Merkel cell carcinoma of skin – current controversies and recommendations

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Abstract

The review covers the current recommendations for Merkel cell carcinoma (MCC), with detailed discussion of many controversies. The 2010 AJCC staging system is more in-line with other skin malignancies although more complicated to use. The changes in staging system over time make comparison of studies difficult. A wide excision with margins of 2.5-3 cm is generally recommended. Even for primary </= 1 cm, there is a significant risk of nodal and distant metastases and hence sentinel node biopsy should be done if possible; otherwise adjuvant radiotherapy to the primary and nodal region should be given. Difficulties of setting up trials owing to the rarity of the disease and the mean age of the patient population result in infrequent reports of adjuvant or concurrent chemotherapy in the literature. The benefit, if any, is not great from published studies so far. However, there may be a subgroup of patients with high-risk features, e.g. node-positive and excellent performance status, for whom adjuvant or concurrent chemotherapy may be considered. Since local recurrence and metastases generally occur within 2 years of the initial diagnosis, patients should be followed more frequently in the first 2 years. However delayed recurrence can still occur in a small proportion of patients and long-term follow-up by a specialist is recommended provided that the general condition of the patient allows it. In summary, physician judgment in individual cases of MCC is advisable, to balance the risk of recurrence versus the complications of treatment.

Introduction

Merkel cell carcinoma (MCC) of the skin, formerly called trabecular carcinoma, is an uncommon, highly malignant primary cutaneous neuroendocrine carcinoma occurring mostly in white, elderly patients.[1] About 78% of patients are older than 59 years. The tumor is most often located in the head and neck region (50.8%) or the extremities (33.7%). The average size is 29 mm at presentation. Clinically, only a presumptive diagnosis of MCC can be established. The definitive diagnosis is made by histology, especially immunohistological methods (detection of intermediate filaments and neuroendocrine markers).[2]

The incidence of MCC has been rising in recent years and is more than the increased incidence of cutaneous melanoma.[3] More than one-third of MCC patients will die from this cancer, making it twice as lethal as melanoma. Its incidence is markedly greater in immunocompromised patients. In these patients we often observe the highly aggressive and deadly course of MCC. The link between tumorigenesis and immunosuppression is well known and the increased prevalence of MCC in human immunodeficiency virus carriers, organ transplant recipients and in patients with hematooncological neoplasias is well recognized.[4-6] In this respect, chronic lymphocytic leukemia seems to be the most frequent neoplasia associated with the development of MCC. Very recently, a newly described virus, the Merkel cell polyomavirus, was found in about 80% of MCC tumor samples. The virus may constitute the missing link between immunosuppression and the development of MCC.[7]

Diagnosis of Merkel cell carcinoma

The clinical diagnosis is made with the typical clinical presentation of a rapidly growing, painless, firm, non-tender, shiny, bluish red, intracutaneous nodule often of mean size 2.9 cm (the range can be from 0.5-5 cm) in diameter. Sometimes it can take the form of a plaque. The tumor is usually localized to sun exposed areas of the head and neck, but does also occur in extremities, trunk, genitalia and the perianal region in a random distribution.

Staging

The staging system of MCC has changed over the years. Readers are cautioned when comparing different series using different staging systems. Yiengpruksawan et al proposed the following classification derived from their experience of 70 cases treated in Memorial Sloan-Kettering Cancer Center in 1991 (Table 1).[8]

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In 1999[9] and 2005,[10] Allen updated the staging system using data from Memorial Sloan-Kettering Cancer Center (Table 2).

In 2010, the American Joint Committee on Cancer (AJCC) Staging System[11] first included the staging system for MCC (Table 3).

The staging system shown in Table 3 is more in-line with other skin malignancies although more complicated to use. The literature used the older staging system making comparison difficult with newer studies that use this AJCC system in the future.

Management of Merkel cell carcinoma

Surgery

Surgery is the mainstay of treatment for MCC if feasible. Controversies in surgical management of MCC include the extent of required surgical margin, the role of sentinel node biopsy (SNB) and node dissection.

What are the risk factors for local recurrence? Geopfert et al suggested that the poor risk factors are primary lesion more than 1.5 cm, resection margin within 2 mm, and lymphatic permeation.[12] Ott et al proposed an adequate resection margin of at least 2 cm is required from their experience in a series of 33 patients treated at the Massachusetts General Hospital.[13] Yiengpruksawan et al reported that local recurrence developed in 4 of 27 patients with margins ≤3 cm compared with none of 11 patients with margins > 3 cm.[5] A wide excision with margins of 2.5-3 cm has been recommended based on studies showing a significant reduction in local recurrence rate by increasing the margins from 1 to 3 cm.[8,14-16]

Despite claims of effectiveness of Mohs surgery, RT is always given after Mohs surgery in

University of Wisconsin. Mohs surgery followed by RT is particularly useful in small facial MCC owing to the better cosmetic outcome.[17] In a Mayo Clinic study, Mohs surgery compares favorably with standard surgical excision.[18] Radiotherapy after Mohs surgery may further reduce persistent metastases, in-transit and nodal disease.[18]

The necessity of elective nodal treatment is another controversial topic in surgery. Opinion varies as to whether small MCC has a low enough risk of nodal metastases that elective nodal surgery or RT can be avoided. Tumor size >1 cm was found to be a poor prognostic factor by Clark JR *et al.*[19] Allen *et al.* found 2 cm to be a significant cutoff for poor prognosis.[10] In the study by Allen *et al.*[9] out of 26 patients in which SNB was performed, 5 had LN metastases and out of these one had a tumor size </=1 cm. In his follow-up paper in 2005, operative LN staging was performed in 71 patients with clinically negative nodes and a total of 16 patients (23%) had positive nodes. Positive nodes were discovered in 24% of patients with tumors <2 cm in diameter and in 20% of patients with tumors >2 cm in diameter (P=0.71).[10] Stawowy et al suggested that if the primary tumor is larger than 2 cm, contains 10 or greater mitoses per high-power field, demonstrates evidence of lymphatic invasion or is composed of the small cell variant, a partial regional node dissection is recommended.[20] Stokes *et al.* reported that MCC </= 1 cm are unlikely to harbour nodal metastases.[21] Only 2/54 patients (4%) with tumor size </= 1 cm had clinical regional node metastases at diagnosis. None of the remaining 52 patients with tumor size </= 1 cm and clinically negative nodes were found to have pathological nodes on surgical staging at the time of presentation. However we have combined our experience with cases from the literature – 105 cases with tumor </= 1 cm, 87 with tumor >1 to <2 cm and 241 with tumor >/= 2 cm.[22] We concluded that for primary tumor with size </= 1 cm, a significant risk of nodal and distant metastases exists and therefore SNB should always be done if general condition of the patient allows (Table 4).[22] If not, adjuvant radiotherapy to the primary and nodal region should be delivered.

Radiotherapy

Primary radiotherapy

In the literature, MCC has a good response to RT. In the Peter MacCallum Cancer Institute, a complete response of measurable tumor was observed in 22 out of 23 sites (96%) with 1 partial response (4%), i.e., an overall response rate of 100%. There was only 1 recurrence in an irradiated site (after a low radiation dose).[23]

Even for distant metastases, palliative RT can give good results. A case of MCC with proven brain metastasis and a solid choroidal tumor responded well to RT and chemotherapy. The patient was alive and neurologically intact in follow-up assessment three years after diagnosis.[24]

Adjuvant radiotherapy

Recently, there is a debate on the role of adjuvant RT. Most authors favor its use. In MD Anderson Cancer Center, postoperative radiotherapy has been recommended routinely.[25,26] From the literature review of 1024 cases, adjuvant RT was associated with a reduced risk of local recurrence (P <0.00001).[27]

The largest series is from the SEER data, showing that the median survival for those patients receiving adjuvant RT was 63 months compared with 45 months for those treated without adjuvant RT. The use of RT was associated with an improved survival for patients with all sizes of tumors, but the improvement with RT use was particularly prominent in patients with primary lesions larger than 2 cm.[28]

A combined series of 110 patients with head and neck MCC from Princess Margaret Hospital of Toronto, Westmead Hospital, and Royal Prince Alfred Hospital of Sydney showed that combined surgery and RT improves both loco-regional control and disease-free survival.[29] 17 patients from Royal Prince Alfred Hospital in Sydney over a 7-year period (median follow-up 16 months) was reported in a separate paper.[30] There were 9 patients who received adjuvant RT to the primary site, without any in-field recurrences; and 8 who received RT to their RLN field, with only 2 developing RLN recurrences - both were SN biopsy positive. The results suggest that SN status may not be an accurate predictor of loco-regional recurrence in MCC. However, they strongly reinforce previous reports that RT, both locally and to regional nodes, provides effective in-field disease control.

Similar striking work to show effectiveness of RT to prevent local recurrence was found by Meeuwissen:[31] all of the 38 patients treated with surgery alone relapsed. The median time to recurrence was 5.5 months. Ten of the 34 patients treated with surgery and RT relapsed. The median time to recurrence was 16.5 months.

In another series, local control could be achieved in all 5 patients irradiated immediately after surgical treatment of the primary tumor. In contrast, an in-field recurrence occurred in 5 of 12 patients irradiated after surgical excision of relapsed disease.[32] Patients undergoing wide local excision, prophylactic lymph node dissection, and adjuvant RT had significantly decreased loco-regional and distant recurrence rates and improved survival when compared with their counterparts.

Table 1. Merkel cell carcinoma Staging System, 1991.

T1	Tumor size 2 cm or less
T2	Greater than 2 cm in maximum diameter
Stage I	Local disease only
Stage II	Positive regional nodes
Stage III	Systemic metastases

Table 2. Merkel cell carcinoma Staging System, 1999, 2005.

Stage I	Primary <2 cm
Stage II	Primary 2 cm or more
Stage III	Nodal disease
Stage IV	Systemic metastases

Table 3. Merkel cell carcinoma Staging System, 2010.

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor (e.g. nodal/metastatic presentation without associated primary)
Tis	*In situ* primary tumor
T1	Less than or equal to 2 cm maximum tumor dimension
T2	Greater than 2 cm but not more than 5 cm maximum tumor dimension
T3	Over 5 cm maximum tumor dimension
T4	Primary tumor invades bone, muscle, fascia, or cartilage
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
cN0	Nodes negative by clinical exam (no pathologic node exam performed)
pN0	Nodes negative by pathologic exam
N1	Metastasis in regional lymph node(s)
N1a	Micrometastasis
N1b	Macrometastasis
N2	In transit metastasis
Distant metastasis	
M0	No distant metastasis
M1	Metastasis beyond regional lymph nodes
M1a	Metastasis to skin, subcutaneous tissues or distant lymph nodes
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites

Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	pN0	M0
Stage IB	T1	cN0	M0
Stage IIA	T2/T3	pN0	M0
Stage IIB	T2/T3	cN0	M0
Stage IIC	T4	N0	M0
Stage IIIA	Any T	N1a	M0
Stage IIIB	Any T	N1b/N2	M0
Stage IV	Any T	Any N	M1

Table 4. Treatment and outcome of 132 patients from a combined series of the institutions of our authors, with different primary tumor sizes (7 patients with unknown size of primary and 6 patients with no primary are excluded in this table). Lower panel adds 288 cases from the literature[14] to the current series, so total number of patients analyzed was 433. (Total %) below indicates the incidence of nodal or distant disease(s) at presentation + later recurrence on follow-up.

Combined series Primary size	N	Surgery to Primary	Surgery to Node	Radiotherapy to Primary	Radiotherapy to Node	LR	LN(total %)	DM(total %)	Any recurrence
≤1 cm	47	46	4[a]	2	12[b]	8(17%)	5+3(17%)	0+8(17%)	14(30%)
>1 to <2 cm	33	32	5[a]	20	11[c]	4(12%)	4+9(39%)	0+6(18%)	17(52%)
≥2 cm	52[d]	51	9[e]	19	12[f]	17(33%)	8+23(60%)	5+16(40%)	40(77%)
χ^2 test P values					0.152	0.002	0.054	0.007	

Literature cases added Primary size	N	Surgery to Primary	Surgery to Node	Radiotherapy to Primary	Radiotherapy to Node	LR	LN(total %)	DM(total %)	Any recurrence
≤1 cm	105	91	4[g]	28	18[g]	24(23%)	9+21(29%)	0+20(19%)	44(42%)[h]
>1 to <2 cm	87	68	12[i]	16	9i	23(26%)	11+23(39%)	0+20(23%)	55(61%)j
≥2 cm	241	186	28[k]	39	20[k]	61(25%)	50+72(51%)	7+72(33%)	160(71%)[l]
χ^2 test P values					0.898	0.015	0.049	0.022	

[a]5 patients had nodes at presentation, of which 4 had surgery to nodal area in addition to primary tumor as well; [b]only 2 of the stage III patients had nodal radiotherapy; [c]only 3 of the 4 stage III patients had nodal radiotherapy after wide local excision of primary and node dissection; [d]at presentation, there are 8 stage III and 5 stage IV patients; DM, total distant metastases at diagnosis and on follow-up; [e]6 of the 8 stage III patients had node dissection in addition to wide local excision of primary tumor; 3 of the 8 stage III patients had nodal radiotherapy after nodal dissection and 1 of the stage III patient had therapeutic nodal radiotherapy after local excision of primary; 1/5 of the stage IV had palliative nodal radiotherapy; LN, total nodal metastases at diagnosis and on follow-up; [g,i,k]2, 3 and 7 had both nodal surgery and radiotherapy respectively; [h,j,l]1, 5 and 15 had unknown recurrence status respectively. LR, local recurrence; N, patient number.

Adjuvant chemotherapy did not diminish recurrence rates nor improve survival. Both loco-regional and distant recurrences significantly decreased survival.[33]

One of the most notable contrary findings is from the series of the Memorial Sloan Kettering Cancer Center. In their study adjuvant RT did not offer any survival benefit, nor improved local control (P=0.76).[10,34] Unfortunately, in this study, only 17% of the 251 patients received adjuvant radiation therapy, and this small number of patients may reflect an underpowered study. One may wonder surgeons from tertiary care centers may have more experience and whether the conclusion can be generalized to small community centers.

The reader should note that the recommended radiation doses are higher than those used in the older literature. For gross positive resection margins, unresectable primary or nodes, RT dose of 60-66Gy/30-33 fractions is recommended in the NCCN guidelines. Our overall summary is shown in Figure 1.[35]

Systemic therapy

Controversies exist regarding the role of chemotherapy in terms of primary concomitant chemo-radiation,[36] and adjuvant chemotherapy after local treatment.

The Trans-Tasman Radiation Oncology Group TROG 9607 enrolled 53 patients with high risk features including: recurrence after initial therapy, involved nodes, primary tumor size greater than 1 cm, gross residual disease

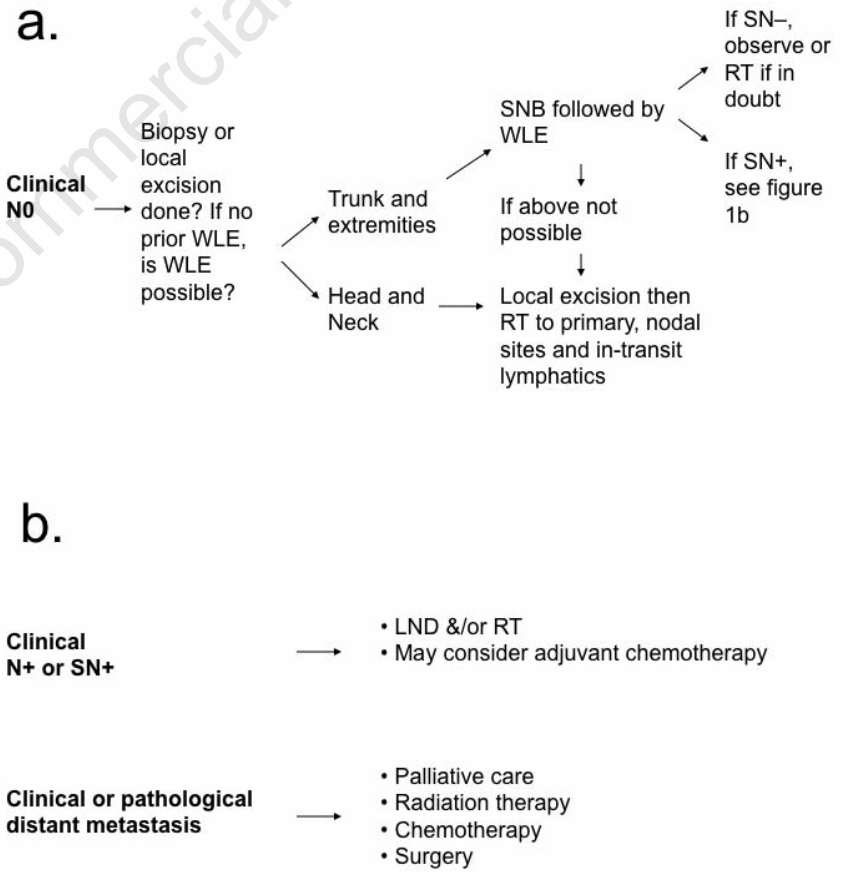

Figure 1. Summary recommendations. LND, lymph node dissection; N0, node negative; N+, node positive; RT, radiotherapy; SN, sentinel node; SNB, sentinel node biopsy; WLE, wide local excision; -, negative.

after surgery, or occult primary with nodes.[37] Treatment regimen included irradiation of the primary site and nodes to a dose of 50 Gy in 25 fractions over 5 weeks and synchronous carboplatin (area under the curve, 4.5) together with intravenous etoposide 80 mg/m^2 days 1 to 3 in weeks 1, 4, 7, and 10. High levels of locoregional control and survival have been achieved with the addition of chemotherapy to radiation treatment for high-risk MCC of the skin. However, a later study found that compared to historical control, the addition of chemotherapy did not significantly increase survival.[38] One would expect treatment results in later era to be better than historical control, the fact that there is no significant increase in survival makes us to conclude therefore, the benefit of concomitant chemotherapy, if any, would not be very great. This coupled with the occurrence in the elderly patients makes adjuvant chemotherapy infrequently reported in the literature. However, there may be a subgroup of patients with high-risk features, e.g. node-positive and excellent general condition, for whom adjuvant chemotherapy may still be considered.

Much of the literature on chemotherapy for MCC used old drugs. Past conclusions on the role of chemotherapy in the initial, adjuvant or salvage settings should be revisited in the future with newer agents, including molecular target agents. As to date, there are no major studies on molecular target agents in MCC yet.

There are occasional reports of cure from treatment with tumor necrosis factor and interferon.[39] A substantial reduction in immunosuppressive drugs in immunosuppressed patients by switching to mTOR inhibitors appears to substantially improve the prognosis in a series with miscellaneous skin neoplasms, although this may not always work in others.[40-43] We await more reports on MCC in the future.

In the future, prophylaxis with vaccination against Merkel cell polyomavirus will hopefully be possible in high-risk patients, as well as therapeutic usage of antisense oligonucleotides or microRNAs, even eventually, complete MCC eradication by affecting the tumor suppressor gene Atonal homolog 1 expression.[3]

Post-treatment follow-up

Local recurrence and metastases generally occur within two years from the initial diagnosis.[44] Therefore patients should be followed more frequently in the first two years: every 1-3 months for the first year, every 3-6 months for the second year and annually thereafter with physical examination and imaging if clinically indicated.[35] Delayed recurrence can still occur in a small proportion of patients and long-term follow-up by specialist is preferred, unless the general condition of the patient or social circumstances precludes this.

Conclusion

Due to rarity of MCC, clinical experience is limited. The literature contains single institutional studies of tertiary centers. Readers should exercise discretion in applying these experiences to smaller centers with less expertise. The present review has highlighted areas of confusion in the literature and summarized the current recommendations in a flow chart.

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