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High somatostatin receptor expression and efficacy of somatostatin analogues in patients with metastatic Merkel cell carcinoma

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Summary

Background Merkel cell carcinoma (MCC) is an aggressive, high-grade, cutaneous neuroendocrine tumour (NET). Agents blocking programmed death 1/programmed death ligand 1 have efficacy in metastatic MCC (mMCC), but half of patients do not derive durable benefit. Somatostatin analogues (SSAs) are commonly used to treat low- and moderate-grade NETs that express somatostatin receptors (SSTRs).

Objectives To assess SSTR expression and the efficacy of SSAs in mMCC, a high-grade NET.

Methods In this retrospective study of 40 patients with mMCC, SSTR expression was assessed radiologically by somatostatin receptor scintigraphy (SRS; n = 39) and/or immunohistochemically when feasible (n = 9). Nineteen patients (18 had SRS uptake in MCC tumours) were treated with SSA. Disease control was defined as progression-free survival (PFS) of ≥ 120 days after initiation of SSA.

Results Thirty-three of 39 patients (85%) had some degree (low 52%, moderate 23%, high 10%) of SRS uptake. Of 19 patients treated with SSA, seven had a response-evaluable target lesion; three of these seven patients (43%) experienced disease control, with a median PFS of 237 days (range 152–358). Twelve of 19 patients did not have a response-evaluable lesion due to antecedent radiation; five of these 12 (42%) experienced disease control (median PFS of 429 days, range 143–1757). The degree of SSTR expression (determined by SRS and/or immunohistochemistry) did not correlate significantly with the efficacy endpoints.

Conclusions In contrast to other high-grade NETs, mMCC tumours appear frequently to express SSTRs. SSAs can lead to clinically meaningful disease control with minimal side-effects. Targeting of SSTRs using SSA or other novel approaches should be explored further for mMCC.

What is already known about this topic?

- Merkel cell carcinoma (MCC) is an aggressive, high-grade neuroendocrine tumour (NET) of the skin.
- Blockade of programmed death 1/programmed death ligand 1 is associated with high response rates in metastatic MCC, but approximately half of patients do not respond and need alternative therapeutic options.
- Somatostatin analogues (SSAs) are frequently used for treatment in low- and medium-grade NETs but are typically not considered for high-grade NETs due to presumably low expression of somatostatin receptors (SSTRs).

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Conflicts of interest
P.N. has served as a consultant for EMD Serono, Merck and Sanofi/Regeneron; his institution has received research funding from Bristol Myers Squibb and EMD Serono. S.B. reports advisory board participation (with honoraria) from Genentech, EMD Serono, Bristol Myers Squibb and Sanofi Genzyme; and research funding to his institution (University of Washington) from Oncosec, EMD Serono, Merck, BMS, NantKwest, Immune Design, Novartis, Nektar and Exicure. H.V. has served as a consultant for MIM Software, Inc. G.A. has received funding from Nihon Medi-Physics. The other authors declare they have no conflicts of interest.

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What does this study add?

- A high proportion (85%) of metastatic MCC tumours express SSTR by somatostatin receptor scintigraphy (SRS), in striking contrast to other high-grade NETs.
- SSAs can lead to clinically meaningful disease control with minimal side-effects in some patients with metastatic MCC who are not candidates for or did not benefit from immunotherapy.

What are the clinical implications of this work?

- The high frequency of SSTR expression by SRS in metastatic MCC, a high-grade NET, offers a strong rationale for therapeutic SSTR targeting, using either SSAs or other emerging approaches.
- SSTR targeting may be especially relevant for those patients with metastatic MCC who are not eligible for or do not respond to immunotherapy.

Merkel cell carcinoma (MCC) is a rare, but highly aggressive cutaneous neuroendocrine tumour (NET). The incidence of MCC was approximately 2500 cases in the USA in 2015 and it appears to be increasing.[1] Forty per cent of patients with MCC present with nodal or distant metastasis at the time of initial diagnosis, and overall one-third of patients with MCC will develop distant metastatic MCC (mMCC).[2–5]

For metastatic or unresectable MCC, systemic treatment is generally the mainstay of therapy. Cytotoxic chemotherapy has a high initial objective response rate; however, responses are seldom durable; the median progression-free survival (PFS) is only about 90 days and toxicity is considerable.[6] Recently, immune checkpoint inhibitors such as antibodies blocking programmed death 1 and programmed death ligand 1 have shown promising efficacy with durable responses. These agents have replaced cytotoxic chemotherapy as the frontline systemic therapy for mMCC, but the durable response rate is only around 50%.[2,7–11] There remains a great unmet need for alternative therapies for patients with mMCC who are either ineligible for or do not have durable responses to immune checkpoint inhibitors.

Somatostatin signalling pathways inhibit cell secretion and cell growth by reducing cell proliferation and angiogenesis and inducing apoptosis.[12–14] Somatostatin analogues (SSAs) such as octreotide have well-established antitumour proliferation effects with minimal adverse events in low- and medium-grade NETs (e.g. gastrointestinal or pancreatic NETs). Expression of somatostatin receptors (SSTRs) is a characteristic feature of low- and medium-grade NETs. Among the five subtypes of SSTR (SSTR1 to SSTR5), SSTR2 and SSTR5 are the most prominently expressed in NETs, which often express multiple SSTR subtypes.[12,15]

However, there are limited data on SSTR expression and its correlation with SSA efficacy for a high-grade NET like MCC, especially in the metastatic setting. High-grade NETs like MCC have typically been thought to lose SSTR expression compared with low- or medium-grade NETs. There are only a few case studies on patients with MCC treated with SSAs. Among these, three patients with metastatic or unresectable MCC showed complete response or stable disease, for a median of 23 months (range 10–36) after starting SSAs.[16–19] Although these cases provide a rationale to treat MCC with SSAs, more data are clearly needed for SSTR expression on mMCC tumours and the efficacy of SSAs in patients with mMCC.

In this retrospective study, we assessed SSTR expression on mMCC tumours by somatostatin receptor scintigraphy (SRS), as this approach is readily available for use in the clinic and a positive result likely indicates therapeutically relevant SSTR expression on tumours. We also compared the results of SRS with immunohistochemistry for selected SSTR in nine patients whose tumour specimens were available. We also aimed to evaluate the efficacy and adverse effects of SSA therapy in 19 patients with mMCC. To the best of our knowledge this represents the largest reported series to date on SSTR expression and SSA therapy in patients with mMCC.

Patients and methods

Study design

In this retrospective study, we analysed the records of patients with pathologically confirmed MCC who had provided written informed consent (between March 2010 and January 2014) for correlative and observational clinical studies related to MCC diagnosis, therapies and outcomes. The study was approved by the institutional review board at Fred Hutchinson Cancer Research Center (FHCRC IRB #6585). Clinical data from medical records were assessed retrospectively for SSTR expression and SSA treatment. The data cutoff date for outcome analyses was 9 April 2018. Patients were staged following the guidelines of the American Joint Committee on Cancer 7th edition staging system.[20]

Patient selection for somatostatin analogue therapy

In a Seattle-based cohort of 1046 patients with MCC, 508 patients had metastatic or unresectable MCC. Among them, 39 patients underwent SRS to evaluate any evidence of SSTR expression on MCC tumours. This would provide a clinical rationale for SSA therapy in this patient population with suboptimal standard treatment options, at a time when clinical trials of immunotherapy were largely unavailable. These patients were generally refractory to or ineligible for cytotoxic chemotherapy or wanted to avoid it due to age or comorbidities. SSA therapy was considered for those patients who had any degree of SRS uptake (low, medium or high) and were looking for alternative therapeutic options to other systemic approaches for their mMCC. The decision to perform SRS and treat with SSAs was completely a clinical decision and was discussed as such with the appropriate patients.

Somatostatin receptor scintigraphy analysis

SRS was performed with ^{111}In-pentetreotide imaging (Octreoscan®: ^{111}Indium-labelled pentetreotide; Mallinckrodt Medical, St Louis, MO, USA). ^{111}In-pentetreotide has a high affinity to bind to SSTR2 and also binds to SSTR3 and SSTR5.[13,21] Following intravenous injection of ^{111}In-pentetreotide, whole-body planar images were obtained at 4 h and 24 h postinjection. If interpretation of the planar images was equivocal, single-photon emission computed tomography with computed tomography (SPECT/CT) was performed. All images were independently re-evaluated by two dual board-certified (radiology and nuclear medicine) radiologists at our institution. They were blinded to the results of the initial scan evaluation and to the clinical outcomes. Disagreement on a particular image evaluation was resolved through discussion between the two radiologists. A semiquantitative scale was developed to analyse ^{111}In-pentetreotide positivity based on the previously described Krenning score for NETs.[22] ^{111}In-pentetreotide uptake on SRS indicates SSTR expression. The degree of uptake can further be described as low when uptake is lower than in the liver but greater than in the blood pool, medium when uptake equals that of the liver, and high when uptake is greater than in the liver. ^{111}In-pentetreotide uptake equal to or less than in the blood pool is considered negative.

Immunohistochemical analysis

For immunohistochemical analysis, nine MCC biopsy tissues were available from nine patients with specific sites including the skin, thyroid, ileum, inguinal and supraclavicular lymph nodes, and liver. All specimens were evaluated for Ki67 (proliferation marker), CK20 (MCC tumour cell marker) and SSTR2. Eight specimens were evaluated for SSTR5, but one specimen was not amenable for SSTR5 staining due to limited tissue. Detailed staining methods are described in Appendix S1 (see Supporting Information).

Two pathologists at our institution scored available MCC tumours for CK20, Ki67, SSTR2 and SSTR5 expression. CK20 stains were scored as either positive or negative. Ki67 was scored as a percentage of positivity. The SSTR stains were scored using the Allred criteria, which combines the percentage of positive cells and the intensity of the reaction product in most of the carcinoma.[23] Allred scores of 0–2 were considered negative and scores 3–8 were considered positive. The pathologists were blinded to the clinical outcomes and there was concordance on all scoring decisions.

Somatostatin analogue efficacy analysis

SSA was administered intramuscularly. The analogue used was octreotide long-acting release (LAR) or Sandostatin LAR®, a synthetic long-acting analogue of somatostatin. The median injection dose was 30 mg (range 20–30). Progression-free survival (PFS) was defined from the start of octreotide LAR therapy to progressive disease or death, as determined using RECIST version 1·1.[24] Patients were considered to have disease control from octreotide LAR if the PFS was $\geq$ 120 days, for the following reasons. Firstly, PFS $\geq$ 120 days would be highly unlikely in mMCC, which typically behaves very aggressively (unlike the indolent low- and medium-grade NETs), and hence would reflect the potential benefit of an SSA. Note that the median PFS with conventional cytotoxic chemotherapy is around 94 days, despite a high response rate of > 50%.[6] Secondly, patients with mMCC typically undergo restaging radiological evaluation every 60–90 days, and hence the 120-day period should ensure at least one objective tumour assessment. Toxicity to octreotide LAR therapy was abstracted based on adverse events mentioned in the clinical reports, and was graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4·0.[25]

Statistical analysis

The statistical methods used in the analyses in our study are largely descriptive, given the limited sample size and the retrospective nature of this study. Continuous variables were summarized using the median, range and interquartile range (IQR) where useful. Groups were compared using the Wilcoxon rank-sum test. Spearman's rank correlation coefficient was used to evaluate associations between continuous markers. Statistical calculations were conducted using Microsoft Excel and R (version 3·6·1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and tumour characteristics

Among 39 patients who underwent SRS, 30 received an SSA, but 12 were not evaluable due to receiving concurrent systemic treatment (e.g. chemotherapy or immunotherapy). One

patient was included for receiving an SSA without undergoing SRS. In total, 19 patients with distant metastatic disease who had an SSA without any other concurrent systemic agents were assessed for SSA efficacy and side-effects (Figure 1).

The baseline characteristics of the 39 patients with mMCC who underwent SRS and the 19 patients with mMCC who received an SSA are presented in Table 1. Of the 39 patients with mMCC, 36 had distant metastases and the remaining three had unresectable, multiple, in transit metastases. Seven of 39 patients (18%) had comorbidities associated with compromised immune function. These were chronic lymphocytic leukaemia (n = 1), long-term use of systemic immunosuppressive medications for autoimmune disease (e.g. rheumatoid arthritis, psoriatic arthritis) (n = 4) and prevention of allograft rejection (n = 2). In the cohort of 19 patients with mMCC for SSA efficacy assessment, eight (42%) received SSA treatment as first-line systemic therapy, whereas the other 11 patients (58%) initiated an SSA after disease progression on other previously administered systemic therapies, most commonly chemotherapy (n = 10, 53%).

Somatostatin receptor scintigraphy

Thirty-three of the 39 patients (85%) had some degree of ^{111}In-pentetreotide uptake on SRS. This was low uptake in 20 (52%) patients, medium uptake in nine (23%), high uptake in four (10%) and no uptake in six (15%) (Table 2). Examples of high and negative tracer uptake on SRS are presented in Figure 2.

Clinical outcomes of somatostatin analogues

Nineteen patients were analysed for the efficacy of SSAs. Seven of the 19 patients had at least one MCC tumour that did not receive any local concurrent treatment, and thus were interpretable for the efficacy of SSA and classified into group I. The best objective responses in this group were partial response in one patient, stable disease in two and progressive disease in four. Therefore, three of the seven patients (43%) had disease control, with a median PFS of 237 days (range 152–358). The clinical details of the patient who had a partial response are presented in Figure 3.

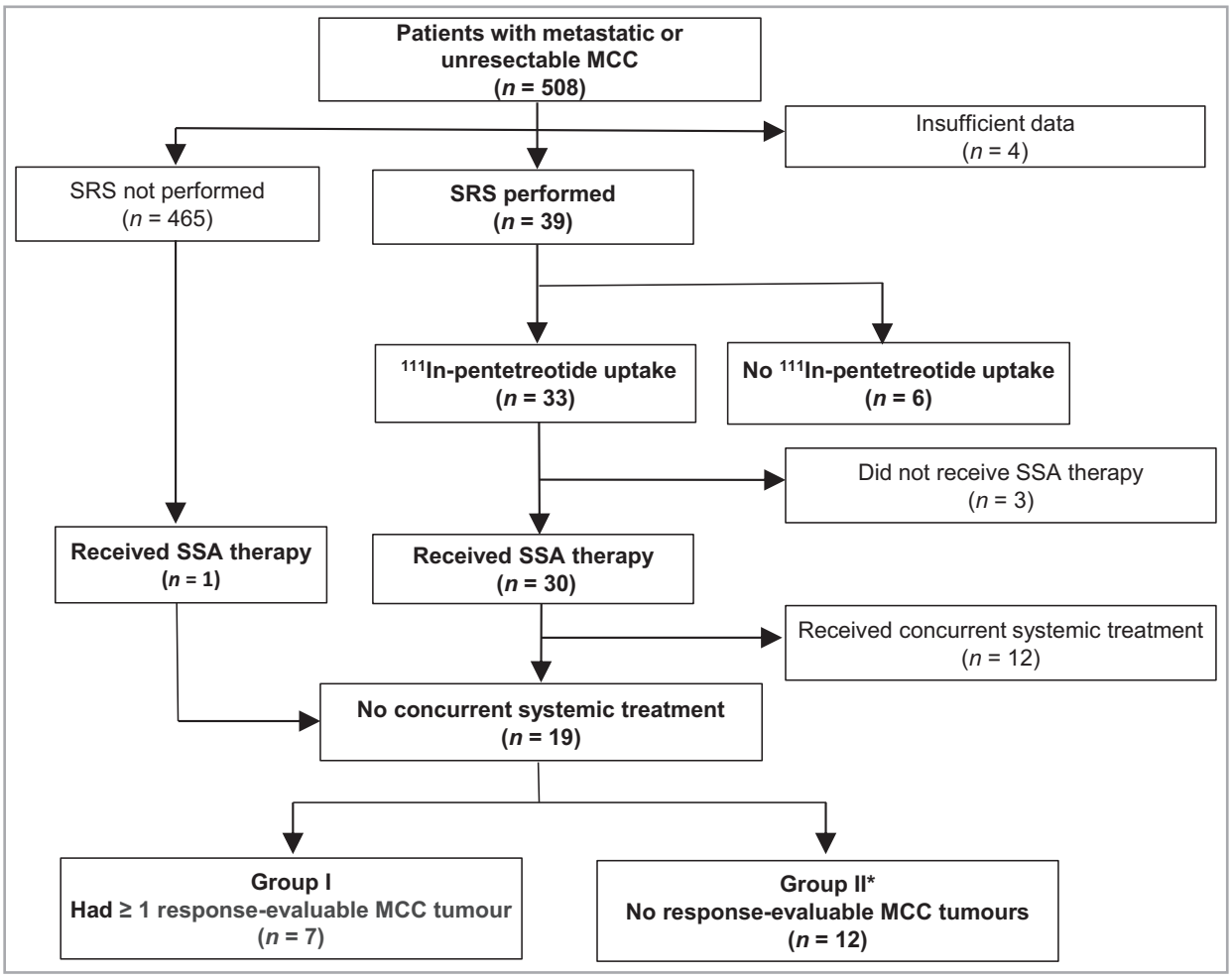

Figure 1 Flow diagram for selection of 39 patients with metastatic Merkel cell carcinoma (MCC) who had somatostatin receptor scintigraphy (SRS) to assess somatostatin receptor expression and 19 patients with metastatic MCC who received at least one dose of octreotide long-acting release. *All target lesions received radiation therapy. These patients were assessed for progression-free survival. SSA, somatostatin analogue.

Table 1 Baseline patient and tumour characteristics of 39 patients with metastatic Merkel cell carcinoma (mMCC) who underwent somatostatin receptor scintigraphy (SRS) and 19 patients with mMCC who received somatostatin analogues (SSAs)

Characteristics	Patients who underwent SRS (n = 39)	Patients who had SSA therapy (n = 19)
Sex		
Male	33 (85)	15 (79)
Female	6 (15)	4 (21)
Age at diagnosis (years)		
< 65	21 (54)	10 (53)
≥ 65	18 (46)	9 (47)
Median (range)	64 (24–84)	64 (24–84)
Stage at initial diagnosis[a]		
I	5 (13)	3 (16)
II	5 (13)	1 (5)
IIIA	11 (28)	5 (26)
IIIB	14 (36)	9 (48)
IV	4 (10)	1 (5)
Immunosuppression		
Absent	32 (82)	18 (95)
Present	7 (18)	1 (5)
CLL	1 (3)	0 (0)
Autoimmune disease[b]	4 (10)	1 (5)
Allograft (renal/cardiac)	2 (5)	0 (0)
MCPyV status[c]		
Positive	17 (44)	11 (58)
Negative	22 (56)	8 (42)
ECOG performance status before SSA		
0		10 (53)
1		7 (37)
≥ 2		2 (10)
Treatment(s) before SSA		
Surgery		18 (95)
Radiation		17 (89)
Systemic therapy[d]		11 (58)
Chemotherapy		10 (53)
Immunotherapy (interleukin-12, 4-1BB)		4 (21)
Pazopanib		2 (11)
Other treatment (interferon intralesional injection)		1 (5)

The data are presented as n (%) unless stated otherwise. CLL, chronic lymphocytic leukaemia; ECOG, Eastern Cooperative Oncology Group; MCPyV, Merkel cell polyomavirus. [a]American Joint Committee on Cancer 7th edition staging. [b]Immunosuppression from treatment of autoimmune diseases, including psoriatic arthritis, rheumatoid arthritis and autoimmune colitis. [c]Virus status assessed by MCPyV T-Ag oncoprotein antibody serology assay or by tumour immunohistochemistry using anti-MCPyV T-Ag antibody (CM2B4). [d]SSA was initiated after disease progression on other previously administered systemic therapies.

The other 12 patients did not have any other systemic agents but received concurrent localized radiation therapy to the mMCC tumours during treatment with the SSA. Hence, they did not have SSA response-evaluable lesions and they were classified into group II. Five of these 12 patients (42%) experienced prolonged disease control, with a median PFS of 429 days (range 143–1757) (Table 3). The details of the eight patients in either group I or group II who benefited from SSAs are summarized in Table S1 (see Supporting Information).

Table 2 Somatostatin receptor expression on Merkel cell carcinoma (MCC) metastases, as determined by ^{111}In-pentetreotide uptake with somatostatin receptor scintigraphy, in 39 patients with metastatic MCC

^{111}In-pentetreotide uptake category	Number of patients (%)
Negative (no uptake detected)	6 (15)
Positive (uptake detected)	33 (85)
Low uptake	20 (52)
Medium uptake	9 (23)
High uptake	4 (10)
Total	39 (100)

Six of 19 patients (32%) reported adverse events related to the SSA: gastrointestinal symptoms such as diarrhoea and abdominal pain (n = 4), pain at the injection site (n = 1) and fatigue (n = 1). The severity of all of these symptoms was grade 2 or less, and none of the patients withdrew the SSA due to adverse events.

Immunohistochemical analysis

All MCC specimens stained positively for CK20 and Ki67; the median Ki67 positivity was 50% (IQR 30–50%, range 5–50%). The median Allred scores for SSTR2 and SSTR5 were 5 (IQR 0–6, range 0–8) and 0 (IQR 0–4, range 0–5), respectively. The results of SSTR expression by SRS uptake and immunohistochemical staining, clinical benefit and pathological features such as MCPyV status, CK20 positivity and Ki67 index are summarized in Table 4. There was no obvious correlation between SSTR expression status by SRS and the results of immunohistochemistry (Table S2; see Supporting Information). The level of SRS uptake was not significantly associated with clinical benefit or pathological features such as MCPyV status or Ki67 index (Table S3; see Supporting Information).

Discussion

In this retrospective study, we assessed the characteristics of SSTR expression on MCC tumours by SRS in 39 patients with mMCC. We found that a high proportion (85%) of tumours had at least some degree of SSTR expression. This is in contrast to other high-grade NETs, where SSTR expression has typically been observed to be uncommon. We also analysed the safety and efficacy of SSA in 19 patients with mMCC who were treated with SSA, some of whom experienced meaningful disease control from SSA therapy, with minimal toxicity. To the best of our knowledge, our study represents the largest cohort to date to assess SSTR expression by SRS in MCC

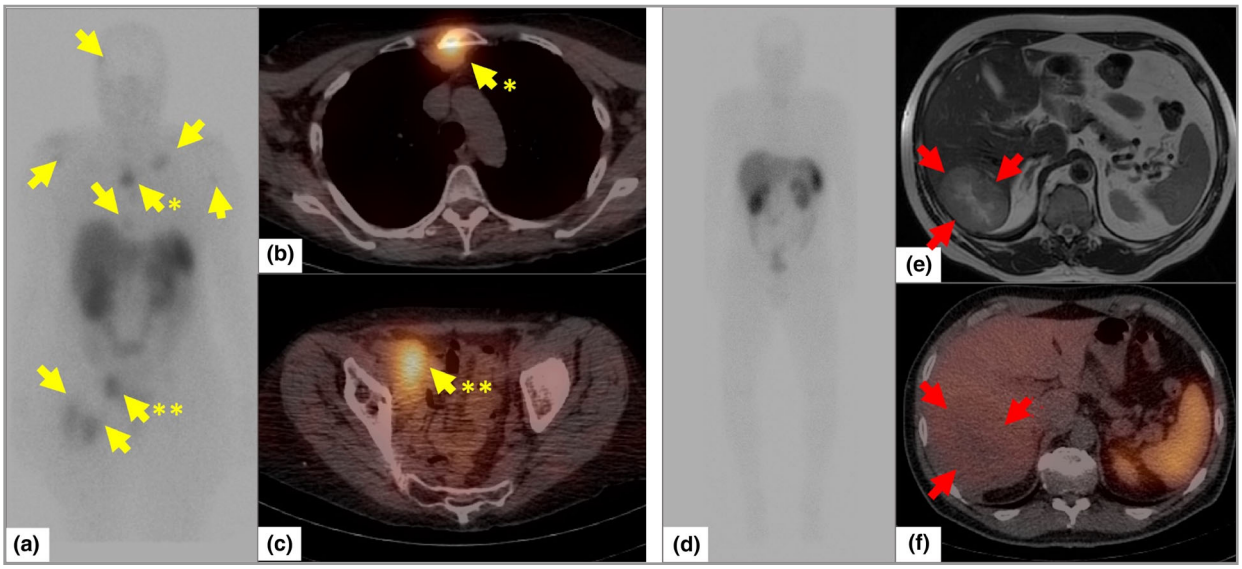

Figure 2 Examples of two patients with Merkel cell carcinoma (MCC) tumours that were positive and negative, respectively, for ^{111}In-pentetreotide uptake on somatostatin receptor scintigraphy (SRS). (a–c) A patient with MCC tumours that bound ^{111}In-pentetreotide. (a) The whole-body planar SRS image demonstrates several foci of increased radiotracer uptake, shown by yellow arrows. (b, c) Fused single-photon emission computed tomography with computed tomography localized a prominent lesion in the sternum, shown by a yellow arrow with an asterisk (b), and in the right external iliac node marked with two asterisks (c). (d–f) A second patient, with an MCC tumour negative for ^{111}In-pentetreotide uptake. (d) Despite the patient having a known, large MCC tumour in the liver, only physiological uptake was noted on whole-body planar imaging. (e, f) However, with SRS, a liver mass seen on magnetic resonance imaging (red arrows) (e) showed ^{111}In-pentetreotide uptake equal to or less than that in the blood pool, suggesting lack of somatostatin receptor expression (f).

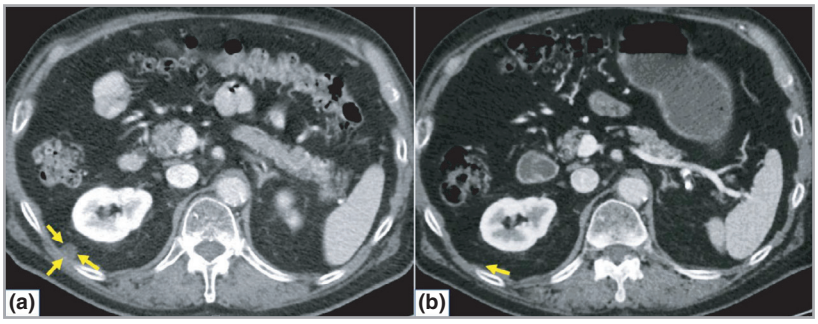

Figure 3 A patient with metastatic Merkel cell carcinoma (MCC) who had an objective response to somatostatin analogue (SSA) therapy. The patient was an 84-year-old man initially diagnosed with a stage IIIA MCC of his right lower extremity, who later developed metastases in the right common iliac lymph node, and a retroperitoneal lesion, shown by the yellow arrows (a). Somatostatin receptor scintigraphy (SRS) demonstrated mild ^{111}In-pentetreotide uptake on his MCC metastases. He received palliative single-fraction radiotherapy to the iliac lymph node and also started an SSA for systemic control. Three months after initiation of SSA, the nonradiated retroperitoneal nodule resolved (b), suggesting response to SSA. The response was ongoing when he died from MCC-unrelated causes of gastrointestinal bleeding from diverticulosis around 8 months later.

tumours in the metastatic setting. Our results provide support for further investigation of SSTR targeting in patients with mMCC and are especially relevant for those patients who may not be candidates for or do not have durable responses with immunotherapy.

SSTRs are commonly expressed in NETs, although the frequency and degree of expression vary by the grade of NETs. SSTR expression, as assessed by SRS, in gastrointestinal and pancreatic NETs appears to differ substantially in low-, medium- and high-grade tumours (100%, 56% and 14%, respectively).[26] MCC is generally considered a high-grade NET as it is poorly differentiated with a high proliferation index.[15,27,28] Therefore, our finding that 85% of mMCC tumours expressed some degree of SSTR is in striking contrast to the low rates of SSTR expression reported in other high-grade NETs.

There are only a few case reports or case series in the literature that have assessed SSTR expression in mMCC by SRS.[3,29,30] In these reports, a total of six patients had mMCC and four patients showed positive SRS uptake. Previously, two large cohort studies reported that approximately 77% and 88% of MCC tumours immunohistochemically expressed SSTRs.[15,31] However, the majority of these cohorts consisted

Table 3 Clinical outcomes in patients who had somatostatin analogue therapy

Outcomes	Group I: patients with response-evaluable MCC lesions (n = 7)	Group II: patients with no response-evaluable MCC lesions (n = 12)[a]
PFS (days), median (range)	73 (18–358)	93 (27–1757)
Experienced disease control[b]		
Number (%)	3 (43)	5 (42)
Days of control: median PFS (range)	237 (152–358)	429 (143–1757)
Best objective response, n (%)		
Complete response	0 (0)	
Partial response	1 (14)	
Stable disease	2 (29)	
Progressive disease	4 (57)	

MCC, Merkel cell carcinoma; PFS, progression-free survival. [a]All target lesions received radiation. [b]Disease control defined as PFS ≥ 120 days.

of localized tumours; only seven and four mMCC tumours were included, of which four of seven (57%) and four of four (100%) expressed SSTR, respectively.[15,31] Thus, there are limited data on SSTR expression of MCC, especially in the metastatic setting. Furthermore, the assessment was performed by immunohistochemistry in these reports, which is not readily available for clinical use.

In our study, SRS was used to assess SSTR expression for clinical treatment planning. We then selected a subset of patients with available MCC tumour specimens for immunohistochemical assessment of SSTR expression, and found no significant correlation of SSTR expression by immunohistochemistry with the results by SRS or with clinical outcomes. Nevertheless, our finding of a high SSTR expression rate in mMCC tumours provides a strong rationale for SSTRs being explored further as targetable receptors for diagnosis and treatment. As a diagnostic tool, SSTR-targeted positron emission tomography/computed tomography (PET/CT) with ^{68}Ga-DOTATATE has emerged as a promising imaging modality to detect recurrences early for other NETs. For patients with MCC, some studies indicate that ^{68}Ga-DOTATATE PET/CT provided good performance for clinical staging and patient management.[32,33]

In our clinical outcome analysis, SSA provided clinically meaningful disease control with minimal toxicity in eight of 19 patients with mMCC. Three of seven patients with response-evaluable MCC tumours (group I) had prolonged stabilization of disease (including one patient with an objective response) that lasted several months, hence supporting the efficacy of SSA monotherapy in carefully selected patients. Several patients in group II experienced a prolonged progression-free interval, including two patients who were progression free at the data cutoff dates at 1757 days and 513 days, respectively. These results were especially meaningful for these patients because they did not have access to other effective therapeutic options (such as immune checkpoint inhibitors) at the time of treatment. Based on these results, we propose that SSA monotherapy should be considered in the clinic in carefully selected patients with mMCC, perhaps those with lower metastatic burden and slower kinetics of progression, whose tumours have evidence of SSTR expression and who may be refractory to or are ineligible for standard immunotherapeutic approaches.

Our preliminary results suggest the potential for targeting of SSTRs in mMCC as a valid therapeutic approach to be investigated further in prospective trials. A phase II study of an SSA (lanreotide, NCT02351128) for advanced MCC has been completed. The preliminary results indicated that seven of 35 patients (20%) derived clinical benefit for more than 6 months.[34] There are SSAs other than octreotide that have high

Table 4 Results of SSTR expression (by immunohistochemistry on MCC metastases and SRS uptake), Ki67 and MCPyV status, and clinical outcomes in nine patients with metastatic MCC who had tumours available for immunohistochemistry

Patient	SRS uptake	SSTR2 expression[a]	SSTR5 expression[a]	Disease control[b]	PFS (days)	Ki67 (%)	MCPyV[c]
1	High	+++	+	N/A	N/A	50	Positive
2	Medium	++	–	N/A	N/A	50	Negative
3	Low	++	–	No	59	30	Positive
4	Low	+	N/A	No	42	50	Negative
5	Low	++	–	Yes (PR)	237	30	Positive
6	Low	–	++	Yes (SD)	152	50	Negative
7	Low	–	–	Yes (SD)	358	5	Negative
8	Low	++	+	Yes	1757	50	Positive
9	Not done	–	–	Yes	513	10	Positive

MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyomavirus; N/A, not available; PFS, progression-free survival; PR, partial response; SD, stable disease; SRS, somatostatin receptor scintigraphy; SSA, somatostatin analogue; SSTR, somatostatin receptor. [a]SSTR2 and SSTR5 were marked as following based on the Allred score: – (0–2), + (3–4), ++ (5–6), +++ (7–8). [b]Disease control was defined as PFS ≥ 120 days. Disease control was not assessed in patients 1 and 2 due to them receiving concurrent systemic treatment or not receiving an SSA. Patients 3, 4, 8 and 9 did not have any concurrent systemic therapy but had concurrent radiation therapy. Patients 5–7 had only an SSA. [c]Status assessed by MCPyV T-Ag oncoprotein antibody serology assay or by tumour immunohistochemistry using an anti-MCPyV T-Ag antibody (CM2B4).

affinities for different SSTR subtypes. Pasireotide, which has a high affinity for SSTR5 and also binds to SSTR1, SSTR2 and SSTR3, has shown efficacy in other NETs.[13,35] Furthermore, there is a phase I clinical trial using a bispecific antibody binding to SSTR2 and CD3 that engages the immune system against advanced NETs (NCT03411915).

In addition, SSTR-targeted peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE has shown promising therapeutic efficacy in patients with other advanced NETs.[36,37] Two cases reported patients with mMCC who had objective responses with minimal side-effects.[38,39] This treatment may be beneficial for mMCC, especially in combination with immunotherapy for possible synergistic efficacy. Lastly, the combination with other systemic regimens such as tyrosine kinase inhibitors (e.g. pazopanib) or mammalian target of rapamycin inhibitors (e.g. everolimus) may further augment efficacy.[40,41] Such options imply further potential of SSTR-targeted therapy for MCC.

Our study has several limitations. Firstly, as this was a retrospective analysis, it is inevitable that biases on patient selection have influenced the results. Secondly, SRS likely underestimates the SSTR expression rate compared with a more sensitive test like ^{68}Ga-DOTATATE. Thirdly, comparison with historical data of SSTR expression rates in other high-grade NETs is fraught with challenges including different methodologies (histological vs. imaging). Fourthly, not all patients undergoing SRS had tumours available for immunohistochemistry. Finally, the overall sample size is small, which affects the statistical significance of the results. Regardless of these limitations, our study provides clinically meaningful data on SSTR expression in patients with mMCC and suggests the potential utility of targeting this pathway for therapeutic purposes.

In conclusion, the majority of mMCC tumours have at least some degree of SSTR expression, which should be explored further for both diagnostic and therapeutic purposes. Carefully selected patients with mMCC can experience clinically meaningful disease control from SSAs with minimal side-effects. SSTR-targeting approaches may be especially useful for patients who do not benefit from other approaches and/or desire minimally toxic and nonimmunosuppressive palliative therapy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Detailed staining methods.

Table S1 Summary of patients who experienced disease control (≥ 120 days) from somatostatin analogue therapy.

Table S2 Correlation of somatostatin receptor scintigraphy uptake with somatostatin receptor 2 and 5 expression by immunohistochemical staining.

Table S3 Comparisons of somatostatin receptor scintigraphy uptake with clinical benefit and pathological features.