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-octreotide" 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.
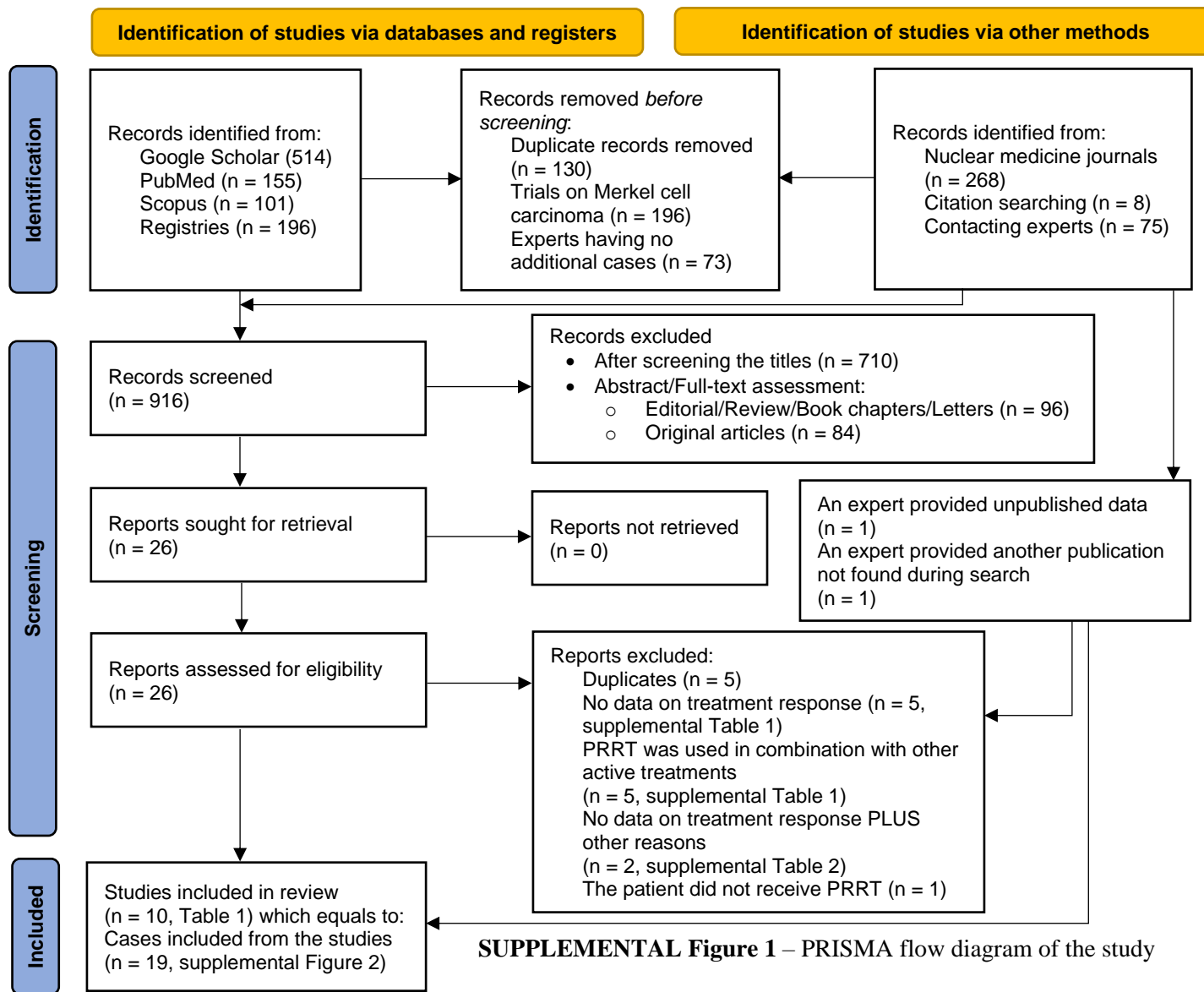
Search results were recorded using an excel file. Results retrieved from each dataset along with its unique search strategy was kept in separate spreadsheets. To remove duplicates, conditional formatting and fuzzy look-up was used. Google scholar outperformed other databases finding 7 of 10 studies (for 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.

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Identification of studies via databases and registers

Identification of studies via other methods

Identification

Records identified from:
  Google Scholar (514)
  PubMed (n = 155)
  Scopus (n = 101)
  Registries (n = 196)

Records removed *before screening*:
  Duplicate records removed (n = 130)
  Trials on Merkel cell carcinoma (n = 196)
  Experts having no additional cases (n = 73)

Records identified from:
  Nuclear medicine journals (n = 268)
  Citation searching (n = 8)
  Contacting experts (n = 75)

Screening

Records screened
(n = 916)

Records excluded
- After screening the titles (n = 710)
- Abstract/Full-text assessment:
  o Editorial/Review/Book chapters/Letters (n = 96)
  o Original articles (n = 84)

Reports sought for retrieval
(n = 26)

Reports not retrieved
(n = 0)

An expert provided unpublished data (n = 1)
An expert provided another publication not found during search (n = 1)

Reports assessed for eligibility
(n = 26)

Reports excluded:
  Duplicates (n = 5)
  No data on treatment response (n = 5, supplemental Table 1)
  PRRT was used in combination with other active treatments
  (n = 5, supplemental Table 1)
  No data on treatment response PLUS other reasons
  (n = 2, supplemental Table 2)
  The patient did not receive PRRT (n = 1)

Included

Studies included in review
(n = 10, Table 1) which equals to:
Cases included from the studies
(n = 19, supplemental Figure 2)

SUPPLEMENTAL Figure 1 – PRISMA flow diagram of the study
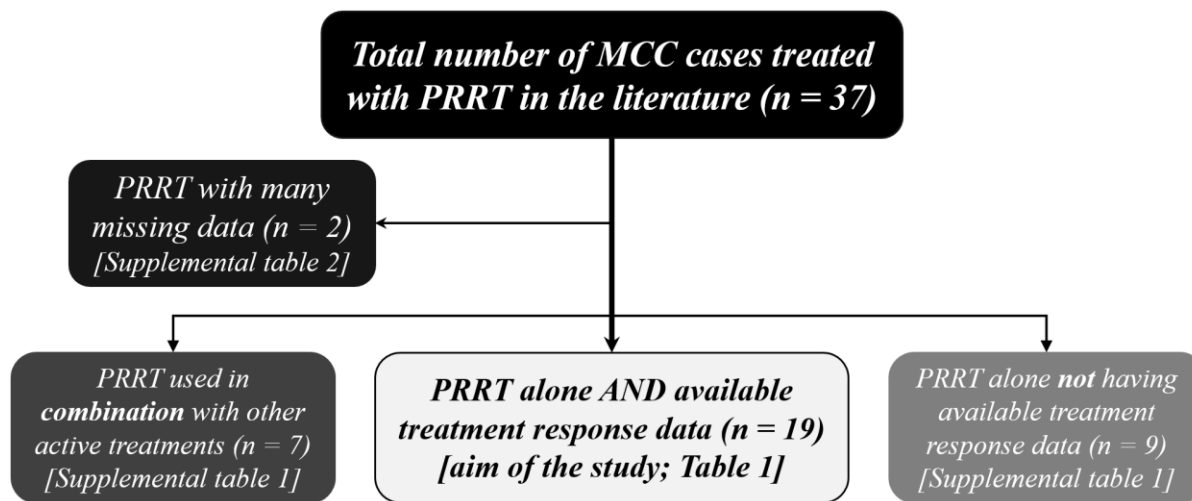
SUPPLEMENTAL Figure 2 – Schema of the cases included in (*2-10*) and excluded from (*11-22*) the study

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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
	67 (M)	NA	Extensive LNs (cervical, abdominal, inguinal)	^{177}Lu-DOTATATE, 14 GBq , 2 cycles		✓†	✓†			8	PR
Salavati, 2012 (16)	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)

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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.

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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*)	<u>78 (F)</u> *	<u>41</u>
Maecke, 2005 (*4*)	43 (F)	<u>>25</u> [†]
Imhof, 2011 (*5*)	<u>70 (M)</u>	<u>18.8</u>
	<u>77 (M)</u>	<u>16</u>
	<u>69 (F)</u>	<u>4.6</u>
	<u>55 (M)</u>	<u>61.4</u>
	<u>54 (F)</u>	<u>25.2</u>
	<u>66 (M)</u>	<u>17.5</u>
	<u>83 (F)</u>	<u>>33.8</u> [†]
	<u>69 (F)</u>	<u>15.9</u>
Cirillo, 2012 (*13*)	80 (M)	17
Villard, 2012 (*6*)	<u>76 (F)</u>	<u>27.2</u>
	<u>73 (F)</u>	<u>22.7</u>
Schmidt, 2012 (*15*)	76 (F)	7
	67 (M)	11
Salavati, 2012 (*16*)	53 (M)	10
Romer, 2014 (*7*)	<u>76 (F)</u>	<u>8.9</u>
	<u>53 (M)</u>	<u>9.4</u>
Basu, 2015 (*8*)	54 (M)	>39 [†]
Nilica, 2016 (*9*)	<u>65 (M)</u>	<u>45</u>
Moghadam, 2019 (*10*)	77 (M)	26
Würzburg center (unpublished data)	<u>76 (M)</u>	<u>53</u>
	<u>75 (F)</u>	<u>22</u>
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.

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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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