant recurrence; (4) the use of systemic treatments.

1.2. Background

Head and neck mucosal melanomas (HNMM) are uncommon malignancies that arise mainly in the nasal cavity and paranasal sinuses, followed by the oral cavity, although they can rarely also arise in the nasopharynx, oropharynx, hypopharynx, and larynx (1). They account for 0.03% of all cancers, 1-4% of all melanomas, 50-60% of all mucosal melanomas and only 4% of sinonasal malignancies. Most

series describe a similar distribution between men and women. The age of presentation peaks at approximately 60 years, although they may occur in any age group (2).

The pathogenesis of HNMM is unknown and no clear risk factors have been identified. Inhaled carcinogens and, particularly, formaldehyde and the products of smoking have been implicated in the pathogenesis of sinonasal mucosal melanomas, in keeping with other malignancies of the nasal cavity (3). A number of attempts have been made to understand the genetic alterations that underpin the development of this disease with the aim of identifying potential therapeutic targets. Genetic profiling of mucosal melanomas has identified a number of differences with cutaneous melanoma, which is mainly driven by ultraviolet light-induced mutations, and has highlighted a number of important signalling pathways (i.e. the RAS/MEK/ERK mitogen-activated protein kinase (MAPK) and PI3K/AKT/PTEN/mTOR pathways) (4,5). These two pathways can be triggered by activation of *C-KIT* which regulates activity of MITF (microphthalmia-associated transcription factor), a transcription factor that is important for melanogenesis and melanocyte function (6). Identification of mutations or genetic alterations is, thus, considered essential as these could be potential targets for therapy. In contrast with melanomas of other locations, few cytogenetic and molecular genetic features have been demonstrated to have a strong prognostication value in HNMM. Some studies have reported *C-KIT* mutation and high Ki67 score as independent factors for survival among patients with HNMM (7).

HNMM occur most frequently in the nasal cavity, where the lateral nasal wall and nasal septum are the most common sites of origin. The maxillary antrum is the most commonly affected paranasal sinus, followed by the ethmoid, frontal and sphenoid sinuses. These tumours are associated with late presentation since HNMM can be largely asymptomatic in its early stages. The majority of patients present with epistaxis and/or nasal obstruction. Other symptoms include facial pressure and proptosis, diplopia or neurological symptoms which may appear in more advanced tumour stages (8). Most sinonasal lesions are polypoid and pigmented and range in colour, varying between dark brown, red and white (9). Around 20% of HNMM arise from the oral cavity, where the majority occur in the mucosa of the upper maxillary alveolar ridge and the hard palate. Most are asymptomatic but those that present with symptoms usually cause pain, swelling and bleeding. Oral lesions are macular or nodular with brown to black pigmentation, although up to 30% can be amelanotic. Satellite lesions may be adjacent to the tumour (10). Primary laryngeal mucosal melanomas are very uncommon. The most frequently affected laryngeal region is the supraglottis, followed by the glottis. Their typical presentation includes hoarseness, haemoptysis, dysphagia and airway obstruction and, in this regard, they are indistinguishable from other laryngeal epithelial malignancies (11). Most patients with sinonasal HNMM are diagnosed with clinically localized disease, nodal metastases being rare at diagnosis. In contrast, up to 50% of patients with oral and 65% of laryngeal mucosal melanomas have lymph node metastases at presentation (12).

A number of staging systems have been proposed and used for HNMM – most notably, those of Ballentyne and the modified version suggested by Prasad et al (13, 14). In 2010 the American Joint Cancer Committee (AJCC) and the TNM staging manuals (7th edition) included specific chapters on HNMM for the first time (15). Comparative studies have shown that AJCC/TNM have more precise value than previous systems (16). The recently published 8th edition of the TNM has been adopted by The International Collaboration of Cancer Reporting (ICCR) and by the British Association of Head and Neck Oncologists (BAHNO) (17, 18). It is important to note that T1 or T2 categories do not exist and that all HNMM are classified as either T3 or T4. In addition, the overwhelmingly poor prognosis of this malignancy is reflected by the fact that all HNMM are classified as stage III or IV.

The natural history of HNMM is characterised by the relatively frequent development of synchronous or early metachronous metastases (19). Indeed, around half of all patients will develop distant metastases during the first year, regardless of the primary treatment (20). Therefore, there is a great need for more effective and less morbid treatment options and strategies should focus not only on local disease control but on reducing distant metastases.

While there is no absolute consensus on optimal management, the primary modality is generally considered to be surgical wide local excision (21, 22). More controversial is the issue of the potential benefit of selective neck dissection and sentinel node biopsy for node-negative patients (23). The role of radiotherapy as adjuvant post-operative treatment remains unclear. Although adjuvant radiotherapy may provide more effective loco-regional tumour control in some specific scenarios, no data have shown that it conveys a survival benefit (24, 25). New studies support a potential role for systemic adjuvant therapy with immune checkpoint inhibitors or targeted therapies following complete resection of high-risk (stages III and IV) melanoma, regardless of primary location (26, 27). The category of advanced HNMM includes patients whose disease cannot be cured by local treatments and for whom management might largely be regarded as palliative from the outset. Thus, advanced disease includes advanced loco-regional as well as metastatic disease. The prognosis of this group of patients remains poor (28). Recent data from the mucosal melanoma subgroup from pooled prospective trials offers evidence of activity and efficacy, albeit relatively modest, of combination immune therapy with higher probability of response than for chemotherapy (29). In addition, small scale studies indicate activity of targeted therapy against HNMM that harbour *c-KIT* mutations with a reasonable probability of response (30).

1.3. Limitations, risks and benefits

Due to its rarity and poor prognosis, there is limited clinical evidence to guide decision-making around the optimal investigations, treatment and follow-up for patients with HNMM. Most reports in the literature are retrospective studies comprising highly heterogeneous patient populations. The GDG found considerable limitations of the evidence-base in the literature and poor quality evidence for most of the recommendations. In weighing up the risks and benefits of any intervention, the GDG has concentrated on an analysis of clinical benefit and, where appropriate, toxicity. Cost-effectiveness analyses were not performed, largely because of a dearth of publications with health economic outcome measures.

2. Methods

The guideline was commissioned by Melanoma Focus, a national charity with a professional core membership undertaking research and education in the field of melanoma and skin cancers. The full guideline and supporting documentation are available on the Melanoma Focus website (https://melanomafocus.com/activities/mucosal-guidelines/mucosal-melanoma-resources/). GDG members were selected to represent centres that provide care to patients with HNMM in the UK and were drawn from the diverse professions involved in delivering care with additional input from a patient, a carer and a project manager. The process was initiated in May 2018, with the first GDG meeting held in July 2018; in all, eight GDG meetings were held over a period of two years. GDG members completed a Declaration of Interest prior to the first meeting, and these were updated as required. As the clinical topic and the associated body of literature is relatively small, it was decided to do one all-encompassing initial literature search and then to sift references for each question within a single database.

The original search was performed in May 2018, with the search repeated to identify new evidence in July 2019. The first search identified a total of 3,883 articles published from 2000 onwards and, after removing duplicated publications and conference abstracts, a total of 1,738 articles were reviewed. In the second search, a total of 135 new articles were screened. Questions were drafted based on inputs from GDG members. Subgroups of content experts on the GDG worked on each topic, agreeing the criteria for including papers, then appraising and extracting references using Cochrane Handbook and GRADE working group recommendations as a guide. The sub-groups were supported and advised by a guideline methodologist (NT). The subgroups presented the evidence review and extraction tables at group meetings where the full GDG discussed the data and formulated evidence statements and recommendations. A great deal of work was done electronically and, following update search revisions, all GDG members received several, iterative drafts of chapters for comment. The evidence was appraised and extracted into tables; see Appendix A (https://melanomafocus.com/wp-content/uploads/2020/04/CC-HN-Appendices.pdf). The guidelines were sent for national and

international peer review on December 2019. After addressing all of the comments, the guidelines were finally approved by all GDG members on March 2020. For further details regarding methodology used, please refer to Melanoma Focus Methods Manual (https://melanomafocus.com/wp-content/uploads/2017/04/Melanoma-Focus-Methods-Manual-V4.2-FINAL.pdf).

3. Recommendations

3.1. Patient Choice and Shared decision-making

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 countrywide should include: a named cancer nurse specialist and consultant with contact details; a designated keyworker who is usually the Cancer 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 follow-up imaging according to a defined schedule or if symptoms or signs develop; and early access to palliative support networks .

4. The patient and/or carer should be offered an opportunity to discuss prognosis.

5. Early referral to services, for example, enhanced supportive care, palliative care support services and support groups should be offered.

3.2. Multidisciplinary Team and Service configuration

1. The specialist melanoma MDT and the head and neck MDT should be linked.

2. Prior to treatment: 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 consensus between the melanoma MDT and the specialist head and neck team.

3. 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.

4. Staging should be confirmed and documented at the MDT, entered in the patient notes and copied to the patient's general practitioner.

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

3.3. General guidance

1. Patients with symptoms or signs lasting approximately 3 weeks or more should be referred to a head and neck clinic via the urgent cancer referral pathway. These include: unilateral nosebleeds; unilateral nasal blockage or obstruction not responding to topical steroids; a lump in the mouth with or without pigmentation or bleeding; a non-healing mouth ulcer.

3.4. Primary management

3.4.1. Diagnostic investigations

1. Ideally, where practicable, imaging should precede biopsy, especially if malignancy is strongly suspected. Depending on clinical presentation, tumour location, route of referral and local service structure, post-biopsy imaging may be considered appropriate.

2. Imaging evaluation of the primary tumour should include contrast-enhanced cross-sectional imaging (either CT or MRI). 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.

3. A representative diagnostic biopsy should be performed. For lesions with a high degree of suspicion for malignancy, an incisional biopsy rather than an excisional biopsy is preferred to allow for subsequent appropriate surgical management.

4. Patients who present with a head/neck lesion and palpable neck lymph node(s) should have pathological confirmation either by FNA or core biopsy of the suspicious node(s).

5. The following histological features of the primary should be included in all reports: 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 one or more melanocytic markers; involvement (or not) of surgical resection margins with either invasive melanoma or melanoma in situ (this may require immunostaining with a melanocytic marker where there are surgery-induced artefacts). Additional features such as presence/absence of pigmentation and presence/absence of necrosis may also be noted.

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

7. 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.

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

3.4.2. Staging procedures before primary treatment

1. Clinicians should use the most recent TNM staging methods for primary HNMM.

2. Local staging should include: examination/inspection to include palpation of cervical nodes and flexible nasendoscopy; CT scan 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 (OPG) of the mandible, maxilla and associated dentition, if required; and ultrasound +/- fine needle aspiration or core biopsy for neck nodes.

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

4. If surgery is being considered, a PET-CT scan and MRI of the brain should be performed pre-operatively to exclude synchronous metastatic disease.

3.4.3. Treatment of the primary tumour

3.4.3.1. Surgery

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

2. Surgery should be performed with the aim of obtaining clear margins of excision.

3. Contraindications to radical surgery include unacceptable morbidity and evidence of intracranial disease with invasion through the dura.

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

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

6. Where possible, surgical management should comprise trans-nasal endoscopic excision for sinonasal mucosal melanoma.

7. Oral cavity and laryngo-pharyngeal mucosal melanomas should be managed by surgical procedures appropriate for cancers of the upper aero-digestive tract of the same site.

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

3.4.3.1.1. Sentinel Lymph Node Biopsy (SLNB) and Elective Neck Dissection

1. 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).

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

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

4. Elective neck dissection should not be performed routinely.

5. 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.

3.4.3.2. Adjuvant radiotherapy

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

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

3. Discussions relating to the use of adjuvant radiotherapy should take into account likely treatment-related toxicities.

4. Photon-based intensity-modulated radiotherapy (IMRT) technique, with or without image guidance, should be the standard of care for post-operative radiotherapy.

5. The recommended dose-fractionation schedule in the post-operative setting should be: 60 Gy in 30 fractions or a biologically equivalent regimen if R0 (margin >5 mm, and MDT recommends post-operative radiotherapy) or R1 (margin 1-5 mm) resection; and 65 Gy in 30 fractions or a biologically equivalent regimen if R2 (margin <1 mm) resection.

6. 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.

8. Elderly patients or patients with poorer performance status should be offered hypofractionated schedules in preference over conventional fractionation.

9. 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.

3.4.3.3. Adjuvant systemic treatment

1. Consider entry to clinical trials for all patients.

2. Offer adjuvant therapies using immune checkpoint inhibitors and, where the appropriate mutation is present, *BRAF*-targeted therapies.

3.4.3.4. Radical radiotherapy

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

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

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

4. There may be a role for palliative radiotherapy alone or in combination with systemic treatment, such as immunotherapy with immune-checkpoint inhibitors.

3.4.3.5. Rehabilitation

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

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

3. In patients at risk of thyroid, adrenal or pituitary dysfunction (secondary to systemic therapy), early involvement of specialist endocrine services is recommended.

4. 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.

3.4.4. Follow-up after primary treatment

1. All patients should have rapid access to clinical review between appointments during follow-up or, after discharge, if they have any concerns. Patients should be followed up for evidence of local, regional and systemic relapse.

2. Clinicians may want to discuss with patients the advantages and disadvantages of surveillance imaging.

3. Following potentially curative treatment or treatment for relapse, all patients should be followed-up as follows. First year: 6 to 8-weekly clinical examination to identify loco-regional disease, 3-monthly imaging to identify systemic disease and 6-monthly brain imaging. Second and third year: 3-monthly clinical examination to identify loco-regional disease, 6-monthly imaging to identify systemic disease and 6-monthly brain imaging. Fourth and fifth year: 6-monthly clinical examination to identify loco-regional disease, 12-monthly imaging to identify systemic disease and 12-monthly brain imaging. More than 5 years: consider either annual review or patient discharge with open, rapid access.

4. The clinical examination should include: visual and palpation 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.

5. Imaging should include: cross-sectional imaging of upper aero-digestive tract, neck, chest, abdomen and pelvis (contrast-enhanced CT scan is preferable) and cross-sectional imaging of the brain (contrast-enhanced MRI scan is preferable). Ultrasound may have a role in assessing suspicious lymph nodes, especially to facilitate fine aspiration cytology.

3.5. Recurrent disease

1. For local or regional recurrence, diagnosis and staging should include: examination/inspection (including palpation of cervical nodes and flexible nasendoscopy); 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); OPG, if required; ultrasound +/- FNA or core biopsy for neck nodes if local relapse; and contrast-enhanced CT or PET/CT scan of the whole body.

2. Systemic treatment should be the treatment of choice for local and loco-regional recurrence in the majority of cases.

3. Salvage surgery is rarely indicated. The 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 and suitability for systemic therapy.

4. Radiotherapy as definitive treatment for local and loco-regional recurrence is rarely indicated. The decision to offer radiotherapy should be made on a case-by-case basis by a specialist MDT. Factors to consider would include: prior radiotherapy and use of concurrent systemic treatment. For patients who have had prior adjuvant radiation, re-irradiation could be considered but preferably in the context of a clinical trial if systemic therapy is not an option. There may be a role for palliative radiotherapy alone or in combination with systemic treatment.

3.6. Advanced and metastatic disease

3.6.1 Systemic treatment for advanced and metastatic disease

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

2. Offer combination immunotherapy (anti-PD1 and anti-CTLA4) for patients judged by the clinician as sufficiently fit and willing to accept a high risk of immune-related adverse events.

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

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

5. For patients with skin metastases, consider treatment with electrochemotherapy or talimogene laherparepvec NICE guidelines (IPG446 and TA410, respectively).

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

3.6.2. Palliative care

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

2. 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 .

3. 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.

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

5. Refer to NICE guideline NG31 for general guidance on end-of-life care.

Conflict of interest statement

GDG members completed a Declaration of Interest form prior to the first meeting, which was subsequently updated. None of the GDG member declared any conflict of interest during the development of these guidelines.

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