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Frequency and locations of systemic metastases in Merkel cell carcinoma by imaging

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Abstract

Background: The primary neuroendocrine skin cancer, Merkel cell carcinoma (MCC), has a well-known predilection to metastasize systemically. However, the experience of systemic metastases in MCC is mainly disseminated through case reports due to the rarity of MCC.

Purpose: To elucidate the frequency and locations of systemic metastasis in MCC by reviewing the imaging of patients with metastatic MCC in a national cohort.

Material and Methods: Patients with diagnosed metastatic MCC by imaging studies in Finland during 1999–2012 were included in this study. We reviewed their imaging studies to evaluate the most frequent sites for systemic metastasis and determined the latency between the primary tumor diagnosis and systemic metastasis. The material includes 30 MCC patients with complete imaging series and 187 examinations, of which 102 (54%) were CT images.

Results: The mean latency from the primary tumor diagnosis to systemic metastasis was 2.1 years and the mean latency between the radiologic diagnosis of the metastases and death was 299 days. Metastases were recorded in several organ systems in most of the cases, and at least two separate metastatic sites in 63% of the cases. Metastatic spread was noted in 60% of the cases in distant lymph nodes. Liver and lungs were the most affected solid organs.

Conclusion: Systemic metastasis in MCC has no predilection site, basically every organ system can be involved. Most of the systemic metastases were recorded during the first two years after the MCC diagnosis.

Keywords
Neuroendocrine carcinoma, skin, systemic metastasis, latency

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Introduction

Merkel cell carcinoma (MCC) is a rare neuroendocrine skin cancer that occurs mainly in fair-skinned, elderly individuals. Globally, 80% of the tumors are initiated by Merkel cell polyoma virus (MCV) DNA integration into the cancer cells early in MCC development (1). MCC has an inherent capacity for early and aggressive local and systemic dissemination (2). Approximately 65–70% of the patients present with clinically localized disease to the skin (American Joint Committee on Cancer [AJCC] stage I or II), 25–26% have palpable regional lymphadenopathy AJCC stage III, and 5–8% have distant metastasis, AJCC stage IV (3,4). The draining lymph node basin is most commonly the first site of metastasis, in 27–60% of the cases (5,6). Distant dissemination occurs in up to 40–50% of patients that develop visceral metastasis, particularly prevalent in the lungs, liver, and bone (7,8). Owing to the aggressive course of the disease, its mortality exceeds those of

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other forms of skin cancers (9). About one-third of the patients die of MCC including all stages and courses of disease (10).

Current treatment guidelines for MCC entail imaging studies during the course of the disease (11), from the preoperative stage to the postoperative follow-up. In addition to the clinical examination, ultrasound (US) of the loco regional nodes and total body positron emission tomography–computed tomography (PET-CT) will complete the staging in preoperative examinations (11) and direct the choice of the surgical treatment modality. In the follow-up, nodal US and CT or PET-CT are proposed (11). However, it is not clear whether imaging has any role in the follow-up of MCC patients.

The rarity of the prevalence of MCC limits the amount of information on the experiences on systemic metastases in MCC and the available information is mainly case reports. Reasons for this paucity of information might lie in the fact that when the disease has metastasized, it is considered incurable (11). This retrospective study was designed to assess the most frequent sites for systemic dissemination in MCC and to determine the latency between the primary tumor diagnosis and systemic metastasis by imaging.

Material and Methods

The study was approved by the Ethics Committee of the Helsinki University Hospital. The Ministry of Health and Social Affairs granted authors the permission to collect the patient data for study purposes. Permission to retrieve all images for study purpose was granted by the National Institute for Health and Welfare. Inclusion criteria for this study was that patient was diagnosed with systemic metastases MCC and images were available for review. No informed consent was required as all the patients had deceased prior to the study commencing.

Our group has gathered primary MCC tumor samples available in Finland since 1978. Immunohistochemistry served to validate all of the diagnoses. To accompany the tumor samples, comprehensive patient records have been gathered from hospital files and Finnish Cancer Registry records. The ongoing MCC projects of our research group continue to use this database.

A total of 57 MCC patients diagnosed between 1979 and 2013 with systemic metastases were identified. Imaging studies of these patients were retrieved for analysis. When autopsy was performed, the autopsy report was compared with the radiologic findings. All medical records and images were reviewed and detailed data on patient and tumor characteristics, including tumor size, location, stage of disease at the time of diagnosis, local recurrence, local and systemic metastasis, and survival, were obtained from the hospital and primary healthcare center files of the patients fitting the inclusion criteria. All included patients were staged according to the AJCC classification for this study (3). A total of 27 patients were excluded from this study because, due to archiving regulations, no imaging studies were available.

Imaging series were re-evaluated blindly by an experienced radiologist (EL), and lesions were categorized on the basis of the anatomical locations. Distant lymph node metastasis was classified as systemic metastasis to the lymph nodes beyond the nearest regional area of the primary tumor.

Results

The study cohort included 30 MCC patients with 187 accompanying imaging series (Table 1). The imaging studies were taken during 1999–2012. There were equal numbers of men and women. The mean age of the patients at the time of the MCC diagnosis was 75 years (age range, 50–89 years). The majority of the patients presented with cutaneous tumors (n = 12/40%) located in the head and neck region. Two patients in this series presented with unknown primary tumor. Cutaneous primary tumor sizes were in the range of 6–100 mm, with a mean of 25 mm. All patients died during the follow-up, with a mean follow-up time of 1088 days (range, 60 days–14.8 years). An autopsy report was available for four patients.

All patients received some type of treatment for their MCC before the detection of the metastases. In 28 patients (93%) the treatment was surgical intervention (Table 1). In 13 (43%) of the cases, surgery was the only treatment before the detection of metastatic spread. The most frequent adjuvant treatment was radiation therapy given to 14 (46%) cases followed by chemotherapy in two cases (7%).

Of the 187 imaging examinations, 102 (54%) were CT images, 62 (33%) were conventional chest X-ray images, 12 (6%) were magnetic resonance imaging (MRI), seven (3.7%) were ultrasound exams, two (1%) were PET-CT, and two (1%) were bone scintigraphy.

The mean latency from the primary tumor diagnosis to systemic metastasis by imaging was 2.1 years (range, 11 days–14.2 years). The mean latency between the radiologic diagnosis of the metastases and death was 299 days (range, 14 days–7.4 years) (Table 2).

Table 3 presents the metastases stratified by their location and frequency. In most cases the patients had metastases in several organ systems, in 19/30 (63%) patients at least two separate metastatic sites were recognized. Metastasis affected the distant lymph nodes in the majority of the cases, 18/30 (60%);

Table 1. Demographic, treatment, tumor, and latency data for 30 patients with MCC.

Patient no.	Age/ gender	Location of the primary tumor	Primary tumor size (mm)	AJCC stage at presentation	Treatments before metastasis	Imaging method	Distant metastasis	Latency from diagnosis to metastas(days)	Latency from metastasis to death (days)	Follow-up (days)
1	82 F	Head and neck	10	IV	Palliative surgery	Body CT, head MRI	Liver, lung, DLN, ST, orbita	104	101	205
2	72 M	Unknown primary	NA	IV	Palliative radiation therapy	US neck, abdomen	DLN	101	21	122
3	60 F	Lower extremity	17	I	Surgery, radiation therapy	THX CT	Heart	984	34	1018
4	84 M	Upper extremity	30	II	Surgery, radiation therapy	Body CT, MRI	Bone, DLN, ST	400	57	457
5	86 F	Lower extremity	11	I	Surgery	Body CT, abdominal US	DLN	544	242	786
6	56 F	Lower extremity	15	I	Surgery	Body CT	DLN	5194	213	5407
7	81 F	Head and neck	13	I	Surgery	BSc	Bone	84	2693	2777
8	87 F	Upper extremity	26	III	Palliative surgery, palliative radiation therapy	BSc	Kidney, bone	4420	57	4477
9	77 M	Parotis/head and neck	25	IV	Surgery, chemo therapy	Neck, THX CT	Liver	11	166	177
10	83 F	Head and neck	20	II	Surgery including SNB, radiation therapy	Body CT	DLN	335	315	650
11	78 F	Head and neck	20	III	Surgery	Body CT	Adrenal gland, DLN	1985	28	2013
12	72 F	Lower extremity	13	I	Surgery	Abdominal, Head CT	DLN, brain	1196	578	1774
13	80 M	Head and neck	14	I	Surgery, radiation therapy	FDG-PET-CT	Liver, DLN	221	95	316
14	73 M	Upper extremity	26	II	Surgery, radiation therapy	Body CT	Liver	948	99	1047
15	61 M	Lower extremity	35	III	Surgery, radiation therapy	Body CT	Liver, pancreas, lung, adrenal	1106	293	1399
16	86 F	Posterior torso	40	II	Surgery	THX CT	Lung	361	18	379
17	78 M	Head and neck	18	I	Surgery, radiation therapy	Body CT	Pancreas, lung, anus, retroperitoneal and peritoneal cavity	859	46	905

(continued)

Table 1. Continued

Patient no.	Age/ gender	Location of the primary tumor	Primary tumor size (mm)	AJCC stage at presentation	Treatments before metastasis	Imaging method	Distant metastasis	Latency from diagnosis to metastas(days)	Latency from metastasis to death (days)	Follow-up (days)
18	78 M	Lower extremity	40	II	Surgery	Body CT	DLN, ST	616	191	807
19	76 M	Lower extremity	100	II	Surgery, radiation therapy	Body CT, MRI	Stomach, ST	NA	143	376
20	87 F	Upper extremity	6	I	Surgery	Abdominal CT	Liver	502	21	523
21	89 F	Lower extremity	30	III	Surgery	Abdominal CT	Pancreas, DLN	882	31	913
22	72 M	Head and neck	10	IV	Palliative radiation therapy, chemotherapy	Abdominal CT	Liver, stomach, lung right, ST, DLN retroperitoneal and peritoneal cavity	527	81	608
23	81 M	Lower extremity	50	II	Surgery including SNB	Neck, body CT	DLN, pancreas	230	242	472
24	66 F	Head and neck	NA	III	Surgery, radiation therapy	FDG-PET-CT	Bone, lung	299	189	485
25	65 F	Upper extremity	10	I	Surgery	Head, body CT	Liver, lung, bone, brain, DLN	119	471	590
26	50 M	Head and neck	20	II	Surgery	Body CT	DLN, ST	366	482	848
27	76 M	Head and neck	15	I	Surgery including neck dissection radiation therapy	Neck, abdomen, THX CT	Spinal cord, bone, DLN, ST, retroperitoneal and peritoneal cavity	303	83	386
28	86 M	Unknown primary	NA	IV	No treatment	Head, body CT	Lung, liver, spinal cord channel, bone, ST	46	14	60
29	68 M	Upper extremity	20	II	Surgery	Body, THX CT, head MRI, neck US	Lungs, DLN, ST, pancreas, brain, pleura	548	110	658
30	74 F	Head and neck	40	II	Surgery, radiation therapy	THX CT, neck MRI	DLN	158	1857	2015

BSc, bone scintigraphy; CT, computed tomography; DLN, distant lymph nodes; FDG-PET-CT, fluoro deoxy glucose positron emission tomography–computed tomography; MRI, magnetic resonance imaging; NA, not available; ST, subcutaneous tissue; THX, thorax; US, ultrasound.

Table 2. Mean latencies between presentation and metastases diagnosis by imaging stratified by time and site of the metastases.

Latency from the MCC diagnosis (years)	Location of tumor	Latency from the MCC diagnosis (months)
<2	Subcutaneous tissue	12
	Liver	13
	Lungs	15
	Distant lymph nodes	16
	Stomach	17
	Retroperitoneal and peritoneal cavity	19
2–3	Pancreas	24
	Brain and orbita	25
	Heart	32
3–4	Kidneys and adrenal glands	38
	Vertebral column and bones	40

Table 3. Sites, numbers of metastases, and imaging modalities in 30 patients with MCC.

Sites of metastasis	Number of patients (n (%))	Multiple/ Solitary (n)	Imaging modality (n)	
Distant lymph nodes	18 (60)	15/3	CT	22
			MRI	3
			US	2
			PET-CT	1
Liver	9 (30)	7/2	CT	8
			PET-CT	1
Lungs	9 (30)	1/8	CT	8
			PET-CT	1
Subcutaneous tissue	8 (27)	5/3	CT	7
			MRI	1
Vertebral column and bones	7 (23)	4/3	CT	3
			BSc	2
			MRI	1
			PET-CT	1
Pancreas	6 (20)	0/6	CT	6
Brain or orbita	4 (13)	1/3	CT	2
			MRI	2
Kidneys or adrenal glands	3 (10)	0/3	CT	2
			BSc	1
Stomach	2 (7)	0/2	CT	2
Heart	1 (3)	0/1	CT	1
Retroperitoneal and peritoneal cavity	3 (10)	2/1	CT	3

the liver and lungs were the most affected solid organs, with 9/30 (30%) cases each.

Typically, metastases in the distant lymph nodes, retroperitoneal and peritoneal cavity, liver, subcutaneous tissue, and bones presented with multiple metastatic foci (Figs. 1 and 2). In the lungs, pancreas, stomach, and heart, the metastasis usually presented as a solitary focus.

Discussion

The imaging studies in patients with metastatic MCC were reviewed. No predilection site for distant metastases were found, as every visceral organ, skeletal system, subcutaneous tissue, and distant lymph nodes were involved. However, there is presently no clear agreement on the role of imaging in the management and follow-up of MCC (12). A recent European consensus advocates follow-up with nodal US together with once a year CT or PET-CT for up to five years (11). The NCCN Clinical Practice Guidelines in Oncology on MCC recommends imaging studies to be performed as clinically indicated during the follow-up (13).

The most frequent metastatic site found in this study was distant lymph nodes. This finding was in concordance with previous studies (12). The liver and lungs were the most frequently affected solid organs, which was in line with previous literature (7,8). Current treatment guidelines for MCC consider surgery the mainstay of treatment (11,13). Sentinel node biopsy is indicated for patients with clinically node negative disease, whatever the size of the tumor, in combination with wide excision of the primary tumor (11,13). Sentinel node biopsy may reveal thus patients with occult metastasis and predict unfavorable course of disease (14,15). Recent data point to the direction that primary tumor size does not predict nodal involvement, which is contrary to an earlier paradigm (16,17). However, when the disease has metastasized, there is currently no established curative treatment (11).

The median time to recurrence in MCC patients was approximately eight months, with 90% of the recurrences occurring within 24 months (5,18,19). Subcutaneous metastases in this series had the shortest mean latency from the MCC diagnosis with a time span of only 12 months, a further 66% of the patients were diagnosed with metastases within 24 months. All patients in this study died a mean of just ten months (range, 14 days–7.4 years) after distant metastases were confirmed. This falls well within the range reported in previous literature, where survivals were just nine to 12 months after metastatic disease was recognized, depending on the study (5,20–22).

MCC was once regarded as an indolent skin tumor (23–25), but it has since proven to be one of the deadliest of skin cancers. Although rare in incidence,

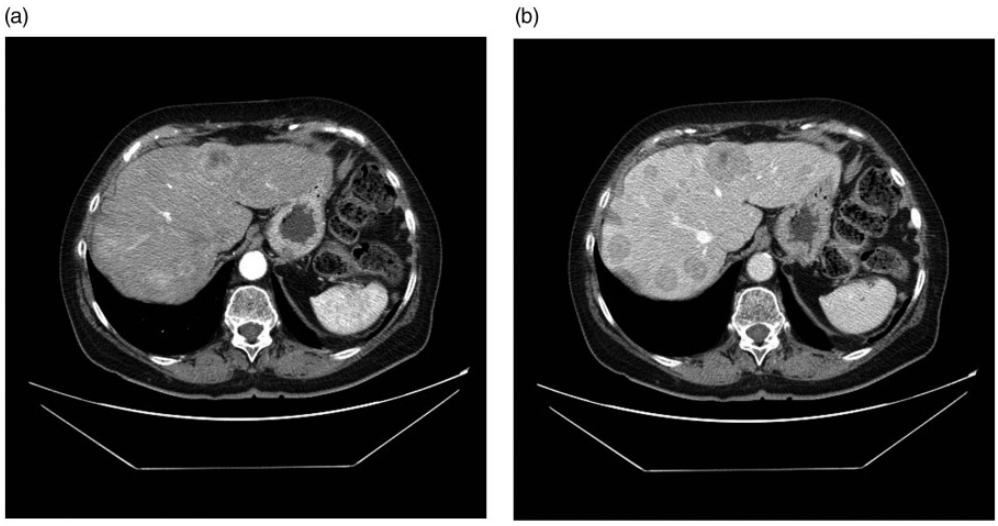

Fig. 1. Multiple liver metastases in a patient with primary tumor in the neck (patient 1). Most of the metastases are enhanced by contrast medium in the arterial phase images (a) and show washout in venous phase images (b).

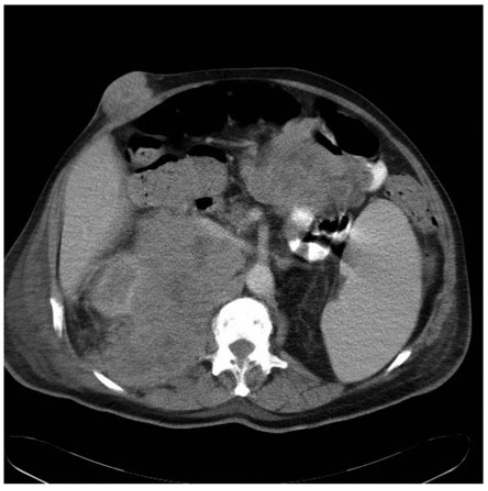

Fig. 2. Large retroperitoneal, peritoneal and subcutaneous metastases in a patient with primary tumor in the neck (patient 27).

in Europe with an annual incidence rate of 1.3/1,000,000 (26), MCC is the second most common cause of skin cancer deaths after melanoma, with an estimated cause-specific death rate of 0.43 per 100,000 persons (27). Most of the MCC patients die with non-localized, i.e. metastatic disease (28), which accords with the findings in other cancers (29). Most of the patients present with localized disease (4). Nevertheless, MCC grows rapidly within just few months (2) and tumor doubling times are five to 12 days, or even as rapid as one to five days in the most aggressive tumor subtypes (30).

This study has several limitations that should be acknowledged. One inherent limitation lies in the retrospective design and relatively small number of patients. Further, most of our imaging studies were performed as clinically indicated. The archiving of images is only 20 years in Finland; therefore, we were not able to get access to all the images of MCC patients with metastatic disease. Although MCC has been recognized and characterized since 1972 (31), it was not until the discovery of the Merkel cell polyoma virus in 2008 (1) that an enormous interest in MCC arose, both in research and reporting clinical experience. The rapidly expanding body of knowledge regarding MCC has just recently generated treatment recommendations (11,13). Apart from studies in the 1980s and 1990s, there has been little interest in reporting the metastatic disease due to the fact that there is no curative treatment for metastatic MCC.

In conclusion, this current study showed that systemic metastasis in MCC has no predilection site or organ, as basically every organ system was involved in our study. Most of the systemic metastases were recognized during the first two years after the MCC diagnosis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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