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Peptide Receptor Radionuclide Therapy in Merkel Cell Carcinoma: A Comprehensive Review

Running title: PRRT for Merkel cell carcinoma

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ABSTRACT

Purpose: Merkel cell carcinoma (MCC) is a rare aggressive skin malignancy, also known as neuroendocrine carcinoma of the skin, with high rates of recurrence and distant metastasis. In refractory metastatic MCC (mMCC), besides immunotherapy, chemotherapy and radiation, peptide receptor radionuclide therapy (PRRT) may be a viable option since this type of tumor can express somatostatin receptors (SSTR).

Methods: We performed a comprehensive review of the literature to evaluate the efficacy of PRRT in mMCC patients.

Results: 37 patients with mMCC have received PRRT (1-5 cycles) with ^{177}Lu- and/or ^{90}Y-labeled somatostatin analogues (cumulative activity: 1.5-30 GBq). Radiographic response was available in 19 out of 28 patients who received PRRT alone. Six (31.6%) out of 19 patients showed objective responses, from partial to complete responses, and no severe adverse events were reported.

Conclusion: Our analysis supports the use of PRRT in mMCC with sufficient SSTR uptake, although the quality of the available evidence is low. Prospective studies in terms of clinical trials are already in development and have started accruing in some parts of the world.

Key Words: PRRT; SSTR; Merkel cell carcinoma; Theranostics, Lu-177;

Peptide Receptor Radionuclide Therapy in Merkel Cell Carcinoma: A Comprehensive Review

Merkel cell carcinoma (MCC) is a rare aggressive skin malignancy. The known risk factors for MCC are immunosuppression and extensive UV exposure. It usually occurs in elderly patients (median age of 70 years), typically arises in the head, neck or extremities, and is slightly more common in males. Treatments for MCC vary depending on the stage of the disease, from complete surgical resection with or without radiation therapy for localized disease to systemic therapies (immunotherapy or chemotherapy) for metastatic disease. The five-year survival rates for patients with metastatic disease were approximately 18% (*1*,*2*). Although the introduction of immune checkpoint inhibitors (ICI) have shown promising results with an approximately 50% objective responses, however about half of mMCC patients experience disease progression or resistance.

At least one-third of MCCs express high levels of somatostatin receptors (SSTR) (*3*,*4*). In some studies, SSTR expression has been reported in as high as 80-100% of MCC (*5*). There have even been reports of using the SSAs for the treatment of MCC. A recent trial of a novel second generation SSA (pasereotide) allowed MCC cancer to participate given the SSTR expression (NCT01652547). All this sets the stage for a new therapeutic option of theranostics/ peptide receptor radionuclide therapy (PRRT) in MCC.

Data on PRRT in MCC exists only in the form of case reports/series. Articles/abstracts pertaining to "PRRT" and "MCC" were systematically searched in the PubMed, Scopus and Google Scholar. Articles/abstracts published until January 2022 were retrieved. The references of all relevant studies were evaluated as well. We also contacted centers who had previously reported experience with SSTR imaging/therapy in mMCC patients (for search strategy/PRISMA flow diagram, information in supplemental Figure 1 and 2) (*6*-*26*). Overall, 37 patients with mMCC have received PRRT with ^{177}Lu- and/or ^{90}Y-labeled somatostatin analogues (DOTATATE/DOTATOC) (Table 1 and Supplemental Table 1 and 2). Fifteen and eighteen patients received ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC, respectively. Four patients underwent tandem PRRT with ^{177}Lu-^{90}Y. The number of PRRT cycles ranged from 1 to 5 with the cumulative activity ranging from 1.5 GBq to 30 GBq. Three patients received PRRT in combination with chemotherapy and four patients received PRRT with immune check point inhibitors.

Of the 37 patients who received PRRT, 18 patients were excluded due to unavailable response data (Supplemental Table 1 and 2) or due to use of PRRT in combination with other active treatments (Supplemental Table 1). Consequently, radiographic response was available for 19 out of 28 patients who received PRRT alone (not in combination with immunotherapy or chemotherapy). Six (31.6%) out of 19 patients showed objective responses, from partial to complete responses, and no severe adverse events were reported (Table 1).

The median overall survival (OS) from start of PRRT was 5 and 8 months in patients receiving PRRT alone and in combination with other active treatments, respectively (Table 1 and supplemental Table 1). Median OS from diagnosis was 22 months (Supplemental Table 3; methods for statistical analyses are described in the supplemental file). Few studies addressed the Merkel cell polyomavirus status or ^{18}F-FDG-PET findings while the majority reported Krenning score (Supplemental Table 4). No significant difference was noted between Krenning scores in terms of objective response to PRRT ($p = 0.86$).

Due to small sample size, retrospective nature of the studies, selection bias, and low-quality evidence, we cannot recommend PRRT for mMCC patients. This, however, lays the foundation for clinical trials in this space. Despite approval of ICIs treatment resistance can occur, and a fair proportion do not respond. 5 out of 7 patients that received PRRT in combination with ICI or chemotherapy showed partial to complete responses which shows better objective responses in this category as compared to PRRT alone group. Novel therapies or combinations are needed to further improve patient outcome. The ongoing GoTHAM trial (NCT04261855) is one example of a clinical trial evaluating immunotherapy avelumab with ^{177}Lu-DOTATAE in patients with mMCC. Results of this and other ongoing trials using theranostics could change the management of mMCC patients soon.

CONFLICT OF INTEREST AND DISCLOSURE

JS has consulted for Novartis and is on the speaker's bureau for Ipsen. DW reports personal fees from Ipsen. PMK reports consultancy/advisory board for Natera, Foundation Medicine, Merck/MSD Oncology, Tempus, Bayer, Lilly, Delcath Systems, QED therapeutics, Servier, Taiho Oncology, Exact Sciences, Ipsen (institution); grant/research funding: Advanced Accelerator Applications, Boston Scientific, Tersera. The other authors have nothing to disclose.

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KEY POINTS:

QUESTION: Is radioligand therapy with ^{177}Lu-DOTATAE effective and safe in mMCC patients?

PERTINENT FINDINGS: Due to small sample size and low-quality evidence we cannot recommend PRRT for mMCC patients however the available data show promising results. This, however, lays the foundation for clinical trials in this space.

IMPLICATIONS FOR PATIENT CARE: ^{177}Lu-DOTATAE could be effective in some mMCC patients with high SSTR expression.

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TABLE 1 – Review of the Studies Evaluating the Treatment response to PRRT Monotherapy in Metastatic Merkel Cell Carcinoma (n = 10)

First author, Year (Reference)	Age (Gender)	Primary location (Size in cm)	Other sites of involvement	Data on PRRT (Type of radiotracer, cumulative dose, # of cycles)	Treatments prior to PRRT					Survival from start of PRRT (months)	Treatment response to PRRT
					Surgery	EBRT	Chemo.	SSAs	ICI		
Meier, 2004 (*7*)	83 (F)	Facial (Left cheek) (3)	Cervical LNs	^{90}Y-DOTATOC, 15.72 GBq, 4 cycles	✓	✓	✓	×	×	27	CR
Bodei, 2004 (*8*)	78 (F) *	Leg (Left)	Pelvic LNs	^{90}Y-DOTATOC, 9.6 GBq, 3 cycles	✓	✓	×	×	×	7	PD
Maecke, 2005 (*9*)	43 (F)	Head	NA	^{90}Y-DOTATOC, 5.4 GBq/m^2, 4 cycles	NA	NA	NA	NA	NA	>19	CR
Imhof, 2011 (*10*)	70 (M)	NA	NA	^{90}Y-DOTATOC, 8.14 GBq, 1 cycle	✓	×	✓	×	×	6.1	PD
	77 (M)	NA	Liver, bone	^{90}Y-DOTATOC, 6.66 GBq, 1 cycle	✓	✓	×	×	×	1	PD
	69 (F)	NA	NA	^{90}Y-DOTATOC, 5.37 GBq, 1 cycle	×	✓	✓	×	×	1.2	PD
	55 (M)	NA	Liver	^{90}Y-DOTATOC, 8.14 GBq, 1 cycle	✓	×	✓	×	×	1.7	PD
	54 (F)	NA	NA	^{90}Y-DOTATOC, 12.96 GBq, 2 cycles	✓	×	×	×	×	13.9	PR
	66 (M)	NA	Liver	^{90}Y-DOTATOC, 14.06 GBq, 2 cycles	✓	✓	✓	×	×	4.5	SD
	83 (F)	NA	NA	^{90}Y-DOTATOC, 15.73 GBq, 4 cycles	✓	✓	×	×	×	9.1	SD
	69 (F)	NA	Liver	^{90}Y-DOTATOC, 11.1 GBq, 2 cycles	✓	×	×	×	×	9.7	PR
Villard, 2012 (*11*)	76 (F)	NA	NA	^{177}Lu-DOTATOC, 12.95 GBq, 2 cycles; ^{90}Y-DOTATOC, 13.88 GBq, 2 cycles	✓	×	×	×	×	15.1	SD
	73 (F)	NA	NA	^{177}Lu-DOTATOC, 14.43 GBq, 2 cycles; ^{90}Y-DOTATOC, 14.43 GBq, 2 cycles	✓	✓	✓	×	×	9.8	SD
Romer, 2014 (*12*)	76 (F)	NA	Bone	^{177}Lu-DOTATOC, 7.4 GBq, 1 cycle	×	✓	✓	×	×	0.7	PD
	53 (M)	NA	NA	^{177}Lu-DOTATOC, 7.4 GBq, 1 cycle	×	×	✓	×	×	1.3	PD
Basu, 2015 (*2*)	54 (M)	Facial (Right malar)	Cervical LNs, liver	^{177}Lu-DOTATATE, 13.14 GBq, 2 cycles	✓	×	✓	✓	✓	>3	PR
Nilica, 2016 (*13*)	65 (M)	Arm (Right forearm)	Widespread (LNs, liver, bone, peritoneum, cardiac)	^{177}Lu-DOTATATE, 14.2 GBq, 2 cycles; ^{90}Y-DOTATOC, 2.4 GBq, 1 cycle	✓	✓	✓†	×	×	5	PD
Noorelahi, 2017 (*14*)	59 (M)	Axilla (Right) (9)	Subpectoal and axillary LNs	^{177}Lu-DOTATOC, 10.62 GBq, 2 cycles	✓	✓	✓	NA	NA	NA	PD
Moghadam, 2019 (*3*)	77 (M)	Facial (Right malar)	Extensive LNs (cervical, supraclavicular, mediastinal, axillary, abdominal)	^{177}Lu-DOTATATE, 5.5 GBq, 1 cycle	✓	✓	✓	✓	×	2‡	PR

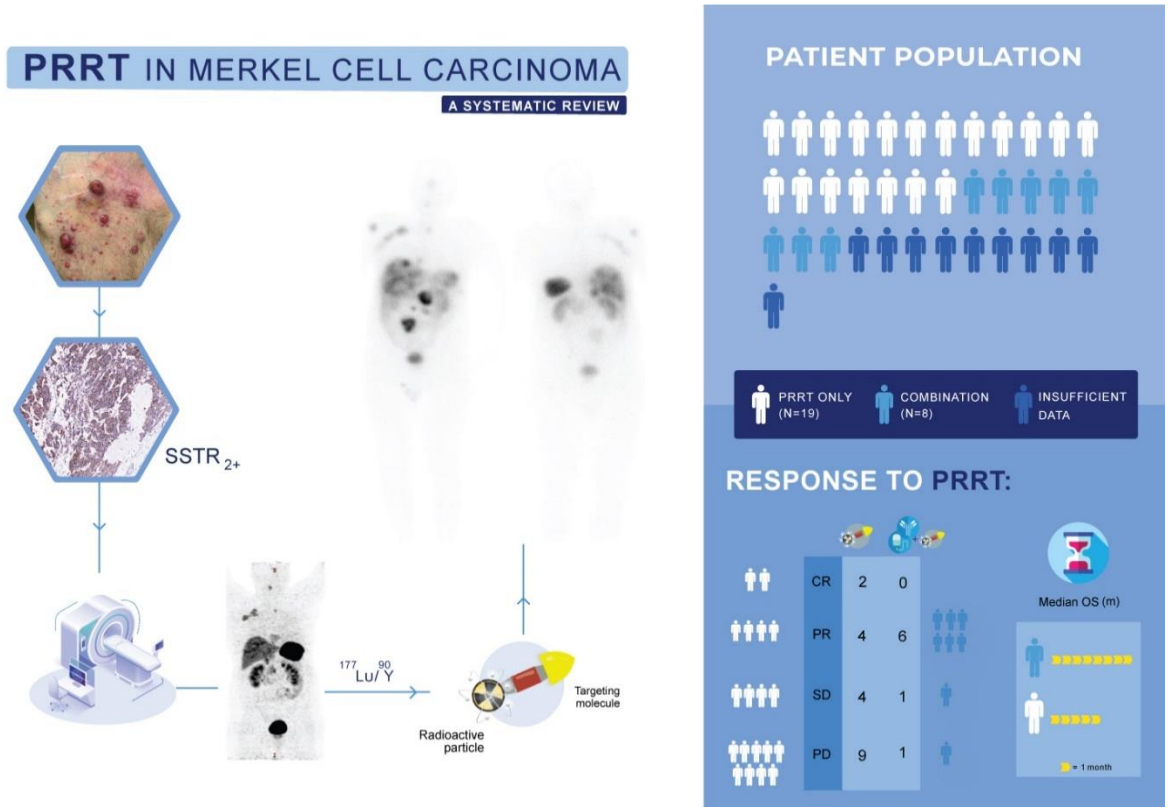
CR = Complete response, ICI = immune checkpoint inhibitors, LN = Lymph node, NA = Not available, PD = Progressive disease, PR = Partial response, SD = Stable disease

* Underlined data were obtained after personal communication with the corresponding authors of that article/unpublished data.

† Intracardiac instillation of the chemotherapeutic drugs due to cardiac involvement.

‡ Death due to other cause (ARDS)

GRAPHICAL ABSTRACT



Supplemental file

Search strategy:

Articles pertaining to Merkel cell carcinoma (MCC) and peptide receptor radionuclide therapy (PRRT) were searched in Google Scholar, PubMed and Scopus. Equivalent terms were covered, as well. These include:

(A) For MCC:

a. "neuroendocrine carcinoma of the skin" OR (trabecular cancer AND skin) OR “merkel cell carcinoma” OR “merkel cell tumor” OR “merkel cell tumour” OR “merkel cell cancer” OR "small-cell carcinoma of the skin" OR "Toker tumor" OR "Toker tumour" OR "cutaneous neuroendocrine carcinoma" OR "trabecular cell carcinoma"
b. Merkel (for hand searching in nuclear medicine journals)

(B) For PRRT:

a. "Y-DOTATATE" OR "Y-DOTA-TATE" OR "90Y-DOTATATE" OR "90Y-DOTA-TATE" OR "[90Y]Y-DOTATATE" OR "[90Y]Y-DOTA-TATE" OR "DOTATATE yttrium Y-90" OR "DOTA-TATE yttrium Y-90" OR "Y-DOTA-TOC" OR "Y-DOTATOC" OR "90Y-DOTA-TOC" OR "90Y-DOTATOC" OR "[90Y]Y-DOTATOC" OR "[90Y]Y-DOTA-TOC"
b. "peptide receptor radionuclide therapy" OR PRRT OR PRRNT OR Lutathera OR "Lu-DOTA-TATE" OR "Lu-DOTATATE" OR "177Lu-DOTATATE" OR "177Lu-DOTA-TATE" OR "[1777Lu]Lu-DOTATATE" OR "[177Lu]Lu-DOTA-TATE" OR "177Lu-DOTA-Tyr3-octreotate" OR "177Lu-DOTA-octreotate" OR "Lutetium oxodotreotide lu-177" OR "(177Lu-DOTAOTyr3)octreotate" OR "Lutetium (177lu) oxodotreotide" OR "(177lutetium-DOTA(O)Tyr3)octreotate" OR “peptide receptor”

Hand searching of the most important nuclear medicine journals, including the JNM, was also performed using the most sensitive key word (i.e. “merkel”). No language restriction was applied and the literature was searched until 22 January 2022. Search was performed by two independent researchers (EA and SZM). In case of discrepancy, consensus method was used. To identify ongoing trials on Merkel cell carcinoma, Cochrane library and clinicaltrials.gov were also checked. We also contacted centers who have had reported somatostatin receptor (SSTR) PET imaging in MCC with a hope of finding new cases being treated with PRRT. Overall, 75 colleagues were contacted during the project in order to obtain more data. The PRISMA 2020 flow diagram is designed according to the guidelines and is shown in supplemental figure 1 (*1*). Schema of the case included in and excluded from the study is shown in supplemental figure 2. Protocol registration was not used for the current systematic review.

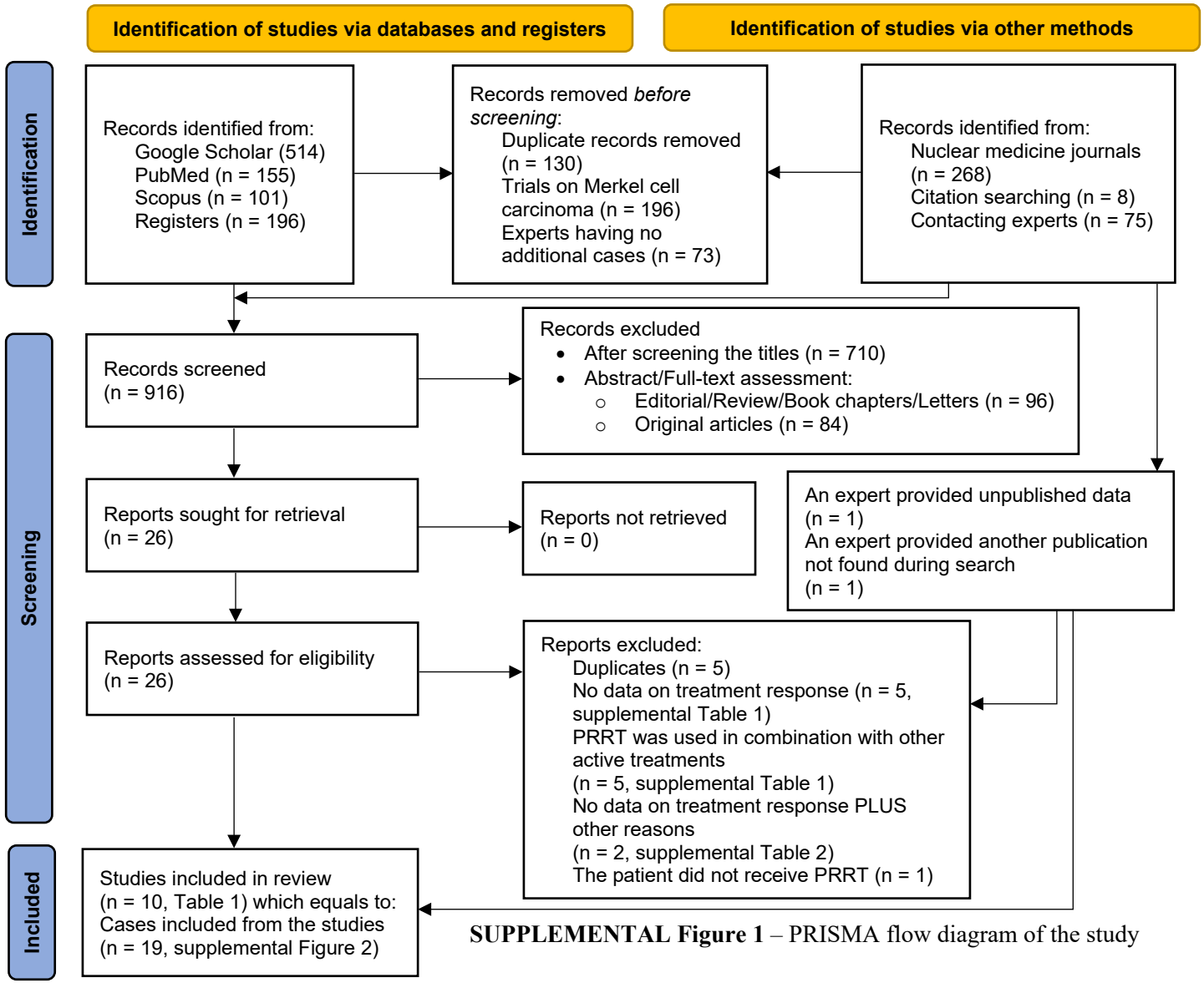
Search results were recorded using an excel file. Results retrieved from each dataset along with its unique search strategy was kept in separate spreadsheets. To remove duplicates, conditional formatting and fuzzy look-up was used. Google scholar outperformed other databases finding 7 of 10 studies (for scientometric purposes, recorded search data is available upon request from the first author).

All studies evaluating the treatment response of PRRT in MCC were included. For more information regarding the excluded MCC cases treated with PRRT and unavailable response data, the reader is referred to supplemental tables 1 and 2.

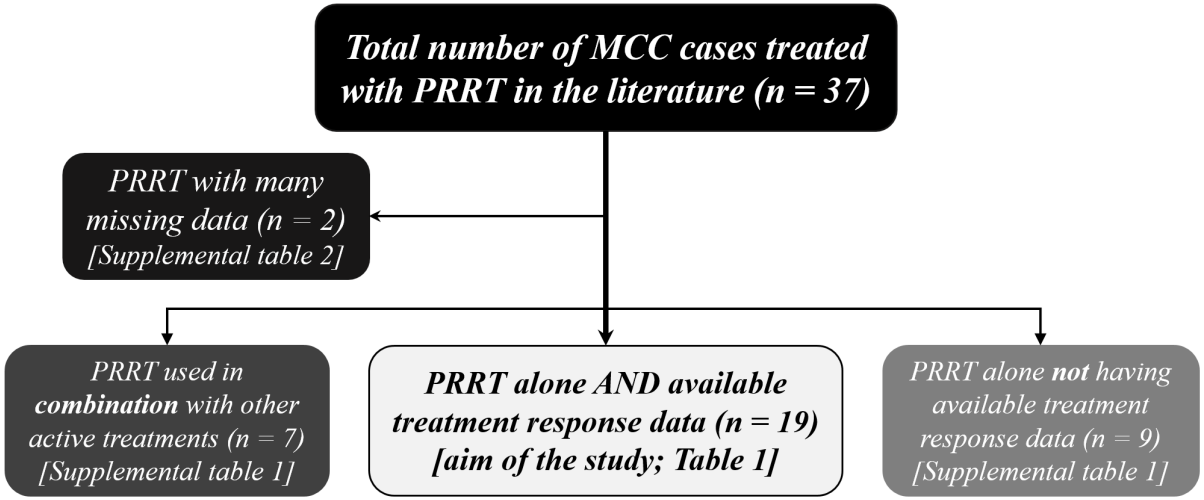
Additional data regarding overall survival of the cases (from histopathological diagnosis), Krenning score, FDG findings and MCPyV status is summarized in supplemental tables 3 and 4.

Statistical analysis:

Kaplan-Meier curves were used to estimate the median overall survival from diagnosis/start of PRRT. For evaluation of objective response in different Krenning scores, logistic regression test was applied.



SUPPLEMENTAL Figure 1 – PRISMA flow diagram of the study



SUPPLEMENTAL Figure 2 – Schema of the cases included in (*2-10*) and excluded from (*11-22*) the study

SUPPLEMENTAL TABLE 1 – Studies excluded due to unavailable treatment response (number of cases = 9) or combination of PRRT with other active treatments (number of cases = 7)

First author, Year (Reference)	Age (Gender)	Primary location (Size in cm)	Other sites of involvement	Data on PRRT (Type of radiotracer, cumulative dose, # of cycles)	Treatments prior to PRRT					Survival from start of PRRT (months)	Treatment response to PRRT
					Surgery	EBRT	Chemo.	SSAs	ICI		
(A) PRRT only											
Barucca, 2006 (*11*)	66 (M)	Gluteal (5)	Inguinal and abdominal LNs	^{90}Y-DOTATOC, 2.84 GBq, 2 cycles	✓	✓	✓	×	×	NA	NA
	57 (M)	Gluteal (3)	Inguinal LNs	^{90}Y-DOTATOC, 3.36 GBq, 1 cycle	✓	×	✓	×	×	NA	NA
	82 (F)	Lateral malleolus	Inguinal LNs	^{90}Y-DOTATOC, 3.95 GBq, 2 cycles	✓	×	×	×	×	NA	NA
Herberg, 2009 (*12*)	66 (M)*	Thigh (Right) (5)	Inguinal LNs, liver	^{90}Y-DOTATOC, 4.44 GBq, 2 cycles	NA	NA	NA	NA	NA	≥3	NA
Cirillo, 2012 (*13*)	80 (M)	Head (0.5)	None	^{177}Lu-DOTATATE, 1.5 GBq, 1 cycle	✓	✓	✓	✓	×	NA	NA
Hamiditabar, 2017 (*14*)	69 (M)	NA	NA	^{177}Lu-DOTATATE, 7 GBq, 1 cycle	NA	NA	NA	NA	NA	NA	NA
	74 (M)	Chest, Back	Extensive LNs (right axillary and subpectoral), Bone	^{177}Lu-DOTATATE, 7.1 GBq, 1 cycle	NA	NA	NA	NA	NA	7.9	NA
Würzburg center (unpublished data)	76 (M)	Arm (Left forearm)	Testes, cervical LNs, lymphangiosis	^{90}Y-DOTATOC, 3.0 GBq, 1 cycle	×	✓	✓	×	×	1	NA
	75 (F)	Facial (Left cheek)	Extensive LNs (facial, cervical, parotidal)	^{177}Lu-DOTATOC, 6.1 GBq, 1 cycle	✓	✓	✓	×	✓	4	NA
(B) PRRT in combination with other treatments											
Schmidt, 2012 (*15*)	76 (F)	Pharyngeal tonsil	Extensive LNs (cervical, axillary), pancreatic head	^{90}Y-DOTATATE, 10 GBq, 2 cycles	✓		✓†			7	SD
Salavati, 2012 (*16*)	67 (M)	NA	Extensive LNs (cervical, abdominal, inguinal)	^{177}Lu-DOTATATE, 14 GBq , 2 cycles		✓†	✓†			8	PR
	53 (M)	Leg (Posterior thigh) (Multiple)	Extensive LNs (right extremity, inguinal, abdominal, thoracic?)	^{177}Lu-DOTATATE, 20 GBq , 2 cycles			✓†			7‡	PD
Kasi, 2019 (*17*)	83 (M)	Shoulder	Widespread (bone, LNs, carcinomatosis, ascites)	^{177}Lu-DOTATATE, 7.4 GBq, 1 cycle	NA	×	×	✓	✓†	9	Near CR
Ferdinandus, 2021 (*18*)	60 (M)	Leg (Right thigh)	Retroperitoneal LNs, bone	^{177}Lu-DOTATATE, 14.8 GBq, 2 cycles	✓	✓	✓		✓†	>5	PR
Sindrilaru, 2021 (*19*)	NA	Arm (Right elbow)	LNs, distant skin, bone	^{177}Lu-HA-DOTATATE, 10.5 GBq, 3 cycles	NA	NA	NA	NA	✓†	8	PR
	NA	NA	LNs, distant skin, bone	^{177}Lu-HA-DOTATATE, 10.5 GBq, 3 cycles	NA	NA	NA	NA	✓†	10	PR

^{177}Lu-HA-DOTATATE = high affinity ^{177}Lu-DOTATATE, CR = Complete response, ICI = immune checkpoint inhibitors, LN = Lymph node, NA = Not available, PR = Partial response, PD = Progressive disease, SD = Stable disease

***** Underlined data were obtained after personal communication with the corresponding authors of that article/unpublished data.

† Treatments used in combination with PRRT.

‡ Death due to other cause (obstructive uropathy)

SUPPLEMENTAL TABLE 2 – Studies excluded due to unavailable treatment response PLUS other reasons (number of cases = 2) *

Authors, Year (Reference)	# of cases excluded (from total # of the cases)	Reasons for exclusion (other than unavailable treatment response)
Stefanova et al., 2012 (*20*)	1 (1)	It was known that a 50-year old female was treated with 5 cycles of PRRT (10 and 20 GBq of ^{90}Y- and ^{177}Lu-PRRT, respectively).
Koukouraki et al., 2006 (*21*)	1 (1)	It was only known that the case was a 55-year old female with primary gluteal lesion and liver metastases treated with ^{90}Y-PRRT

* In the study of Epstude et al., 2013 (*22*), the patient did not finally receive PRRT based on personal communication with the corresponding author and therefore, not counted in this table.

SUPPLEMENTAL TABLE 3 – Studies with available survival data (from diagnosis)

First author, Year (Reference)	Age (Gender)	Survival from diagnosis (months)
Meier, 2004 (*2*)	83 (F)	36
Bodei, 2004 (*3*)	78 (F) *	41
Maecke, 2005 (*4*)	43 (F)	>25 †
Imhof, 2011 (*5*)	70 (M)	18.8
	77 (M)	16
	69 (F)	4.6
	55 (M)	61.4
	54 (F)	25.2
	66 (M)	17.5
	83 (F)	>33.8 †
	69 (F)	15.9
Cirillo, 2012 (*13*)	80 (M)	17
Villard, 2012 (*6*)	76 (F)	27.2
	73 (F)	22.7
Schmidt, 2012 (*15*)	76 (F)	7
	67 (M)	11
Salavati, 2012 (*16*)	53 (M)	10
Romer, 2014 (*7*)	76 (F)	8.9
	53 (M)	9.4
Basu, 2015 (*8*)	54 (M)	>39 †
Nilica, 2016 (*9*)	65 (M)	45
Moghadam, 2019 (*10*)	77 (M)	26
Würzburg center	76 (M)	53
(unpublished data)	75 (F)	22
Ferdinandus, 2021 (*18*)	60 (M)	>20 †
Sindrilaru, 2021 (*19*)	NA	15

* Underlined data were obtained after personal communication with the corresponding authors of that article/unpublished data.

† Lost to follow-up or unavailable data regarding survival after the given time.

SUPPLEMENTAL TABLE 4 – Other Findings of Significance Reported in the Studies Evaluating the Usefulness of PRRT in Metastatic Merkel Cell Carcinoma

Relevant clinical question?	Number of cases addressed by the relevant literature (References)
What was the MCPyV status of the cases?	1 (*18*): MCPyV-positive
How was the Krenning score of the cases?	25 (*3-12*, *16*, *18*, and Würzburg center (unpublished data)) - grade I (n = 2) (*5, 7*) - grade II (n = 5) (Würzburg center (unpublished data), *6*, *7*, *11*) - grade III (n = 14) (*4-6*, *8*, *9*, *11*, *12*) - grade IV (n = 4) (*3*, *10*, *16*, *18*)
Which studies reported FDG findings?	5 (*9*, *11*, *16*, and Würzburg center (unpublished data)) - Nilica et al. (*9*): Hypermetabolic lesions in the right axilla, cerebral left parietal, peritoneal near right colon flexure. - Barucca et al (*11*): Case #2 (57-year old male): Superior mesenteric conglomerated lymph nodes. - Salavati et al. (*16*): Hypermetabolic lesions in the right calf (SUVmax 11.4), and a chain of FDG avid lymph nodes (SUVmax 16.5), extending from the right inguinal to the right iliac and para-aortic region. - Würzburg center (unpublished data): 1. Case #1 (76-year old male): Hypermetabolic lesions supraclavicular left (SUVmax 6.2), in the left shoulder (SUVmax 5.4), right humerus (SUVmax 3.4), left humerus and forearm (SUVmax 3.5), mediastinal (SUVmax 5.9), sternal (SUVmax 2.8), right hilum (SUVmax 3.0) and left femur (SUVmax 3.2) (concordant to SSTR). 2. Case #2 (75-year old female): Hypermetabolic lesions in the region of the left cheek, the left orbit (SUVmax 5.2), submental (SUVmax 4.9) and left mandible (SUVmax 7.3) (concordant to SSTR).

MCPyV = Merkel cell polyomavirus

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