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Review

Management of regional metastatic disease in cutaneous malignancy of the head and neck. 3. Merkel cell carcinoma

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Abstract

This is the third of three articles that give an overview of the current evidence for management of the neck and parotid in patients with cutaneous cancers of the head and neck. In this paper we discuss Merkel cell carcinoma (MCC) and review the latest evidence for management of the regional nodes.

Keywords: Merkel cell carcinoma; sentinel node biopsy; neck dissection; lymphatic metastasis

Introduction

In this paper, the third in a series outlining an overview of the current evidence for management of the neck and parotid in patients with cutaneous cancers of the head and neck, we discuss Merkel cell carcinoma (MCC), which is a rare and highly aggressive neuroendocrine malignancy of the skin involving Merkel cells. First described by Toker in 1972 as "trabecular carcinoma of the skin",[1] the name was changed to Merkel cell carcinoma because the tumour cells resemble Merkel cells, which are present in the basal cells of the epidermis, particularly around hair follicles. Merkel cells act as mechanoreceptors for gentle touch stimulation, are associated with afferent sensory nerves, and have neuroendocrine features.[2] MCC is thought to originate from either the Merkel cell or the pluripotent stem cell of the basal layer. Pathogenesis is not completely understood, but in 2008 a new polyomavirus, Merkel cell polyomavirus (MCPyV), was found in 80% of patients with MCC, and its monoclonal integration in the host genome suggests that viral infection precedes clonal expansion of the tumour.[3]

The incidence of MCC is increasing in the US (0.6/100 000); it tripled between 1986 and 2001, and quadrupled up to 2006.[4] About 46% - 53% of cases affect the head and neck, 35% - 38% the extremities, and 11% - 17% the trunk.[4,5] The largest reported series of patients with MCC of the head and neck in the UK identified 39 over a 12-year period,[6] and the annual number of newly-diagnosed cases of cutaneous MCC of the head and neck is around 140.[7,8]

MCC predominantly affects elderly white people with a mean (range) age at diagnosis of 76.2 (75.5-76.8) years in women and 73.6 (73.1-74) in men.[4] In a large study of 3780 patients, only 4% were younger than 49 years, and the disease was seen more in men (61.5%) than in women (38.5%).[4] Most patients diagnosed were white (94.9%). Immunosuppression is a risk factor and, compared with the general population, there is an increased risk for those with chronic lymphocytic

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Table 1
Important features of Merkel cell carcinoma.[16]

Acronym	Meaning
A	Asymptomatic/ lack of tenderness
E	Expanding rapidly
I	Immunosuppression
O	Over 50 years of age
U	Site exposed to ultraviolet light on a person with fair skin

leukaemia (30-fold), those who are HIV positive (13-fold), and those who have had organ transplants (10-fold).[9,10]

The correlation between MCC and ultraviolet (UV) radiation is well known. The incidence of MCC in people treated with UVA photochemotherapy is high, and many patients have a history of other skin cancers associated with sun exposure.[11,12] A history of melanoma is also linked to a threefold risk.[12]

MCC is highly aggressive, and more than one in three patients die of the disease. The disease-specific death rate is therefore higher than it is for melanoma. Almost one-third of patients present at primary diagnosis with in-transit metastases or lymph node metastases.[5] In 2016, immunotherapy was confirmed to result in a survival benefit for patients with stage IV disease.[13]

In view of the fact that over half the cases of MCC occur on the head and neck, oral and maxillofacial surgeons are likely to be among the first to encounter it, and should be familiar with its diagnosis and management.[4] On the head and neck, it can present special problems because adequate resection margins can be difficult to achieve, and lymphatic drainage is more variable than it is in other sites.[14] It is also associated with a worse prognosis.[15]

In this review we outline staging, the role of sentinel lymph node biopsy (SNB), and surgical, radiological, and medical management, including the emerging role of immunotherapy.

Clinical investigation

Most patients present with a firm non-tender nodule that varies in colour on skin that has been exposed to the sun (red or blue, skin-coloured, or rarely, yellow).[16] It often develops and enlarges over weeks to months, but can progress more gradually.[16]

A focused history and complete examination of the skin and lymph nodes is mandatory for all patients with suspected MCC. Heath el al reported that its important features can be summarised by the acronym AEIOU (Table 1).[16] In their series of 195 patients, 89% showed three or more of these features.

Staging

Unlike other skin cancers, the TNM staging of MCC in the eighth editions of both the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is currently the same. New editions of the Royal College of Pathologists' skin cancer datasets based on the UICC system were introduced in the UK in 2018.

The eighth TNM classification was based on 9387 prospectively enrolled patients with MCC from the US National Cancer Database, who were diagnosed between 1998 and 2012. It includes lymph node status as established by SNB or lymphadenectomy, which is considered an important feature in the management of the disease.[17] The new eighth TNM edition includes important changes for MCC. It provides important information on both staging and prognosis, and has separate criteria for clinical and pathological staging, which reflects a more definitive role for SNB.

Clinical information, which must now be recorded and made available to the reporting pathologist for staging purposes in the pT1 subdivision, includes whether histologically involved nodes are clinically occult or detectable. The pT1 to pT4 categories remain unchanged. The diameter of the lesion should be a clinical measurement, in preference to a pathological one.[18]

Patients with nodal disease but no known primary tumour ("unknown primary") are now staged separately from those who have nodal disease and a "known" primary tumour. Node-positive patients with an unknown primary have better survival outcomes than node-positive patients with a primary cutaneous site,[19] and for this reason, these two subtypes of stage III disease are separated. In these cases the primary may have regressed spontaneously or arisen in the node itself. It is possible that the immune system can eliminate the primary tumour in those with an unknown primary, and is therefore better able to eliminate other microscopic disease that may have spread elsewhere in the body.

Management

Initial staging procedures (Fig. 1)

Initial assessment should include a complete examination of the skin and regional lymph nodes. A biopsy is necessary to confirm the presence of MCC. If possible, this should be a narrow excision with primary closure, and if not, an incisional biopsy.

Primary tumour

Sixty-five per cent of patients have local disease without clinical or pathological evidence of the involvement of the regional lymph nodes or metastatic disease.[20] Five-year overall survival in these patients is 55.6%, and there is a progressive reduction in overall survival for those with larger primary lesions (T1: 55.8%, and T4: 31.8%, respectively).[17]

Wide local excision is the first-line treatment for stage I and stage II disease (node negative) followed by adjuvant radiotherapy.[21] Any reconstruction involving complex tissue movement should be delayed until confirmation of negative

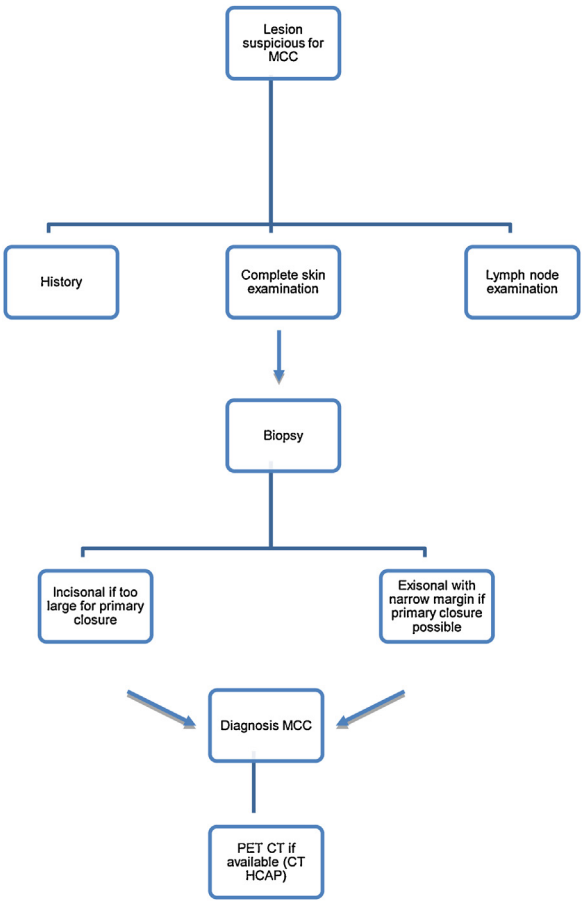

Fig. 1. Management of a patient with a skin lesion suspicious for MCC (HCAP = head, chest, abdomen, pelvis).

histological wide excision margins, and SNB should be done where indicated at the same time as wide local excision.[22]

Current management of the primary tumour is based on its clinical diameter. The National Comprehensive Cancer Network (NCCN) has suggested margins of 1–2 cm with excision to investing fascia of muscle or pericranium when clinically feasible.[23] A margin of 2 cm often cannot be achieved in the head and neck because of the anatomy, and it may be appropriate to be surgically conservative. If margins are close or involved, and further surgery is not deemed appropriate, radiotherapy should be given to increase the probability of achieving local control. If adjuvant radiotherapy is planned, early initiation should be considered after reconstruction.[23]

MCC is a non-contiguous tumour, and Mohs micrographic surgery has shown poorer results than wide local excision.[24] Mohs is not recommended for MCC in the UK.

Investigation of N0 disease: the role of imaging, elective lymph node biopsy, and sentinel node biopsy (Fig. 2)

Imaging

Positron emission tomography-computed tomography (PET-CT) is the imaging of choice and is used to evaluate distant metastases and guide treatment plans. It is preferred as MCC is 18-fluorodeoxyglucose (FDG-18) avid, and PET-CT has a sensitivity of 92% and a specificity of 100% for metastatic disease.[23] Uptake, however, which is within the reference range, does not exclude MCC that has low proliferative activity. In a review of 102 patients, PET-CT changed the staging and primary treatment in 22% of cases.[25] CT or magnetic resonance imaging (MRI) with contrast is used when PET-CT is unavailable or contraindicated. It is considered superior to CT for the identification of metastases to bone. Cerebral metastases are extremely uncommon and, to our knowledge, only 12 cases have been reported.[26] MRI of the brain with contrast is recommended only in patients with neurological signs or symptoms.

Sentinel lymph node biopsy

SNB is increasingly offered to patients with biopsy-confirmed MCC as a staging tool when there are clinically and radiologically negative nodes and no evidence of distant metastases (N0M0). It is an important staging tool that may contribute to regional control, and should be done at the same time as wide local excision of the scar of the excision of the residual primary tumour, as previous excision can affect lymphatic drainage and lead to false negatives.[27] SNB upstages one third of patients,[28,29] and can be used to identify stage III disease, but there is insufficient evidence to show that it improves survival.[30] The pattern of metastasis within a positive sentinel node may be valuable for staging.[31]

In patients who are not suitable technically or physiologically for operation, radiation therapy to the primary tumour alone or primary tumour and regional nodes is an alternative.[32] If SNB cannot be done, follow up with ultrasound and clinical examination of the regional nodes every four months has been recommended,[21] but this has implications for resources.

Investigation of clinically suspected nodal disease

Tissue confirmation (fine needle aspiration, core biopsy, or open biopsy) is indicated if there is clinical suspicion that the lymph nodes are involved. If MCC is identified, wide local excision of the primary and treatment of the nodal basin (dissection of regional lymph nodes or if not possible, radiotherapy) are indicated if there is no evidence of distant metastases.[23]

If an open biopsy is negative, SNB is still indicated, as it is in patients with no clinical evidence of involved lymph nodes (N0),[23] but it should be remembered that the accuracy of SNB in a previously operated neck may be reduced.

Management of established nodal disease (Fig. 3)

Regional lymph nodes are involved (stage III disease) in about one-third of patients (26% -32%) at presentation. This includes those with occult disease detected at SNB, and those with clinically-detected and confirmed involvement of the

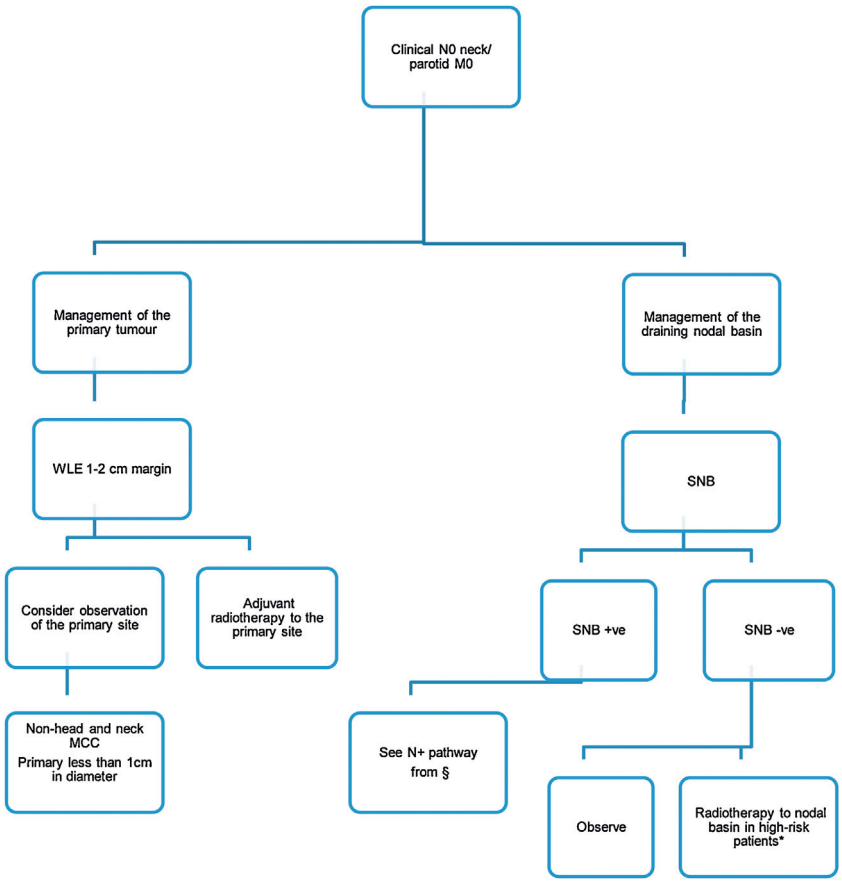

Fig. 2. Management of the clinically negative neck or parotid in patients with MCC after negative systemic staging (M0) (*primary tumour more than 1 cm in diameter, head and neck primary, positive or close surgical margins, level VI, immunocompromised patient; WLE = wide local excision; SNB sentinel node biopsy).

regional lymph nodes or in-transit metastases. Five-year survival has been reported as 39.7% in patients with positive regional nodes, 26.8% in those with clinically detected disease, and 41.1% in those with in-transit disease. Patients with an unknown primary accounted for 3.6% of those with MCC,[20] and five-year overall survival was 42.2%.[20]

Treatments include lymphadenectomy with or without radiotherapy, or definitive radiotherapy to the regional lymph nodes.[33] In patients with stage IIIB disease who have neck dissections, adjuvant radiotherapy is likely to be recommended if there is extracapsular spread or multiple nodes are involved.[23] The risk of local recurrence or systemic disease in those with a positive sentinel lymph node is high, and adjuvant treatment can be considered. The absence of disease in the regional lymph nodes is the most important predictor of survival.[4] If the SNB is positive but no distant metastatic disease is detected, definitive treatment of the regional lymph nodes is indicated. This could be completion lymph node dissection where possible, which may be followed by adjuvant radiotherapy, or therapeutic radiation therapy to the nodal basin.

Therapeutic lymphadenectomy for stage III disease is recommended in suitable patients. Dissection should include involved parotid tissue (P+) and involved levels in the neck (N+), and should extend to nodal levels in which there is a high risk of occult nodal disease.[34] Extra care should be taken of the superficial lymphatic nodal system, which is not usually considered in cases of mucosal squamous cell carcinoma (SCC) of the head and neck, but as there is a paucity of studies on lymphatic spread specific to MCC, advice on nodal management in MCC has been extrapolated from data on cutaneous SCC.

Management of the parotid gland in patients with P+/N0 disease (Fig. 4)

The superficial lobe of the parotid is a common site for nodal metastasis, and "therapeutic" parotid surgery usually means a superficial parotidectomy. Involvement of the skin, deep lobe, or facial nerve will require a more extensive resection.

In patients with clinical metastatic disease that is deep to the plane of the facial nerve, and preoperative facial nerve palsy, radical total parotidectomy is the operation of choice.[35] Those with disease that involves the facial nerve at operation, but who have normal nerve function preoperatively, can be

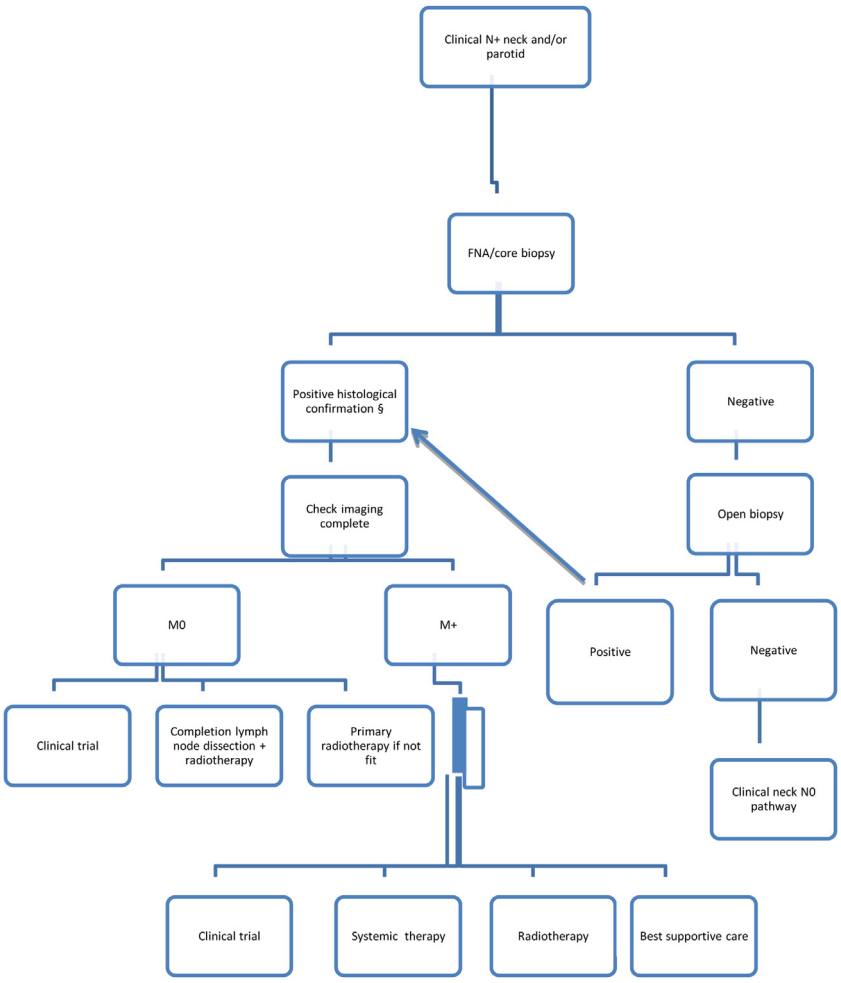

Fig. 3. Management of patient with MCC and a clinically positive neck or parotid.

treated successfully with a nerve sparing approach and timely adjuvant radiotherapy.[36]

Management of the neck in patients with P+/N0 disease (Fig. 5)

Involvement of the parotid gland correlates with a high incidence of occult involved neck nodes in cutaneous SCC (36%),[37] and it is likely that the incidence in MCC will be similar if not higher, given its more aggressive nature.

The common sites for occult neck metastases are level II (including the external jugular node) and level III. P+/N0 cutaneous malignancies of the anterior facial skin may show occult disease in the facial nodes and in level I, while primary tumours in the posterolateral scalp or neck usually metastasise to occipital or post-auricular nodes and levels IV and V. A selective approach to elective neck dissection in these patients may be appropriate (in addition to therapeutic parotidectomy), with dissection of levels I-III for facial primaries, levels II and III for those of the anterior scalp, and levels II-V for those of the posterior scalp and neck. Level I can be omitted except for midline facial primaries.[38,39]

Management of the parotid and neck in patients with P+/N + disease (Fig. 6)

In patients with involvement of the parotid gland and neck, therapeutic parotidectomy and comprehensive neck dissection are recommended. The rate of level V involvement, which is 30% in patients with cutaneous SCC, is likely to be even higher in those with MCC.[37] Many patients with this disease burden, however, will have previously had distant disease and if so, operation will not be appropriate.

Radiation therapy

MCC is a radiosensitive malignancy. Adjuvant radiotherapy should be used routinely,[40,41] and wide-field adjuvant radiotherapy to encompass the primary site, in-transit tissue, and first echelon lymph nodes after operation, is recommended.[42]

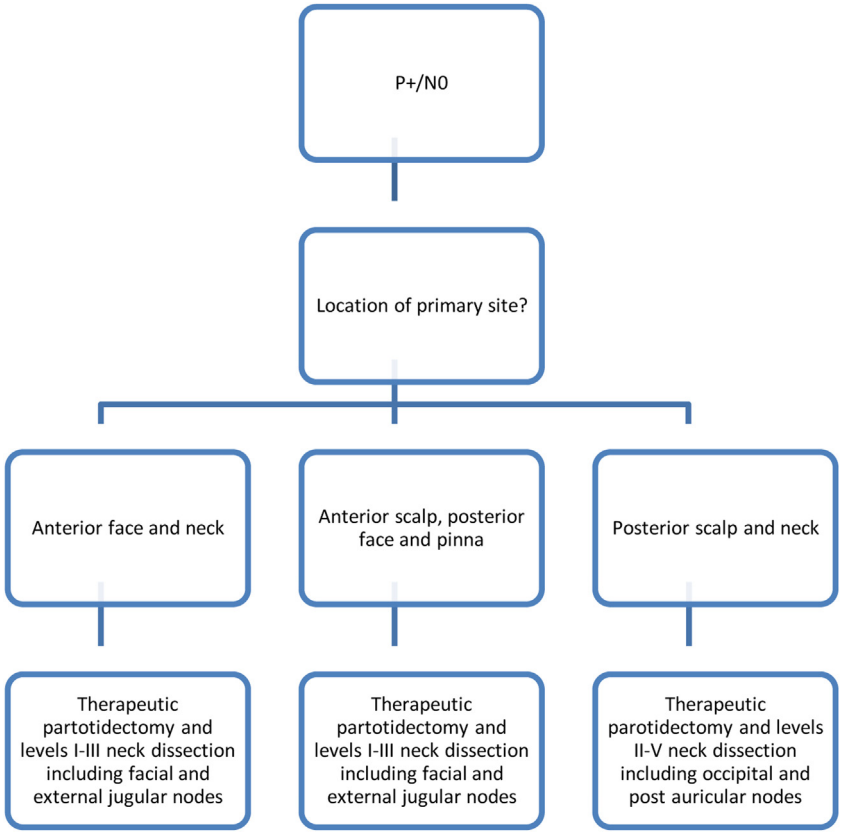

Fig. 4. Surgical management of patient with MCC (M0), established nodal disease in the parotid, and a clinically and radiologically negative neck.

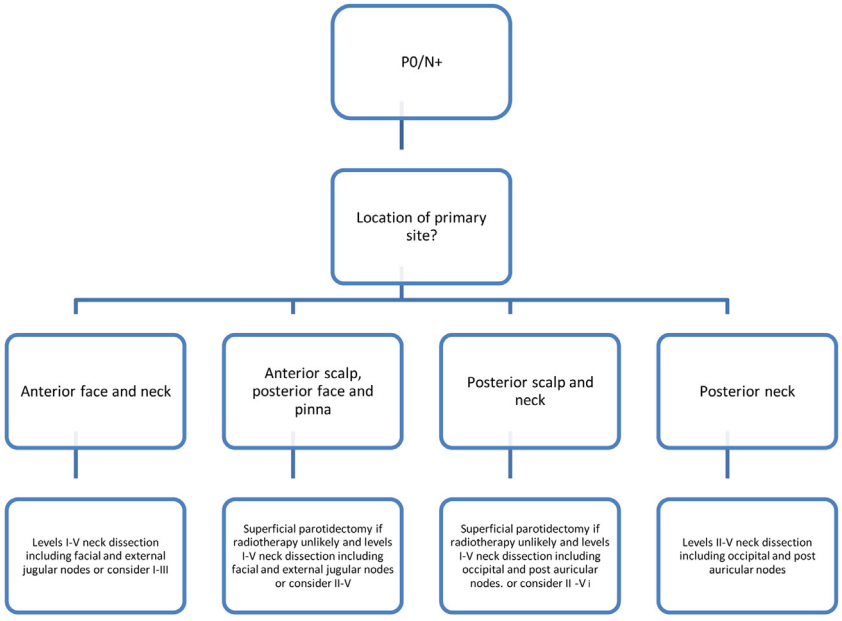

Fig. 5. Surgical management of patient with MCC (M0), established nodal disease in the neck, and a clinically and radiologically negative parotid.

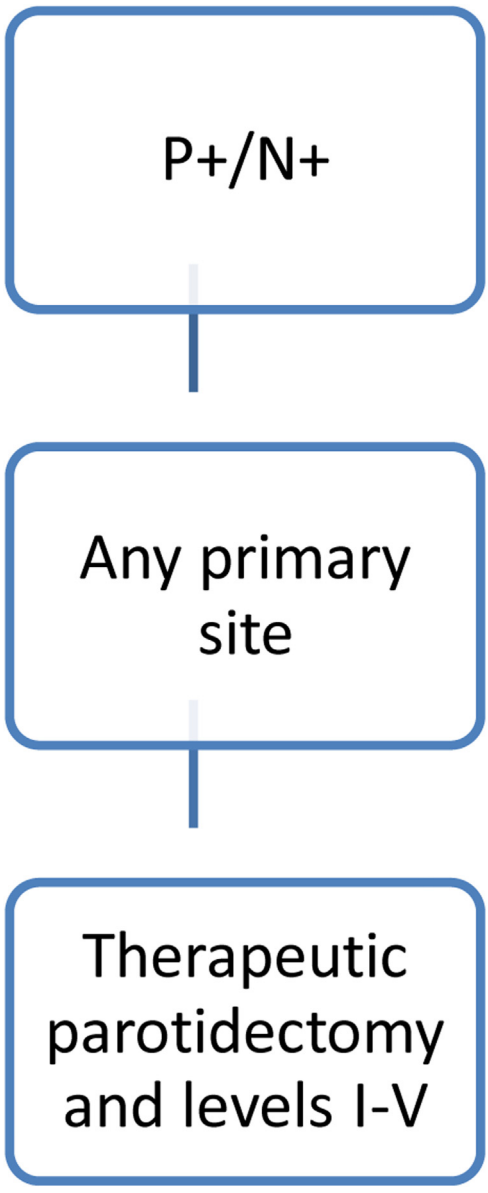

Fig. 6. Management of patient with MCC (M0) and established nodal disease in both the parotid and neck.

It should also be considered in the presence of any of the following: a histologically excised primary tumour more than 1 cm in diameter, head and neck primary, positive or close surgical margins, lymphovascular invasion, multiple nodes (more than N1), extracapsular extension, or an immunocompromised patient.[23] Adjuvant radiotherapy achieves better local control than operation alone,[43] but observation can be considered in selected patients who have small tumours (less than 1 cm in diameter) that have been completely excised, or after wide excision margins of more than 2 cm in those with negative sentinel lymph node biopsies and no lymphovascular invasion or immunosuppression.[23] A large retrospective analysis of 1187 cases from the SEER database showed that after operation, overall survival in patients who had adjuvant radiotherapy was longer than it was in those who did not (median survival 63 months compared with 45 months; $p = 0.0002$).[44]

In an analysis of 6908 patients with MCC from the National Cancer Database,[45] adjuvant radiotherapy showed a survival benefit in those whose lymph nodes were not involved (stage I or II).

An analysis of three pooled prospective trials in patients who had adjuvant radiotherapy for high-risk MCC found that the status of margins before radiotherapy had no impact on the time to locoregional failure.[46] Radiotherapy is acceptable as the primary treatment when complete excision is not feasible or has been declined by the patient.

Distant metastases

At initial presentation 8.4% of patients have distant disease.[17] Five-year overall survival in this group is 13.5%.[17] If distant metastatic disease is identified, a tissue diagnosis should be obtained (when possible) before systemic treatment.

Chemotherapy

Although operation and radiotherapy provide excellent locoregional control, one third of patients will develop distant metastatic disease (stage IV).[16] Chemotherapy is not recommended for local or regional disease, as no survival benefit has been shown.[23] Before 2016 and the introduction of immunotherapy, the most common treatments for inoperable, metastatic MCC were cisplatin or carboplatin with or without etoposide.

Although MCC is chemosensitive, the duration of response is short. The largest single-centre retrospective analysis of patients with distant metastatic disease showed a 55% response rate in those who had first-line chemotherapy, but median progression-free survival was 94 days, and median overall survival 9.5 months.[47]

Immunotherapy

The PD1- PDL1 immune checkpoint pathway is a key therapeutic target in the reactivation of immune responses against various types of cancer.[48] Pembrolizumab, an anti-PD1 monoclonal antibody, has been used in patients with advanced MCC with a response rate of 56%. Progression-free survival at 6 months was 67%, compared with 24% for chemotherapy (based on historical data), and these results led to it being included in the 2018 NCCN guidelines as an option for the treatment of metastatic MCC.[23] In a second trial in which the anti-PDL1 antibody avelumab was used as second-line treatment in cases that progressed after chemotherapy, 82% of patients had maintained their initial response at a median (IQR) follow up of 10.4 (8.6-13.1) months.[49]

Interestingly, the response to immune-checkpoint blockade seems to be independent of the expression of MCPyV or PDL1. In a phase I/II study, progression-free and overall survival at three months was 82% and 92%, respectively, in 25 patients who were treated with the anti PD-1 monoclonal antibody nivolumab.[50]

Targeted treatment

Targeted treatments are also showing some promise. The tyrosine kinase inhibitor pazopanib has been shown to have activity against metastatic MCC in at least one report.[51] In the United Kingdom, the UKMCC-01 trial of its use in metastatic MCC reported clinical benefit in 9/16 patients (partial responses in 3 and stable disease in 6).[52]

Survival

Overall 10-year survival for MCC is 57.3% but this varies depending on age at diagnosis, anatomical location, stage, and size of the tumour.[4] Five-year survival in patients with regional and distant disease, was 52% and 17%, respectively, in a large European registry,[53] and 47.8% and 20.1%, respectively, in the SEER study.[4] Wherever feasible, patients should be offered the opportunity to be included in a clinical trial.[23]

Follow up

Of the patients treated with curative intent, approximately half develop recurrent disease, and 90% of the recurrences occur within two years.[4] There is no consensus regarding follow up. The NCCN recommends clinical review every 3-6 months for the first three years and every 6 -12 months thereafter, but does not recommend routine surveillance imaging.[23] However, for high-risk patients (stage IIIB or higher, or those with immunosuppression), routine surveillance imaging should be considered (PET-CT or CT of the head, chest, abdomen, and pelvis, if not available). The European guidelines recommend clinical review and ultrasound of lymph nodes every four months for three years, then every six months for five years, with consideration of PET-CT annually.[21] Testing for MCPyV oncoprotein antibodies at initial investigation has recently been suggested to guide radiological surveillance. If the patient is oncoprotein positive, a rising titre can be an early indicator of recurrence.[54]

Future

The relative rarity of MCC and the lack of randomised controlled trials mean that it is difficult to standardise management. Optimal treatment depends on the collaboration of several specialties and multidisciplinary input. Advances in immunotherapy are likely to have a major impact on the management and outcomes of the disease.

Summary

MCC is a rare aggressive neoplasm, and half of the cases occur on the head and neck. PET-CT should be used for staging, and operation with adjuvant radiotherapy is the mainstay of primary treatment for stage I/II disease. SNB should be offered to patients with clinically and radiologically N0M0 disease for accurate nodal staging, and treatment should be coordinated so that SNB is done at the same operation as wide local excision, as previous wide excisions can alter lymphatic drainage. SNB accurately stages patients and directs further treatment of the regional nodes. Patients should be managed by a multidisciplinary team.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Not required.

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