

Imaging of Merkel Cell Carcinoma

What imaging experts should know

TO BE FAMILIER WITH RATIONALE BEHIND THE ORDER AND
CREATE ACTIONABLE AND CLINICLLY RELEVENT REPORTS

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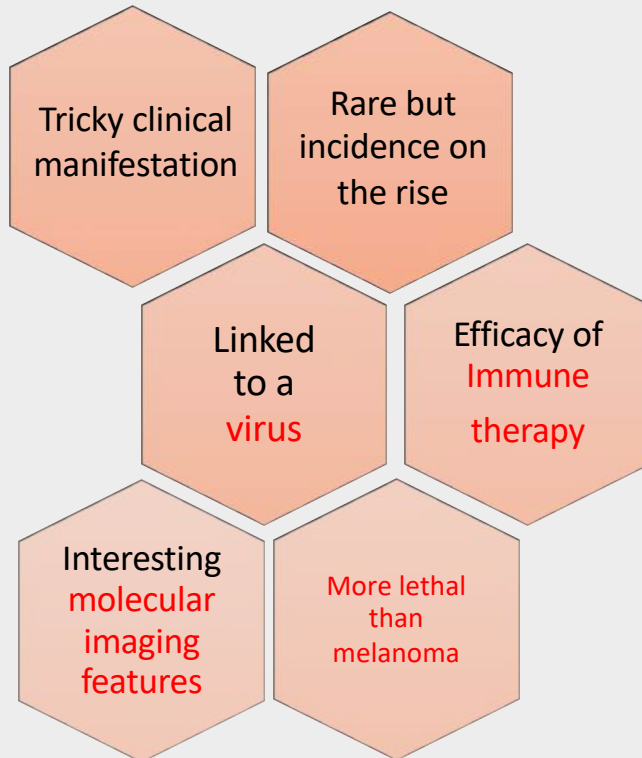




Introduction

Merkel cell carcinoma (MCC) is gathering more and more attention...

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2. Origin of MCC
3. Clinical manifestation
4. Risk factors
5. MCPyV
6. Staging
7. NCCN guideline
8. Immunotherapy
9. Role of imaging
10. SNLB
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13. FDG PET/CT
14. SSTR imaging
15. CNS metastasis
16. Bone metastasis
17. Metastasis to uncommon organs
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19. Take home messages



The purpose of this exhibit is to understand/review...

1. Pathophysiology and clinical behavior of Merkel cell carcinoma (MCC).
2. MCC's aggressive features and the important role of imaging in the management.
3. The Merkel cell polyomavirus (MCPyV) as a cause of MCC.
4. Utility of a blood test that detects antibodies to the MCPyV.
5. Different clinical approaches in antibody producers and non-antibody producers.
6. Neuroendocrine features of MCC with somatostatin receptor (SSTR) expression which can be imaged by SSTR seeking nuclear medicine studies.
7. Various imaging manifestations of MCC on different modalities.



Where does MCC come from?

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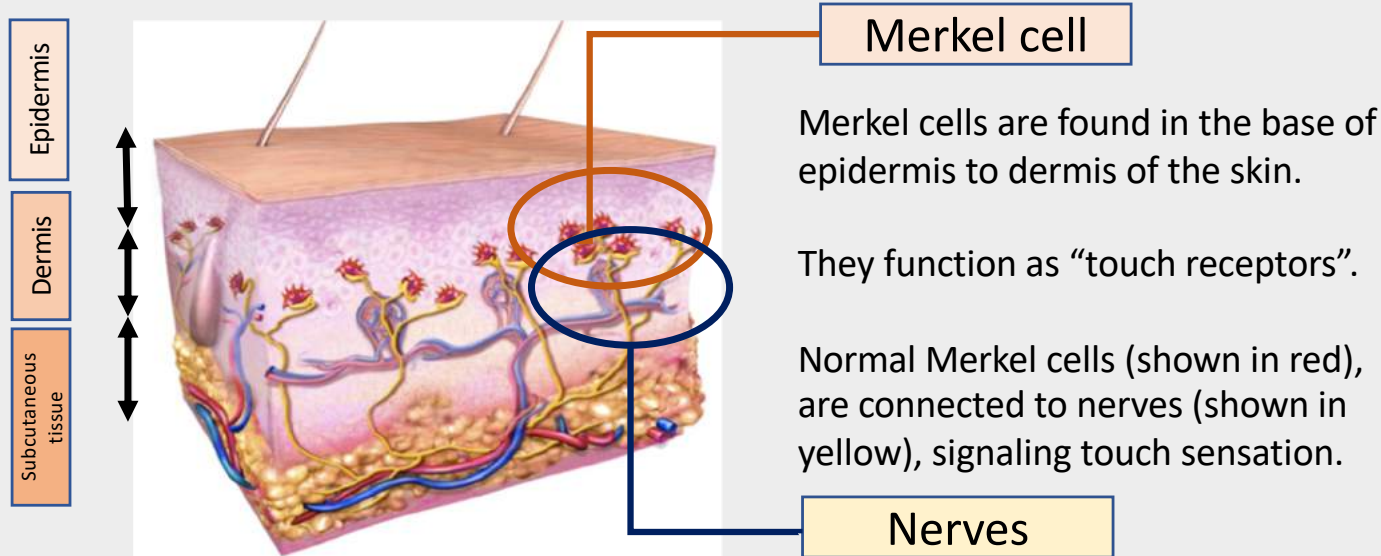


Figure Copyright by Paul Nghiem, MD, PhD & Quade Medical Group.

Merkel cells are ***not*** the origin of MCC.

MCC is named after ultrastructural and immunophenotypic resemblance to sensory Merkel cells in the skin¹.

MCCs are most frequently found in the dermis but **can arise from any layer of the skin** from intraepidermal to subcutaneous².

Fundamental evidence on the MCC cell of origin is yet to come into view.

1. Harms PW, Clin Lab Med 37 (2017) 485–501
2. Harms PW, et. al. Nat Rev Clin Oncol 2018 Oct 4. [Epub ahead of print]



MCC is unique and tricky cancer

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Tricky clinical features

MCC typically develops **rapidly** and manifests as firm, nontender, dome-shaped red, purple or violet nodule.

It has a predilection for the sun-exposed area, such as head, neck and extremities, however, it can occur anywhere in the body.

"It can fool even the best clinicians"
A majority of MCC lesions (56%) were **presumed to be benign** at biopsy.

Heath M et. al. J Am Acad Dermatol 2008;58:375-81.

MCC is more lethal than melanoma

Mortality rate

~40% for MCC

Becker JC et al., Ann Oncol, 2010

~8% for melanoma

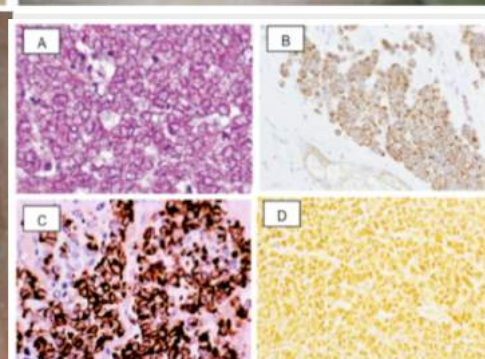
2007-2013 SEER Cancer Stat Facts.

Increasing incidence

2500 cases/year in US in 2013. The incidence is expected to increase to 2835 in 2020 and to 3284 in 2025.

From 2000 to 2013, solid cancers increased by 15%, melanoma by 57%, and Merkel cell carcinoma by **95%**.

Harms et. al. Ann Surg Oncol (2016) 23:3564–3571



5-year survival rate from the 8th edition AJCC staging system

Localized disease	51%
Nodal involvement	35%
Distant metastasis	14%



Risk factors

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Risk factors:

- Age (> 65 years)
- Fair skin
- Sun exposure
- Chronic immune suppression
- **Merkel cell polyomavirus** in ~80% cases.

Risk of developing MCC increases in patients with immunosuppression.

- HIV patient : 8 times greater *Engels et. al. Lancet 2002;359:497-498*
- Organ transplant patient: 25 times greater
Penn et. al. Transplantation. 1999;68(11):1717-1721.
- Chronic Lymphocytic leukemia: 40 times greater
Heath et.al J Am Acad Dermatol 2008;58:375-81.

*However, 90% of MCC patients are not immune suppressed.

MCC's AEIOU

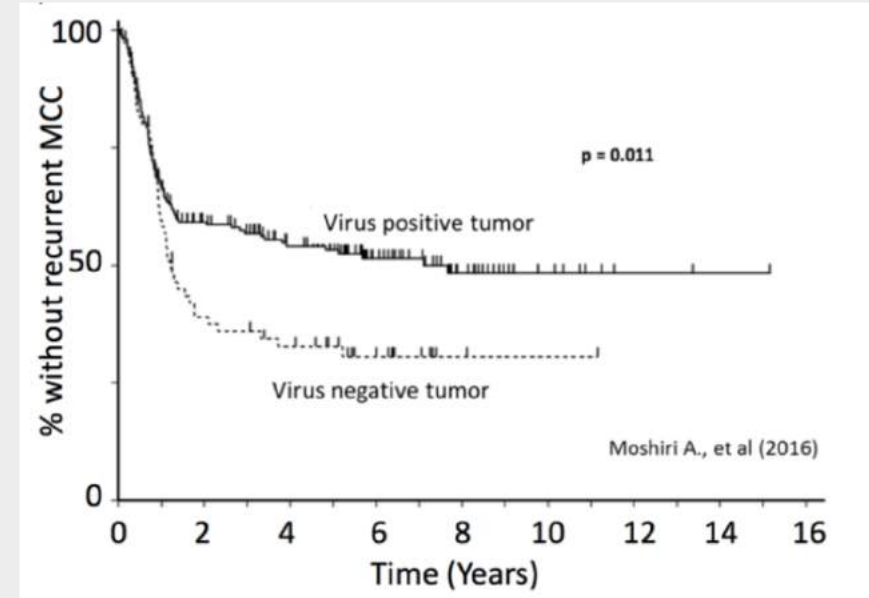
- A** Asymptomatic
- E** Expanding rapidly
- I** Immunosuppression
- O** Older Patients
- U** UV exposure



Merkel Cell Polyoma Virus (MCPyV)

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- The Merkel cell polyomavirus (MCPyV) is causally linked to 80% of cases whereas 20% are caused by extensive UV mutations.
- MCPyV is the only known human onco-virus in the polyomavirus family
- Antibodies against MCPyV oncoprotein antigens are associated with tumor burden and serve as a “tumor marker”.
- The test is much cheaper (~\$300/test) than imaging studies (3,000-\$100,000/scan)



Different approach based on MCPyV oncoprotein antibody status.

Antibody producers

Routine radiologic scans can be reduced as the antibody serves as “tumor marker”.

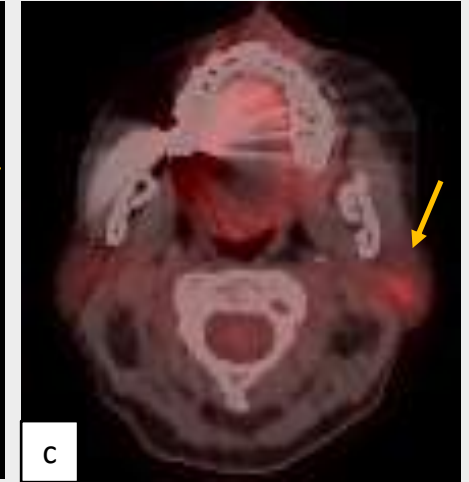
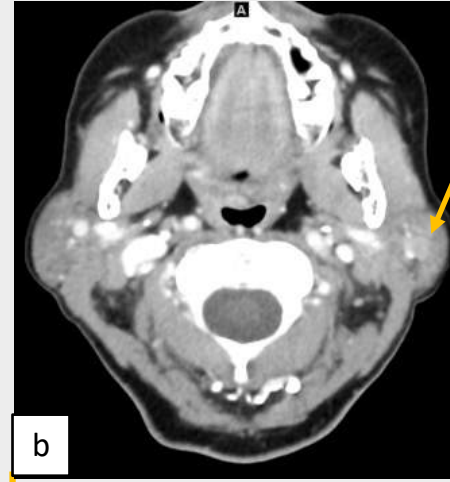
Non-Antibody producers

Must be followed by **frequent imaging studies**.

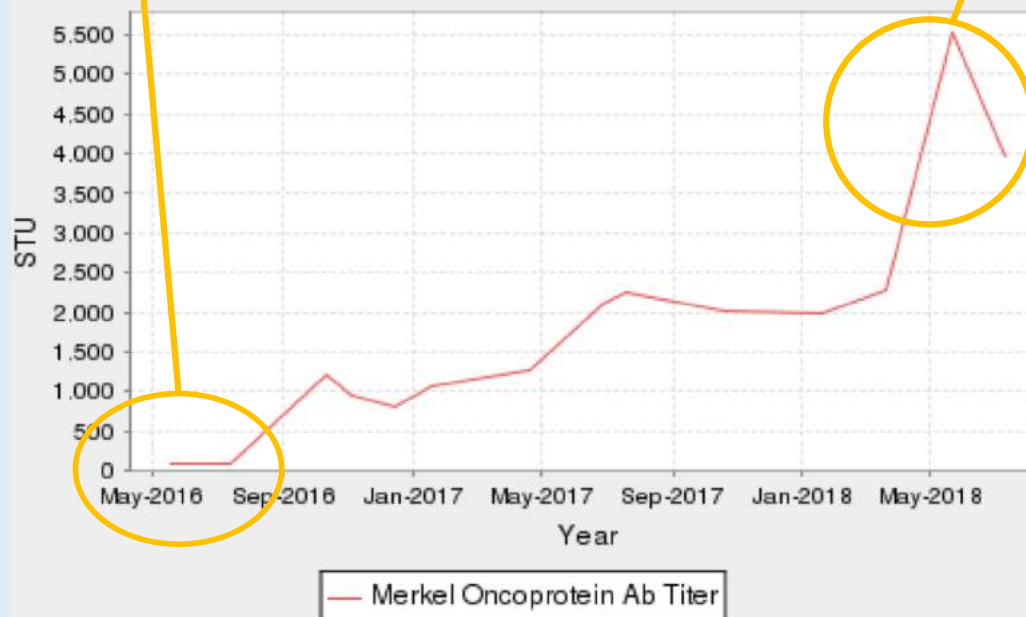


MCPyV oncoprotein antibody producer

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Lab Trend: 'Merkel Oncoprotein Ab Titer'



65-year-old woman with stage I MCC of the left cheek s/p wide local excision and negative SNLB on 02/2016.

(a) Post-operative oncoprotein titer was negative and contrast CT showed no evidence of disease.

Oncoprotein antibody titer had been continuously increased which prompted imaging evaluation.

(b) Contrast Neck CT shows a small enhancing nodule in the left parotid gland.

(c) F¹⁸ FDG PET/CT shows increased FDG uptake in the corresponding nodule.

US guided biopsy was performed and recurrent MCC was pathologically confirmed.



AJCC (American Joint Committee of Cancer) Staging 8th edition

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Stage		Primary Tumor	Lymph Node	Metastasis
0		In situ (within epidermis only)	No regional lymph node metastasis	No distant metastasis
I	Clinical*	≤ 2 cm maximum tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
I	Pathological**	≤ 2 cm maximum tumor dimension	Nodes negative by pathologic exam	No distant metastasis
IIA	Clinical	> 2 cm tumor dimension	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIA	Pathological	> 2 cm tumor dimension	Nodes negative by pathological exam	No distant metastasis
IIB	Clinical	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by clinical exam (no pathological exam performed)	No distant metastasis
IIB	Pathological	Primary tumor invades bone, muscle, fascia, or cartilage	Nodes negative by pathologic exam	No distant metastasis
III	Clinical	Any size / depth tumor	Nodes positive by clinical exam (no pathological exam performed)	No distant metastasis
IIIA	Pathological	Any size / depth tumor	Nodes positive by pathological exam only (nodal disease not apparent on clinical exam)	No distant metastasis
		Not detected ("unknown primary")	Nodes positive by clinical exam, and confirmed via pathological exam	No distant metastasis
IIIB	Pathological	Any size / depth tumor	Nodes positive by clinical exam, and confirmed via pathological exam OR in-transit metastasis***	No distant metastasis
IV	Clinical	Any	+/- regional nodal involvement	Distant metastasis detected via clinical exam
IV	Pathological	Any	+/- regional nodal involvement	Distant metastasis confirmed via pathological exam

Clinical detection of nodal or metastatic disease may be via inspection, palpation, and/or imaging

In transit metastasis

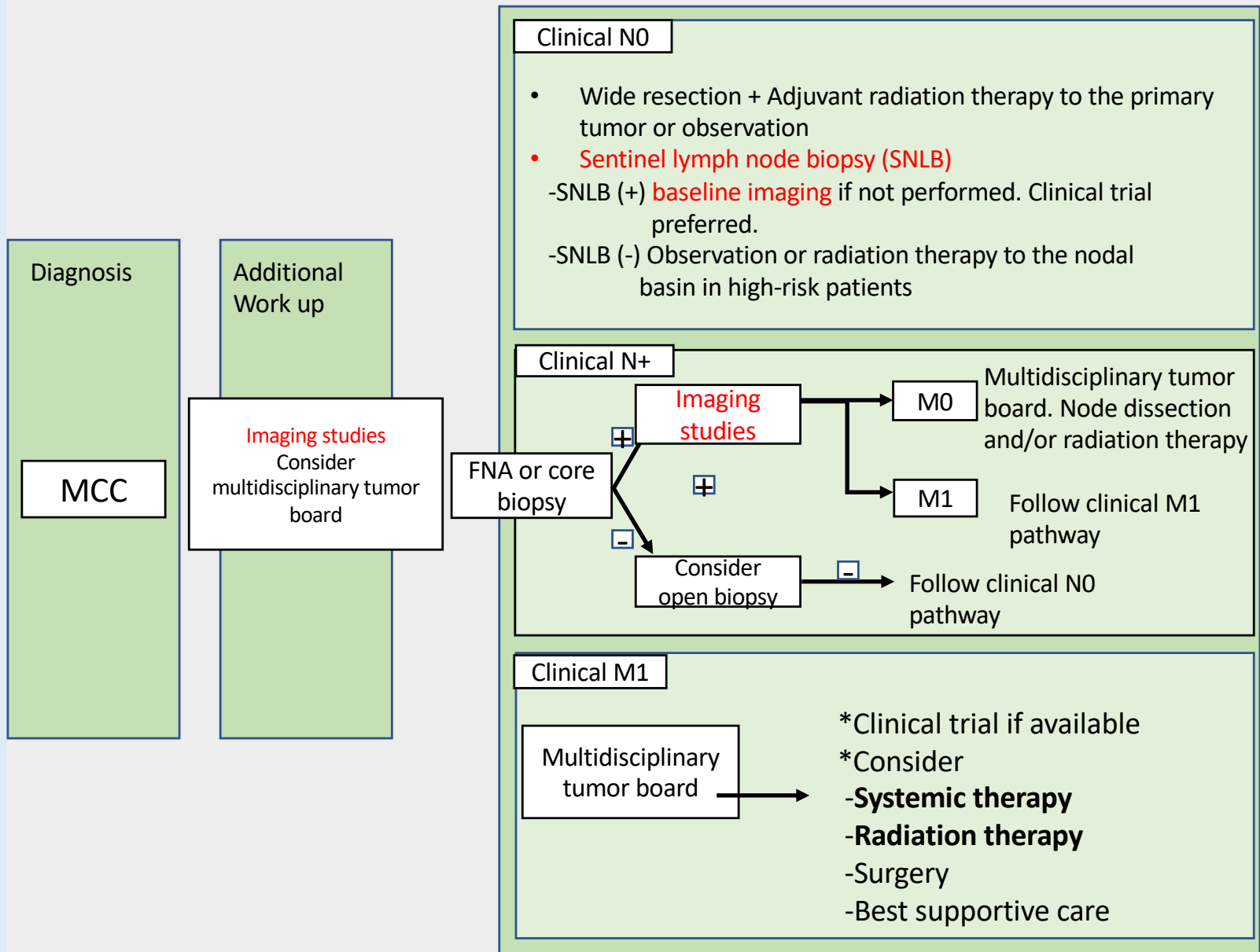
A tumor distinct from the primary lesion and located either

- 1) between the primary lesion and the draining regional lymph nodes or
- 2) distal to the primary lesion



NCCN guidelines

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Immunotherapy has changed NCCN guidelines

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-2016

Chemotherapy only

2017

Immunotherapy (Pembrolizumab) was listed as one of the systemic therapy options

2018

Immunotherapies (avelumab, pembrolizumab, nivolumab) are **preferred as 1st line therapy**

Checkpoint inhibitors disable the **PD-L1 (programmed cell death-ligand 1)** protein on cancer cells, activating the immune system to attack the tumor cells.

Cytotoxic chemotherapy is associated with a high initial objective response rate (ORR), however responses are **seldom durable** with the median progression-free survival (PFS) of about 94 days, and toxicity is considerable.

Iyer JG et.al. Cancer Med 2016; 5(9):2294–2301

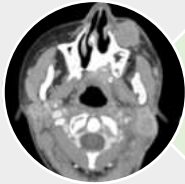
Food and drug administration (FDA)-recently approved immunotherapy with PD-1/PD-L1 antibody have demonstrated promising long-term benefit.

Nghiem et.al. N Engl J Med, 2016; 374: 2542–52



Role of Imaging

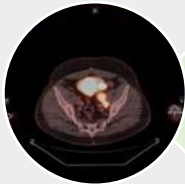
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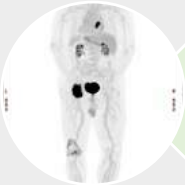
Local staging, surgical planning and radiation planning



Sentinel lymph node biopsy



Systemic staging

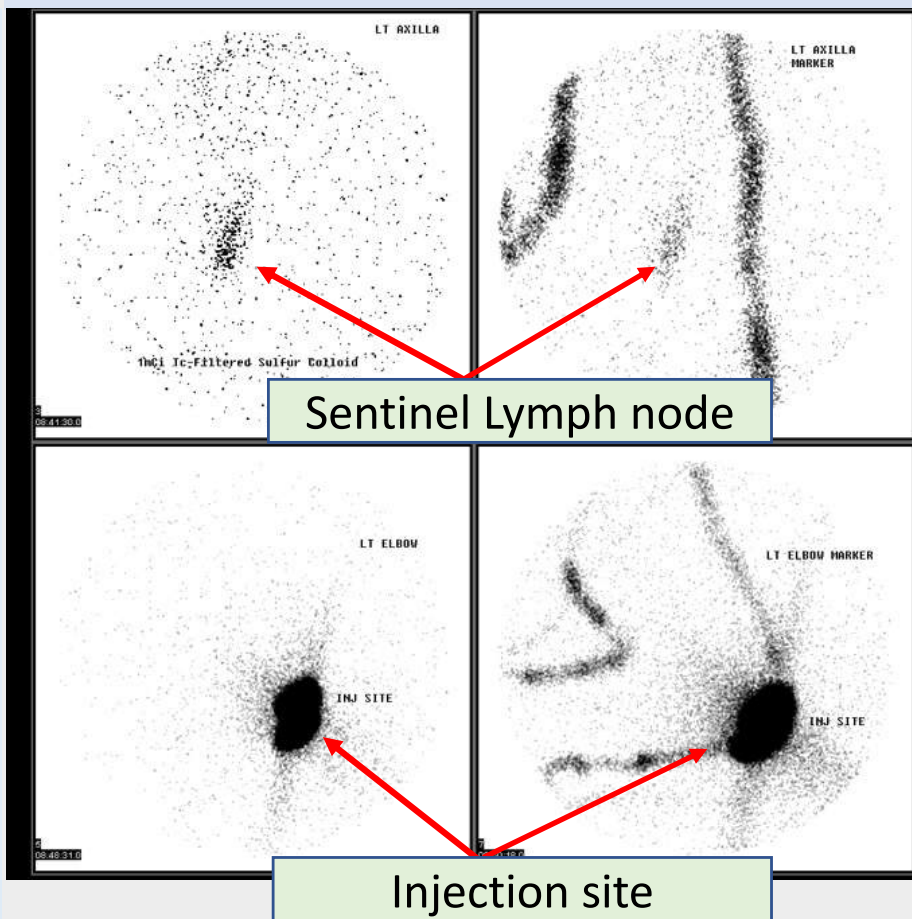


Evaluation of treatment response and follow-up



Sentinel Lymph node biopsy (SNLB)

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Procedure:

Tc99m Sulfur Colloid

1 mCi (0.2 micron Filtered) was injected intra-dermally at four locations around the primary tumor/tumor biopsy site.

Multiple static images of the expected lymph nodal basin to localize SNL.

Hand probe is used to confirm the node.

Occult nodal metastasis is common in MCC and SNLB should be recommended for all patients with primary MCC.

Patients with a positive SLN have a higher risk of in-transit recurrence and may benefit from adjuvant radiation with inclusion of the in-transit field in amenable cases.

J.R. Sims et al. Sur Oncol 2018 27; 11-17

In patients with stage I and II MCC, SNLB is more sensitive than FDG PET/CT

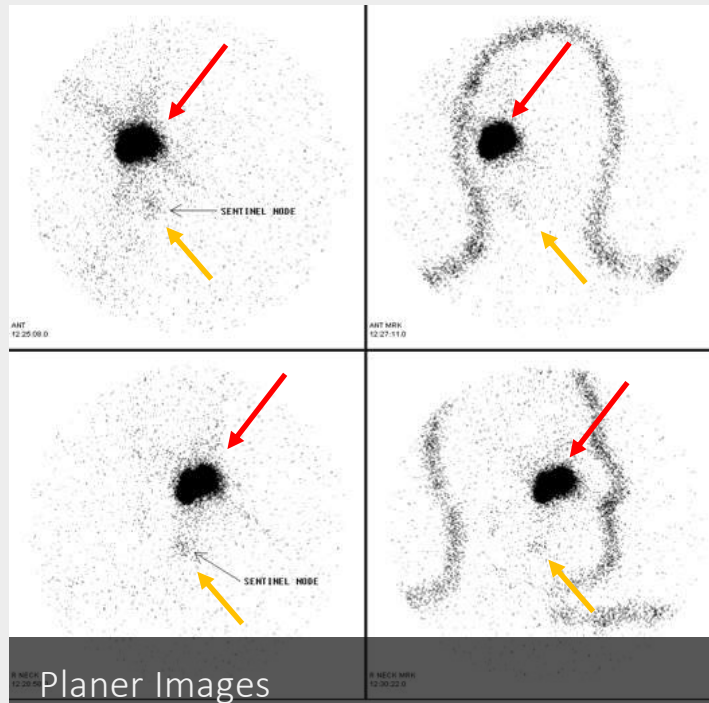
Liu et.al. Australas J Dermatol 2017 58, 99–105

SLNB should be performed before wide local excision or Mohs micrographic surgery, because surgical excision before SNLB may **alter the lymphatic drainage patterns**.



Sentinel Lymph node biopsy (SNLB)

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Planer Images

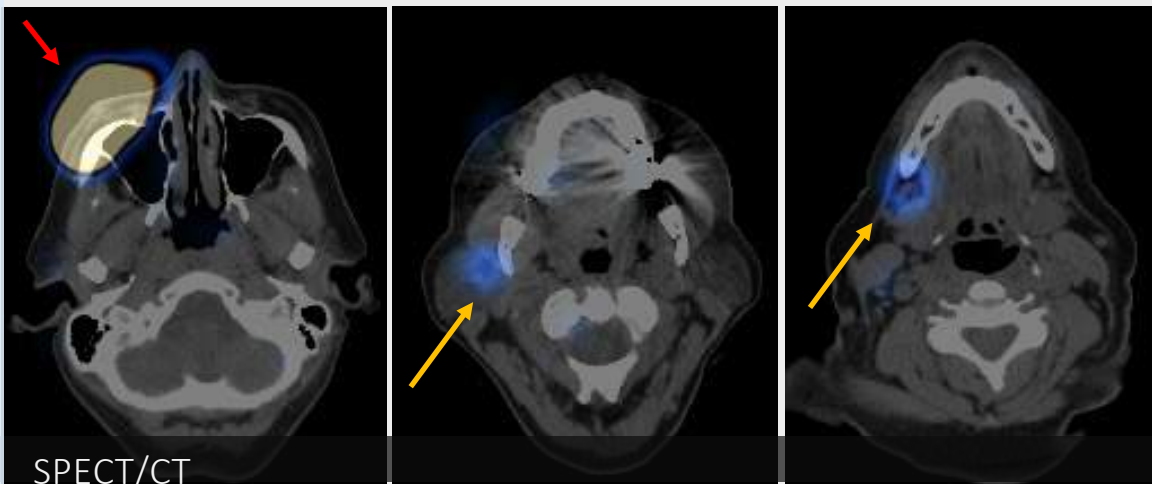
For anatomically complex areas, or when planar image are difficult to interpret, SPECT/CT can be performed to localize SNL. In addition, higher contrast resolution of SPECT allows visualization of foci undetected on planar images.

In our institution, SPECT/CT is routinely performed for MCC of the head and neck due to its anatomical complexity.

Planer images obtained after radiotracer injection around the primary lesion (red arrow) in the right cheek. There is a faint uptake below the injection site (yellow arrow).

However, **it is difficult to localize the focus** on planar images only.

← Injection site ← Sentinel lymph node

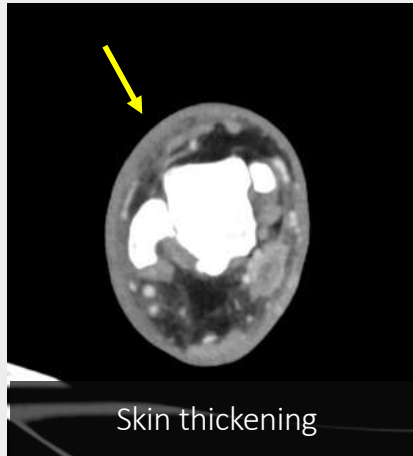


SPECT/CT demonstrates the focus in the right parotid gland. There is **additional node** in the right submental region which was not visualized on planar images.

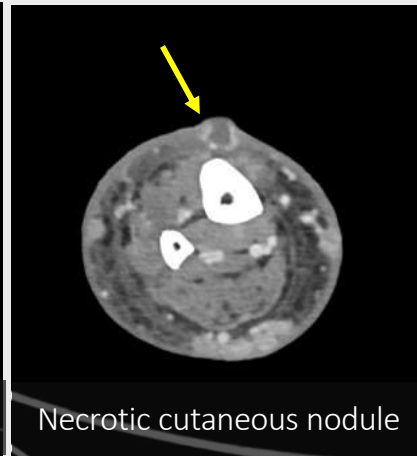


CT imaging patterns of primary/regional MCC lesions

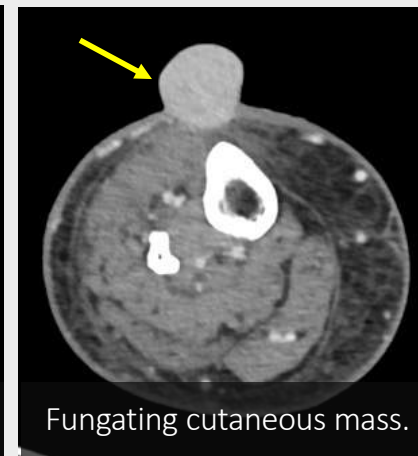
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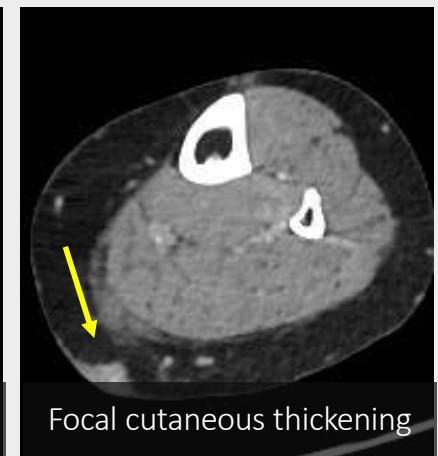
Skin thickening



Necrotic cutaneous nodule

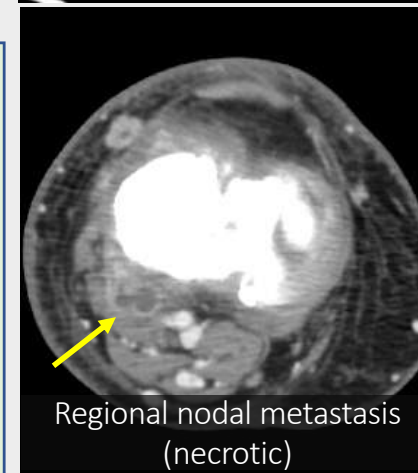


Fungating cutaneous mass.

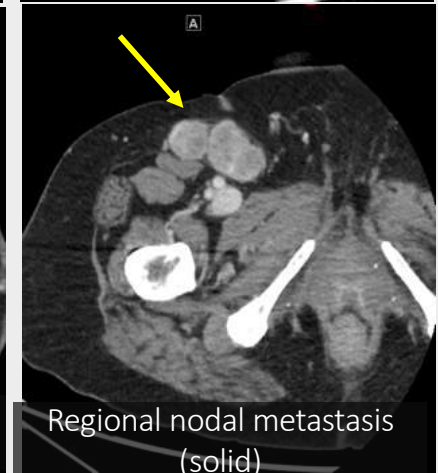


Focal cutaneous thickening

- Primary lesion can manifest as cutaneous or subcutaneous mass/nodule or skin thickening.
- Many patients are referred for imaging after resection of the primary lesion.
- In-transit and satellite cutaneous metastases can occur. MCC have tendency to “skip”



Regional nodal metastasis (necrotic)



Regional nodal metastasis (solid)

Patients with nodal or presumed metastatic MCC with **no identifiable primary skin lesions** can have **better prognosis**.

→ An antitumor immune response has been proposed to underlie both the primary tumor regression and improved patient outcomes in such patients.

Vandeven et.al Clin Cancer Res 2018 15;24(4):963-971



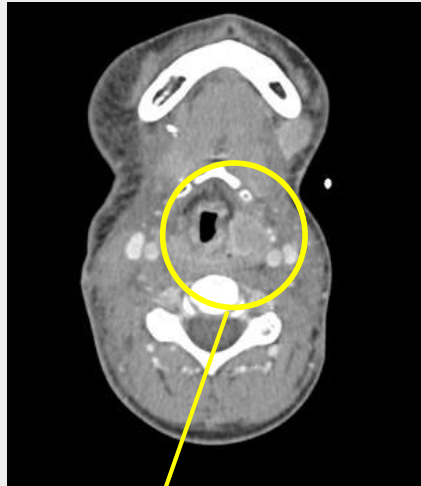
Evaluation of local invasion

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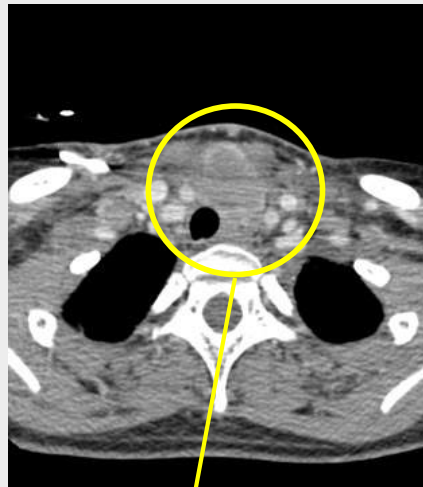


Subcutaneous mass is not invading bone

Necrotic nodal metastasis is abutting the left carotid artery



Necrotic tumor in the left pyriform sinus is abutting the airway



Necrotic tumor is abutting the trachea

In locally advanced disease or advanced metastatic disease, imaging plays an important role determining the localization of the lesion and identifying loco-regional invasion to surrounding organs.

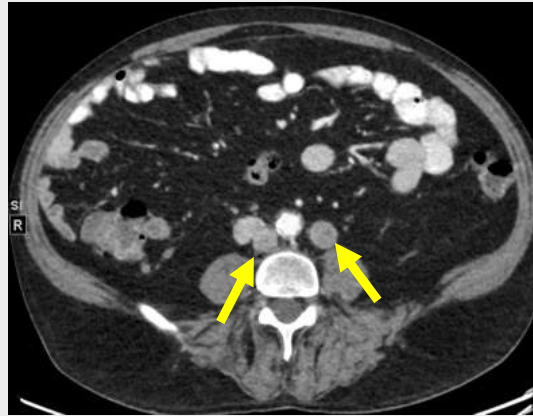
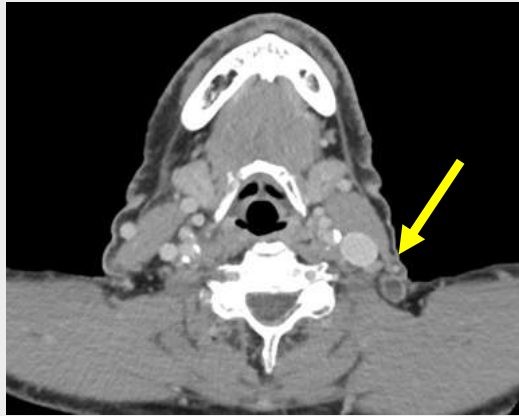
This is especially important in head and neck disease, due to its anatomical complexity.

Accurate evaluation is necessary for **surgical** and/or **radiation therapy planning**.



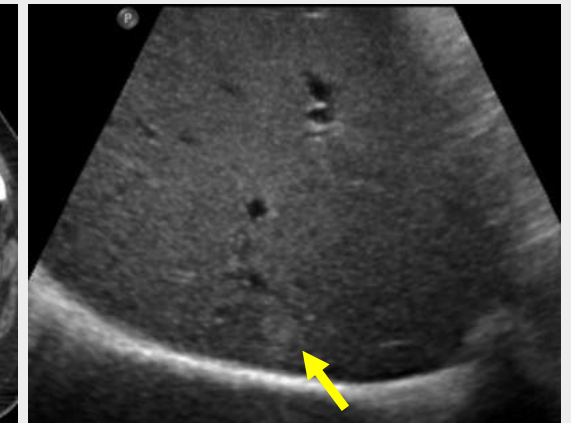
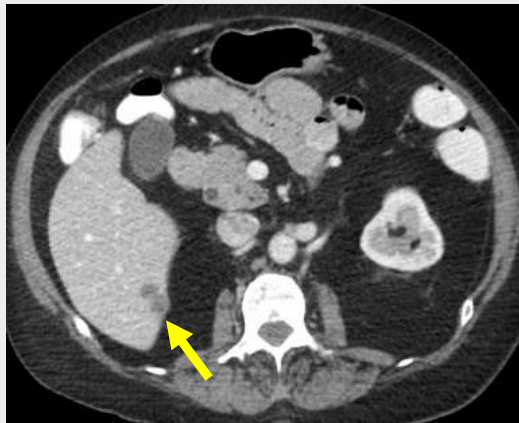
Detecting nodal/distant metastasis

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MCC has a **high propensity for nodal metastasis** with 27- 31% presenting with clinical nodal disease. In addition, another 16-38% have occult nodal metastasis determined by SNLB.

J.R. Sims et al. Surgical Oncology 2018 27; 11-17



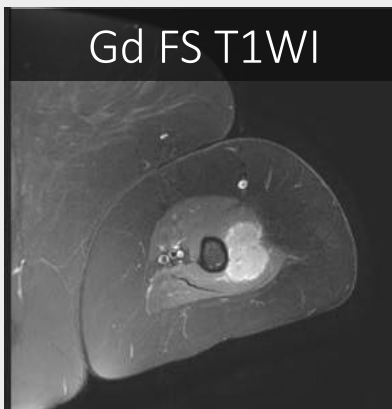
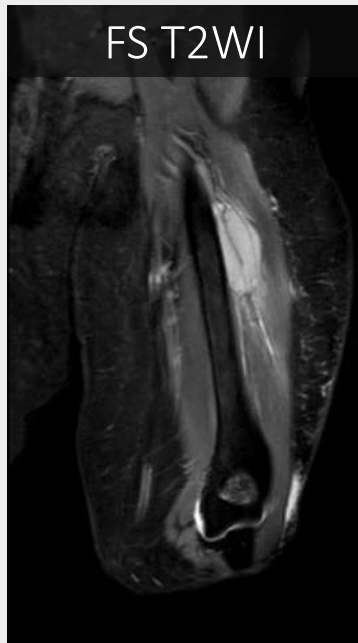
Liver Metastasis

- Non-specific hypoattenuating lesion.
- Typically hypoenhancing compared with surrounding liver parenchyma.
- Hyperechoic on Ultrasound



MRI patterns of primary/regional MCC lesions

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70-year-old female with MCC of the left upper extremity status post resection and radiation. Follow-up MRI of the left upper extremity demonstrates a lobulated T1 isointense, T2 hyperintense, enhancing mass within the lateral arm involving the lateral head of the triceps and brachialis muscles.

MRI characteristic of MCC

- Skin thickening
- Subcutaneous reticular stranding
- Subcutaneous soft tissue mass
- Perifascial muscular and intramuscular metastases.
- Adjacent large lymph node masses with retained, compressed internodal fat

MR signal

- Isointense on T1WI
- High intensity on T2WI, Fat saturated T2WI.
- Diffuse enhancement on Gadolinium administration
- Tumor necrosis.
- Large lesions can demonstrate inhomogeneous signal intensity on both T1WI and T2WI.
- Focal central increased signal on T2WI within large lesions has been described as being associated with histologically proven central necrosis and hemorrhage
(*Skeletal Radiol* 1998; 27:396–399)

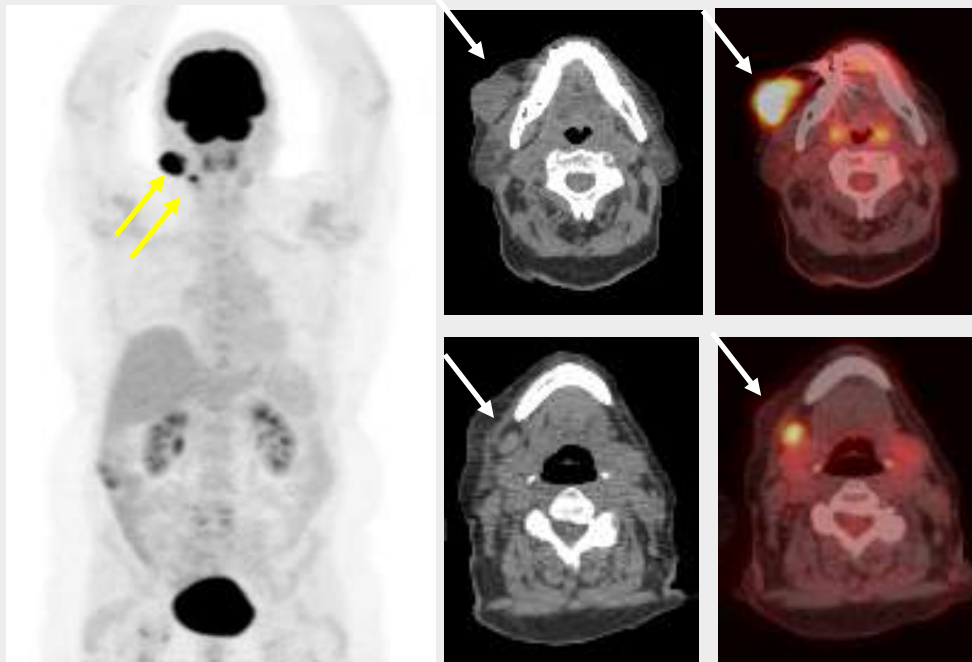
The skin, subcutaneous masses, and reticular stranding histologically were found to be caused by lymphangitis carcinomatosa and soft-tissue lymphatic metastases.



F¹⁸-FDG PET/CT

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F¹⁸-FDG PET/CT is a good modality for staging and increasingly used



66-year-old female with MCC of the right cheek. Staging F¹⁸-FDG PET/CT demonstrates hypermetabolic primary mass in the right cheek and hypermetabolic right submandibular lymph node (arrows), suggesting metastatic nodal disease.

- PET-CT is useful for detection of nodal involvement and distant metastasis.
- Staging F¹⁸-FDG-PET significantly influenced treatment decisions in approximately **one-third of cases** of MCC and should be considered in the routine pre-treatment work-up. Post-treatment PET was not found to be prognostic.

Poulsen M. et. al. J Med Imaging Radiat Oncol. 2018 ;62(3):412-419

- FDG-PET/CT performed as part of the initial management strategy tended to upstage MCC patients with more advanced disease

Hawryluk et. al. J Am Acad Dermatol 2013;68:592-9



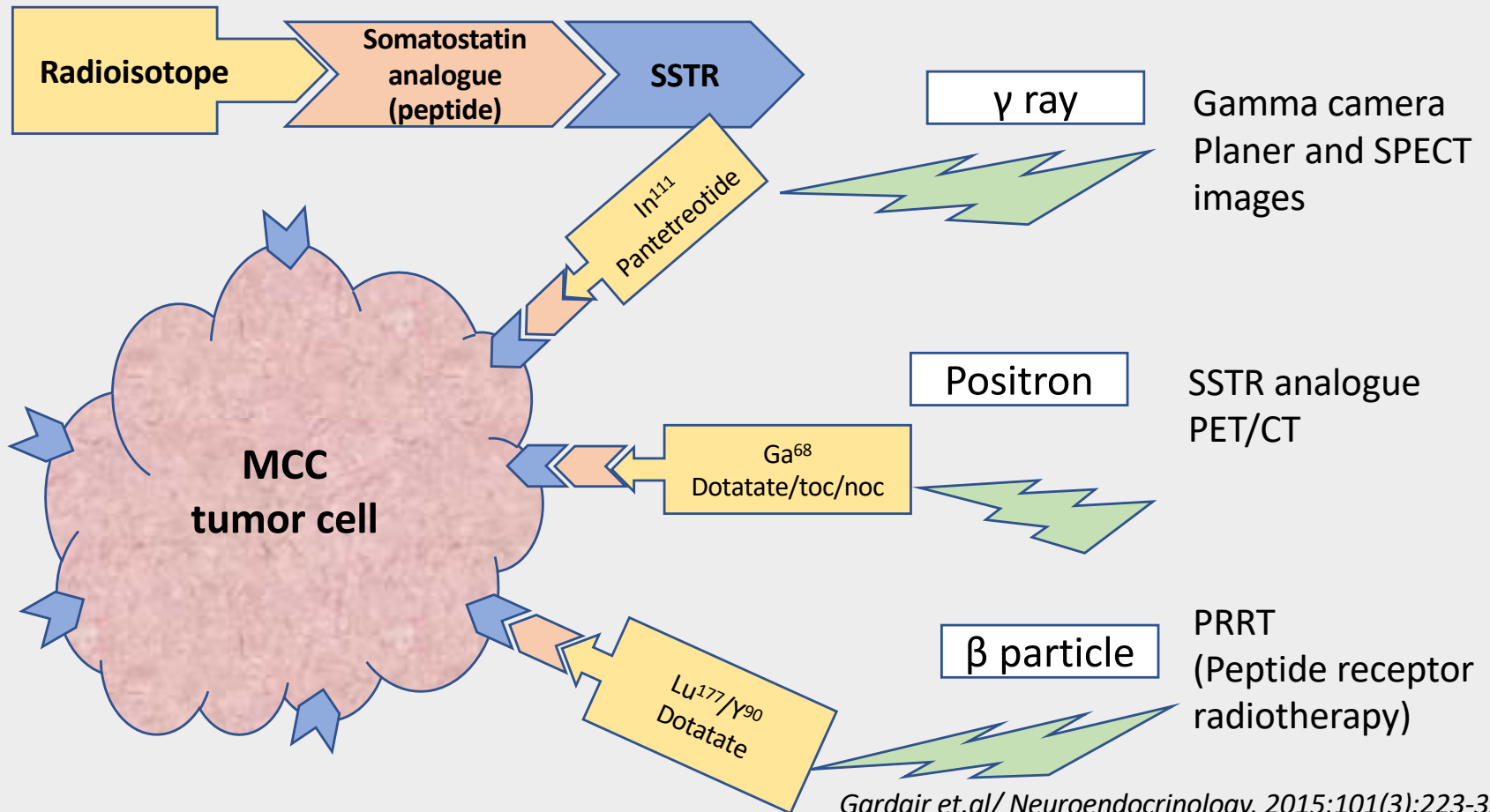
Somatostatin receptor seeking nuclear medicine

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MCC is a unique cutaneous **neuroendocrine tumor (NET)** and exhibits **somatostatin receptor (SSTR)** on the tumor cell surface.

MCC has higher affinity to **SSTR type 2A and 5**, like other NETs

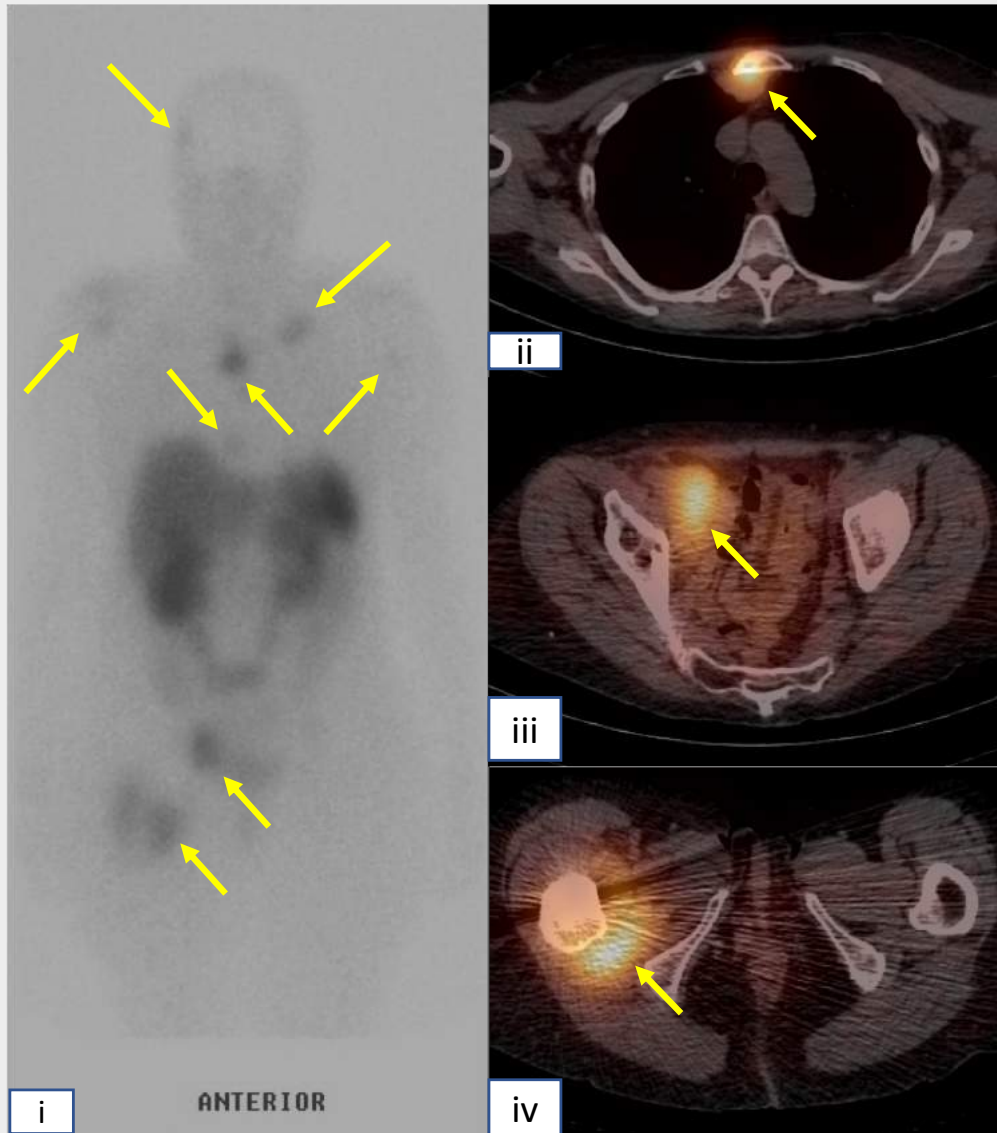
If tumor expresses SSTR, Somatostatin Analogue can be used for treatment in selective patients.





In¹¹¹-Pantetreotide scintigraphy (OctreoScan™)

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Radiolabeled Indium¹¹¹-Pantetreotide

Commercially available Somatostatin receptor binding radiotracer that can be used for scintigraphic imaging.

It has high affinity to **SSTR type 2 and type 5 (remember MCC has high expression of SSTR type 2 and 5)**, to a lesser extent with subtype 3, and not at all with subtype 1 and 4.

(i) Whole body planar image demonstrates several foci of increased radiotracer uptake, some greater than liver. Fused SPECT/CT localized these foci in the Sternum (ii), right external iliac node (iii), soft tissue mass around the right proximal femur (iv), as well as in left subpectoral soft tissue, right calvarium, right scapula, left proximal humerus or cardiophrenic node (Images not shown)



Ga⁶⁸ Somatostatin analogue PET/CT

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Gallium ⁶⁸ (Ga⁶⁸) DOTA-Tyr³ - Octreotate (DOTATATE), G⁶⁸-DOTA-NAI³-octreotide (DOTANOC) or Ga⁶⁸-DOTA-Tyl³- Octreotide (DOTATOC) are PET tracers with high affinity to SSTRs and can be used for neuroendocrine tumors

Much higher special resolution

Shorter scanning time
Patient can be scanned after **45-60 min** after radiotracer administration vs **24-72 hours** for Octeoscan

Quantification
Since it is PET/CT, quantification of several parameters (such as SUV) is possible.

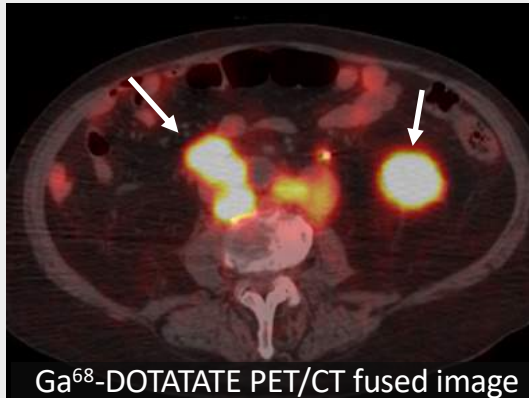


Ga⁶⁸-DOTATATE PET MIP image

70-year-old male with MCC of the left posterior knee s/p wide resection. Ga⁶⁸ Dotatate PET/CT demonstrates intense radiotracer uptake in the left supraclavicular, mediastinal, retroperitoneal and pelvic regions (arrows), suggesting metastatic disease with somatostatin receptor expression.

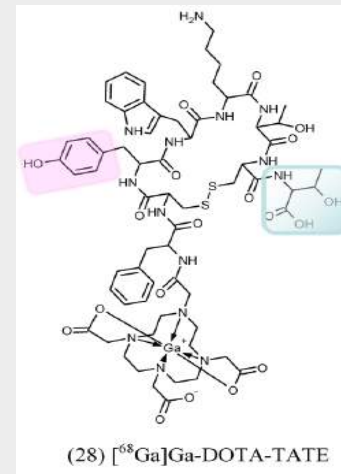


Ga⁶⁸-DOTATATE PET/CT fused image



Ga⁶⁸-DOTATATE PET/CT fused image

Ga **68**: T $\frac{1}{2}$ is **68** min



Velikyan I. *Theranostics* 2014;4(1):47-80.

SSTR analogue PET has higher sensitivity for **bone, soft tissue and brain** disease but lower sensitivity for liver and lung disease compared to CT. Combined PET/CT has a significant impact on patient management.

Buder et al. *BMC Cancer* 2014, 14:268



Radiotracers clinically available (FDA-approved) in the USA (as of 2018)

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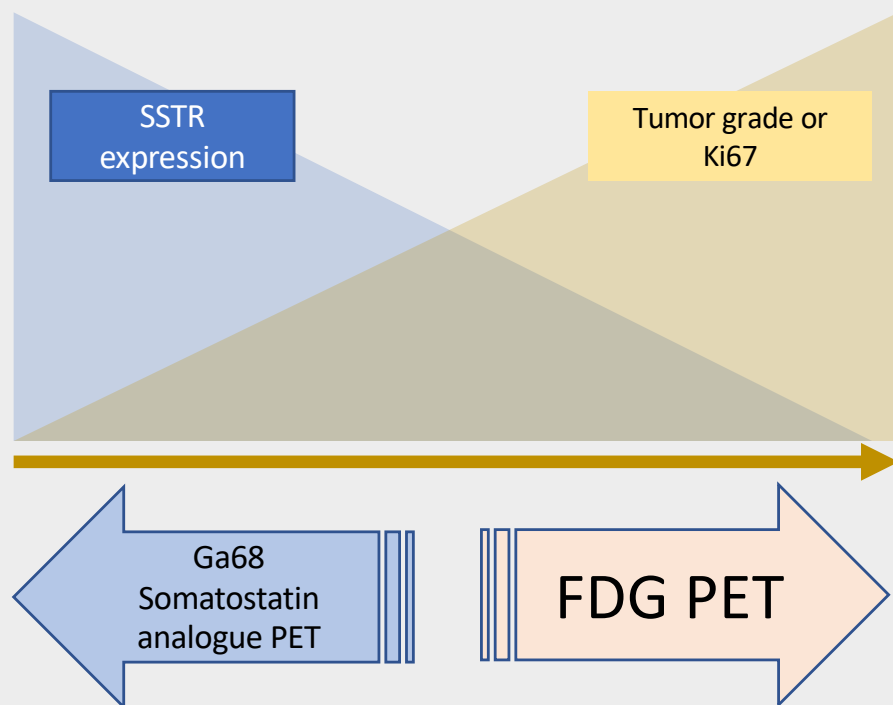
	In¹¹¹ Pentetreotide (OctreoScan™)	Ga⁶⁸ Dotatate (NETSPOT™)	F¹⁸-FDG
Biomechanism	SSTR binding (mainly SSTR type 2 and 5)	SSTR binding (mainly SSTR type 2)	Glucose metabolism
Physical half life	2.8 days	68 minutes	110 minutes
Camera	Gamma camera/SPECT	PET	PET
Principle mode of decay	Electron Capture	Positron decay	Positron decay
Production	Cyclotron	Generator	Cyclotron
Timing of scan after tracer injection	24 hours (4 hour, 48 hour, 72 hour scan can be considered)	45-60 minutes	60 minutes
Spatial resolution	Low	High	High
Quantification of lesion activity	No	Yes (SUV)	Yes (SUV)
Patient preparation (may vary depending on institution)	No dedicated fasting is needed	No dedicated fasting is needed	At least 6 hours of fasting is need. Strict glucose control is needed for diabetic patients



Which PET scan to be used for MCC?

F18-FDG vs Ga⁶⁸ - Somatostatin analogue

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In Gastrointestinal NET, there is an **inverse relationship** between World Health Organization (WHO) or The European Neuroendocrine Tumor Society (ENETS) tumor grade based on Ki-67 and SSTR expression rate.

In non-MCC NETs, Ga⁶⁸-somatostatin analogue PET/CT is recommended for lower grade tumor with low Ki 67 expression (**<20%**). FDG PET is recommended for higher grade, more aggressive tumor.

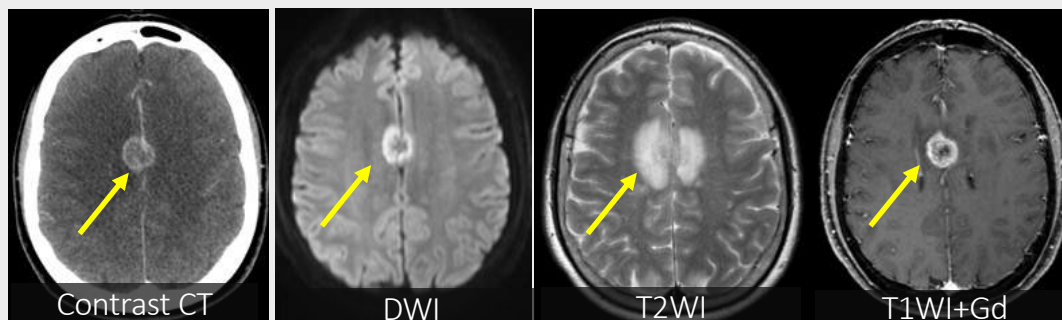
Little is known regarding association between SSTR expression, tumor grade and Ki 67 in MCC.

Preliminary study showed that **Ga68-somatostatin analog PET/CT provides good and equally diagnostic performance as F18-FDG PET**. These results do not suggest that 18F-FDG PET/CT should be replaced by 68Ga-somatostatin receptor imaging. It could, however, be considered in selected cases of SSR positive MCC , i.e., “personalized medicine.”

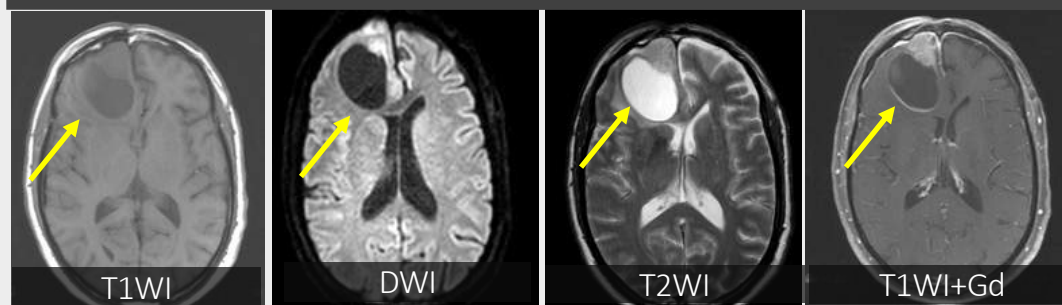


Imaging patterns of MCC Central nervous system metastasis

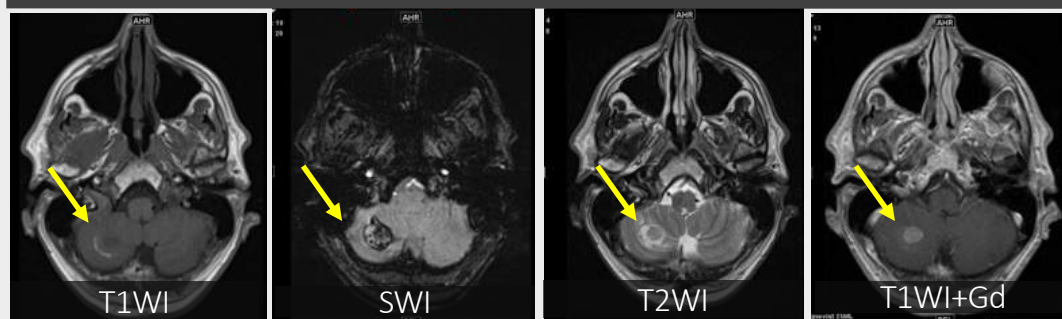
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Solid enhancing nodule/mass with vasogenic edema

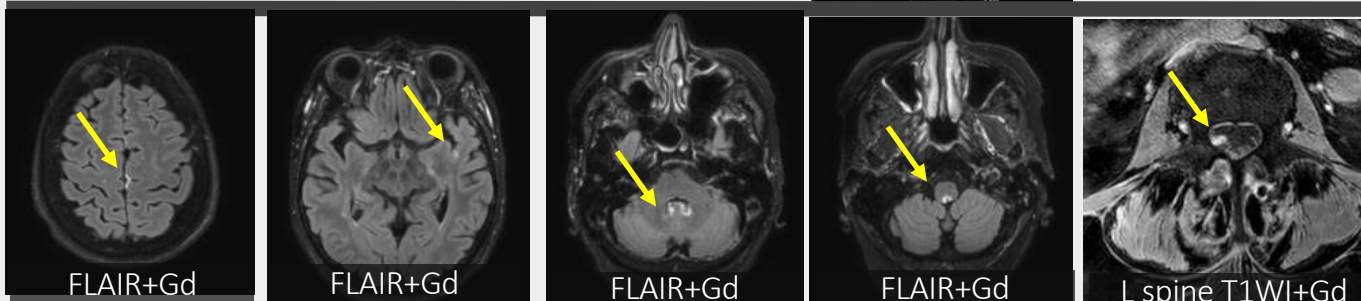


Cystic mass with enhancing solid component



Enhancing mass with hemorrhage

*Note linear hyperintensity along the right cerebellar mass on T1WI and with blooming on susceptibility weighted image (SWI)



Leptomeningeal metastasis



MCC metastasis to the brain

Rare. Previously reported Brain metastasis site include

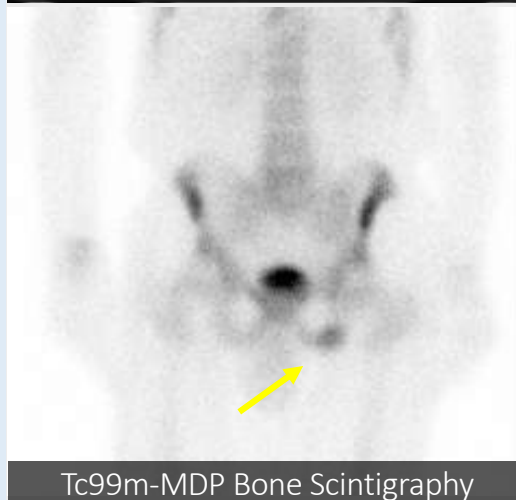
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Lead author		Site of brain metastasis	Primary site	Modality	Findings
Jacob AT	61 M	R thalamus	R parotid gland.	MRI	Cystic mass with enhancing nodule.
Honeybul	65 M	Left temporal lobe	No primary lesion found. Dx'd by R axillary nodal metastasis.	MRI	Enhancing parenchymal nodule.
Feletti	65 M	Pituitary	R groin	MRI	Heterogeneous enhancing mass.
Abul-Kasim	65 M	Leptomeninges	Unknown	MRI	Enhancing meningeal nodule with surrounding vasogenic edema. Leptomeningeal thickening.
Seaman	78 M	L cerebellopontine angle	Right groin	CT, MRI	Heterogeneously enhancing in the intracranial extraaxial mass with vasogenic edema.
Barkdull	55 M	R cerebrum	scalp	CT, MRI	Direct intracranial invasion from bone metastasis to the calvarium.

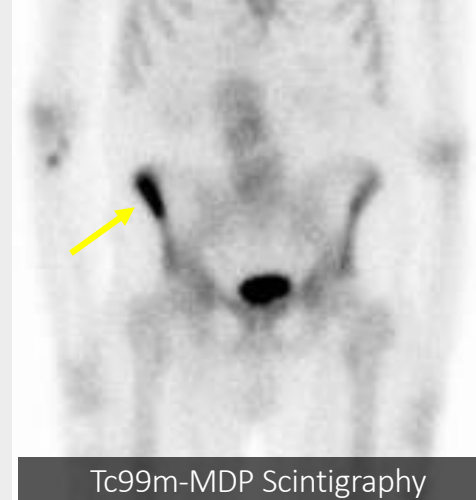


Bone metastasis

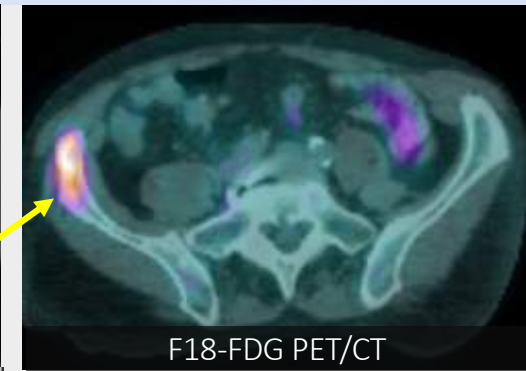
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Case 1: CT demonstrates sclerotic lesion in the left ischium (yellow arrow). Tc99m-MDP bone scintigraphy demonstrates focal radiotracer activity (black arrow)



Case:2
No suspicious bone lesion is identified on CT.
Both Tc99m-MDP bone scintigraphy and F18-FDG PET/CT demonstrate increased radiotracer activity in the right iliac crest (arrow). The lesion was biopsied and confirmed as metastatic MCC.



FDG PET or Bone scintigraphy has **higher sensitivity** for osseous metastasis than CT

Hawryluk et. al. J Am Acad Dermatol 2013;68:592-9

SSTR analogue PET has **higher sensitivity** for bone metastasis than CT

Buder et al. BMC Cancer 2014, 14:268

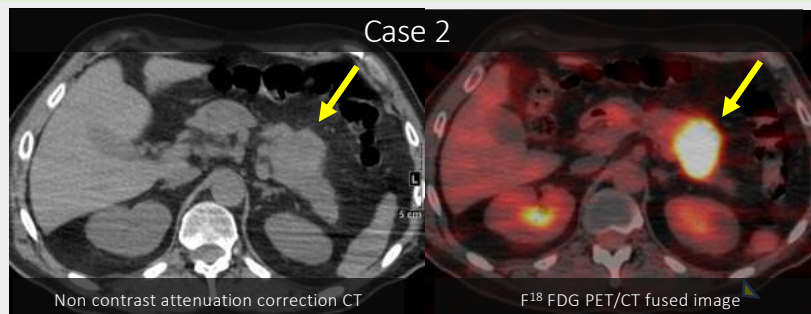
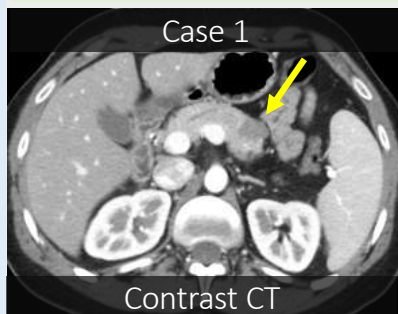
Osseous involvement of MCC, although rare, has been described in facial bones, cranium, tibia and spine.



MCC can metastasize to weird places...

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In advanced malignancy with widespread disease, metastasis can occur in uncommon organs. In our experience at one of the largest MCC centers in the world, it is felt that **MCC metastases to these organs might occur earlier than previously anticipated.**



Pancreas (case 1, 2)

Metastasis to the pancreas is rare in general. However, our preliminary data (unpublished) shows MCC has higher rate of pancreas metastasis than melanoma (5% vs < 1%)

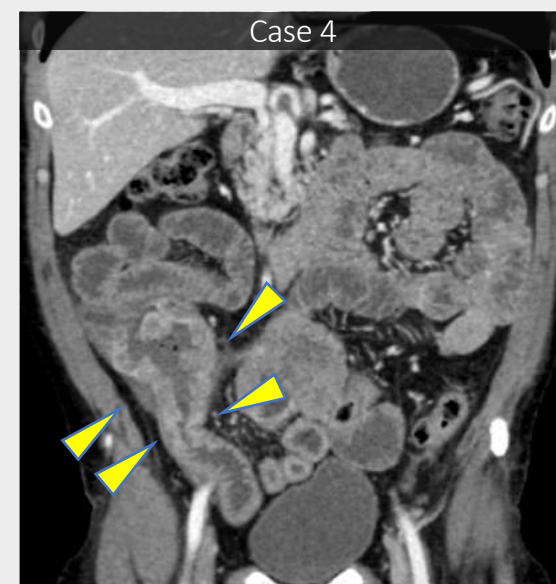


Muscle (case 3)

Posterior planar image and SPECT/CT of In-111 Pentetreotide scintigraphy show faint radiotracer uptake in the left psoas muscle (arrows). Post-Gadolinium fat suppressed MRI shows irregular enhancing mass in the left psoas muscle (arrow head)

Colon (case 4)

Coronal contrast CT shows wall thickening in the distal ileum with aneurysmal dilatation and partial small bowel obstruction.

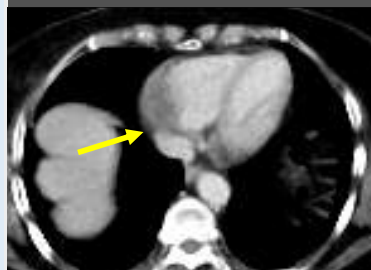




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Case 1



Contrast CT



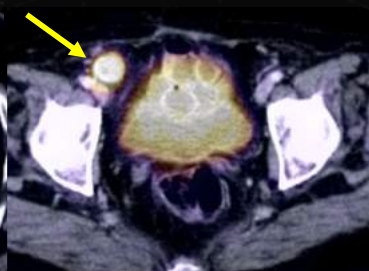
Contrast CT



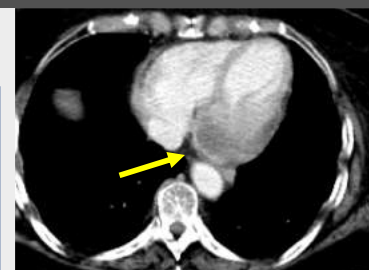
Metastasis to the right atrium was irradiated and diminished. However, several months later the patient had recurrence at the base of the left ventricle.



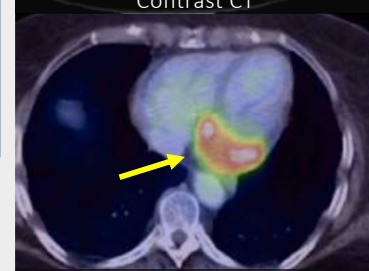
PDG/PET CT



PDG/PET CT



Contrast CT

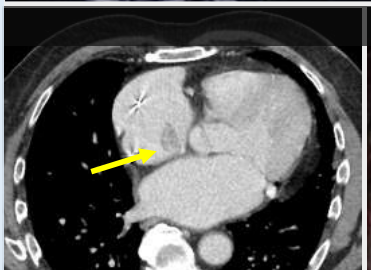


PDG/PET CT

Heart

Cardiac metastasis is rare. Due to its invasiveness, it is difficult to obtain pathologic confirmation. Thus, imaging is important to establish diagnosis of this rare manifestation.

Case 2



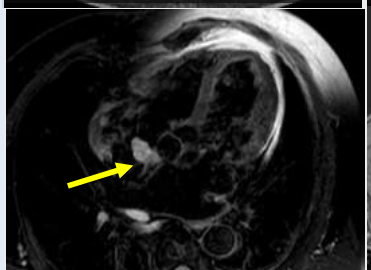
Contrast CT



PDG/PET CT



PDG/PET CT



FS-T2WI



Gd perfusion image



Contrast CT

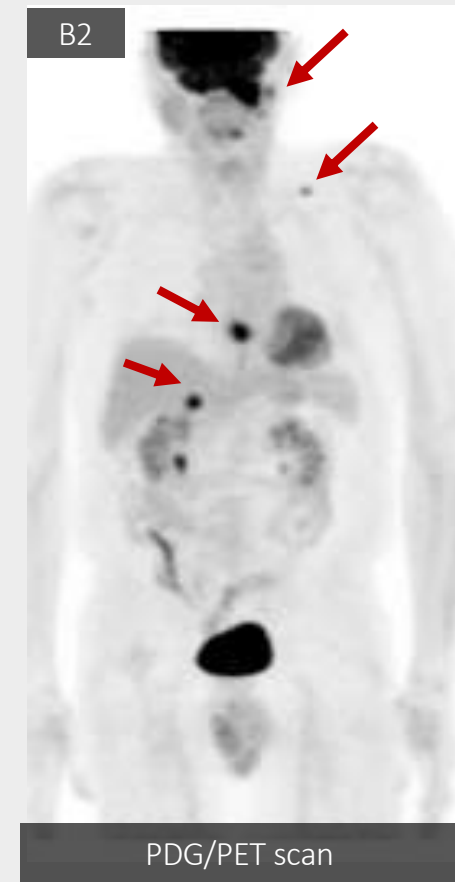
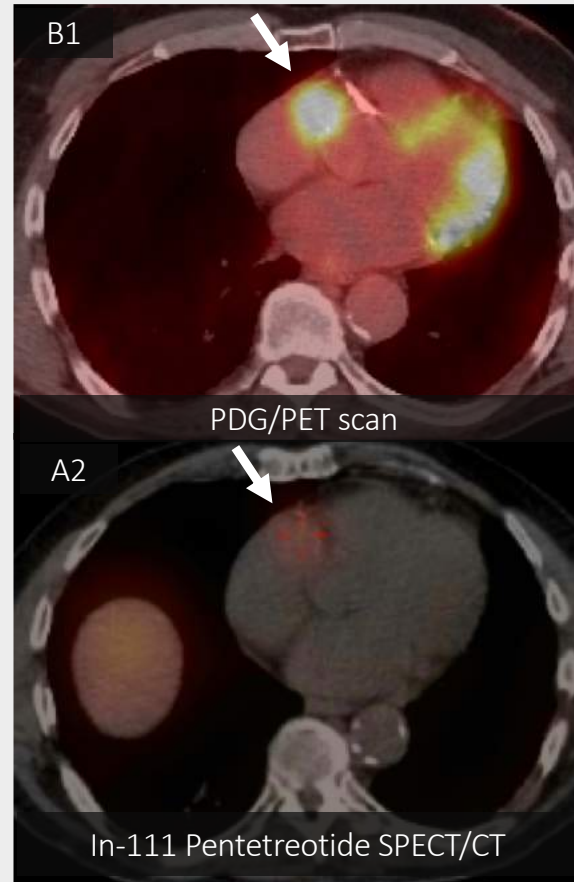
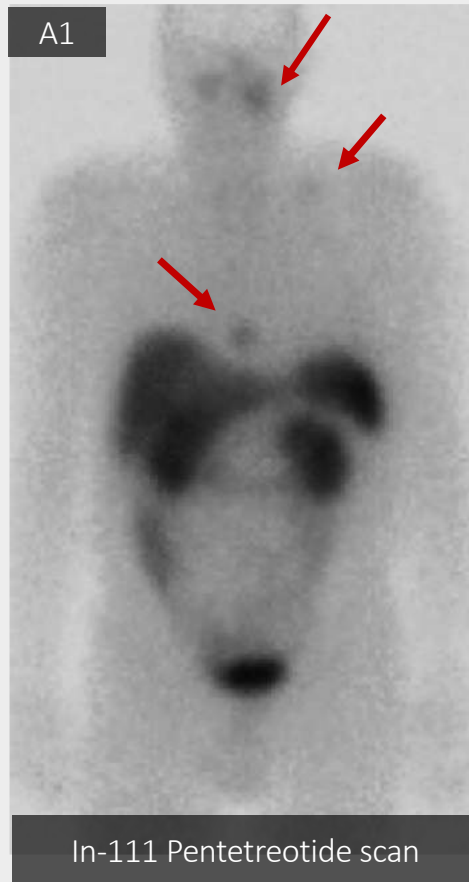




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Cardiac metastasis diagnosed by both In^{111} -Pentetreotide scintigraphy and F^{18} FDG PET/CT



73-year-old man with recurrent MCC. In^{111} -Pentetreotide scintigraphy (A1,2) show increased radiotracer uptake within the bilateral maxillary sinuses, left supraclavicular lymph node, right adrenal gland (not shown) and right atrium (arrows), indicating somatostatin receptor expression within these known sites of MCC recurrence.

F^{18} -FDG PET/CT (B1,2) shows increased FDG uptake in the same areas (arrows).



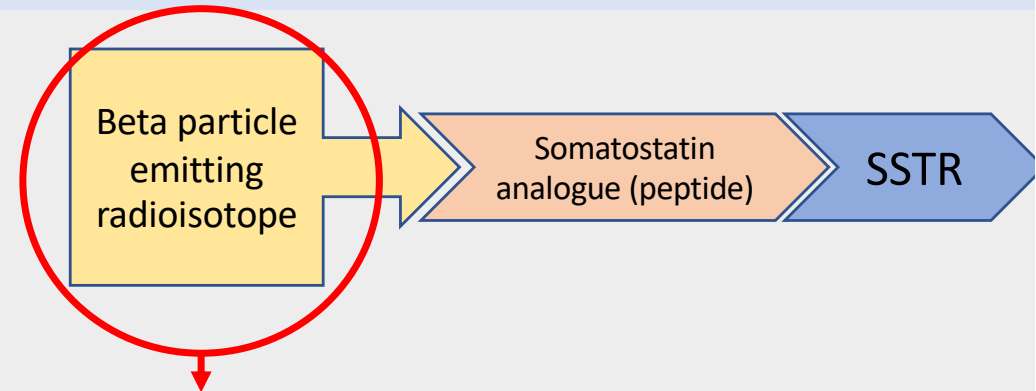
Peptide Receptor Radionuclide therapy (PRRT)

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[⁹⁰Y-DOTA⁰,Tyr³] Octreotide

[¹⁷⁷Lu-DOTA⁰,Tyr³] Octreotide

[¹⁷⁷Lu-DOTA⁰,Tyr³] Octreotate



The SSTR binding peptide is paired with a **beta particle emitting radioisotope** using a chelator (bonding agent). The beta particle irradiate tumor cells.

- Delivers radionuclides directly to tumor cells via SSTR.
- Used for SSTR-positive metastatic well-differentiated GI NETs in Europe since 1990s.
- Retrospective analysis showed promising results for GI NETs.

FDA recently approved Lutetium ¹⁷⁷-Dotatate for GI NETs in Jan 2018.

Currently, there are a few case reports that demonstrated favorable result on MCC.

Basu et.al. J Nucl Med Technol. 2016 Jun;44(2):85-7

Salavati et.al. Ann Nucl Med. 2012 May;26(4):365-9

However, MCC is very radiosensitive tumor and further investigation is warranted to evaluate efficacy of PRRT on MCC as it might have potential benefit.



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MCC is an aggressive cutaneous cancer with tricky clinical manifestation

Merkel Cell Polyoma Virus (MCPyV) is causally linked to its development

Antibody to the MCPyV oncoprotein can be used as a “tumor marker ”
in antibody producers

Immunotherapy is now a first line systemic therapy

MCC has unique neuroendocrine features with somatostatin receptor expression which can be used for molecular imaging such as In^{111} based scintigraphy (SPECT/CT), Ga^{68} based PET/CT, or potentially Peptide Receptor Radionuclide Therapy (PRRT)



References

1. Harms PW. Update on Merkel Cell Carcinoma. Clin Lab Med 2017;37(3):485–501.
2. Harms PW, Harms KL, Moore PS, et al. The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol 2018;
3. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 2008;58(3):375–381.
4. Becker JC. Merkel cell carcinoma. Ann Oncol 2010;21 Suppl 7:vii81–85.
5. Harms KL, Healy MA, Nghiem P, et al. Analysis of Prognostic Factors from 9387 Merkel Cell Carcinoma Cases Forms the Basis for the New 8th Edition AJCC Staging System. Ann Surg Oncol 2016;23(11):3564–3571.
6. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. Lancet 2002;359(9305):497–498.
7. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation 1999;68(11):1717–1721.
8. Voelker R. Why Merkel Cell Cancer Is Garnering More Attention. JAMA 2018;320(1):18–20.
9. Bichakjian CK, Olencki T, Aasi SZ, et al. Merkel Cell Carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2018;16(6):742–774.
10. Iyer JG, Blom A, Doumani R, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med 2016;5(9):2294–2301.
11. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N Engl J Med 2016;374(26):2542–2552.
12. Sims JR, Grotz TE, Pockaj BA, et al. Sentinel lymph node biopsy in Merkel cell carcinoma: The Mayo Clinic experience of 150 patients. Surg Oncol 2018;27(1):11–17.
13. Liu J, Larcos G, Howle J, Veness M. Lack of clinical impact of 18 F-fluorodeoxyglucose positron emission tomography with simultaneous computed tomography for stage I and II Merkel cell carcinoma with concurrent sentinel lymph node biopsy staging: A single institutional experience from Westmead Hospital, Sydney. Australas J Dermatol 2017;58(2):99–105.
14. Vandeven N, Lewis CW, Makarov V, et al. Merkel Cell Carcinoma Patients Presenting Without a Primary Lesion Have Elevated Markers of Immunity, Higher Tumor Mutation Burden, and Improved Survival. Clin Cancer Res 2018;24(4):963–971.
15. Anderson SE, Beer KT, Banic A, et al. MRI of merkel cell carcinoma: histologic correlation and review of the literature. AJR Am J Roentgenol 2005;185(6):1441–1448.
16. Poulsen M, Macfarlane D, Veness M, et al. Prospective analysis of the utility of 18-FDG PET in Merkel cell carcinoma of the skin: A Trans Tasman Radiation Oncology Group Study, TROG 09:03. J Med Imaging Radiat Oncol 2018;62(3):412–419.
17. Hawryluk EB, O'Regan KN, Sheehy N, et al. Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. J Am Acad Dermatol 2013;68(4):592–599.
18. Velikyan I. Prospective of ⁶⁸Ga-radiopharmaceutical development. Theranostics 2013;4(1):47–80.
19. Buder K, Lapa C, Kreissl MC, et al. Somatostatin receptor expression in Merkel cell carcinoma as target for molecular imaging. BMC Cancer 2014;14:268.
20. Taralli S, Sollini M, Milella M, et al. 18F-FDG and 68Ga-somatostatin analogs PET/CT in patients with Merkel cell carcinoma: a comparison study. EJNMMI Res 2018;8(1):64.
21. Jacob AT, Alexandru-Abrams D, Abrams EM, Lee JYK. Stereotactic radiosurgery for merkel cell carcinoma brain metastases. J Clin Neurosci 2015;22(9):1499–1502.
22. Honeybul S. Cerebral metastases from Merkel cell carcinoma: long-term survival. Journal of Surgical Case Reports 2016;2016(10):rjw165.
23. Feletti A, Marton E, Rossi S, Canal F, Longatti P, Billeci D. Pituitary metastasis of Merkel cell carcinoma. Journal of Neuro-Oncology 2010;97(2):295–299.
24. Abul-Kasim K, Söderström K, Hallsten L. Extensive central nervous system involvement in Merkel cell carcinoma: a case report and review of the literature. Journal of Medical Case Reports [Internet] 2011 [cited 2018 Oct 23];5(1). Available from: <http://jmedicalcasereports.biomedcentral.com/articles/10.1186/1752-1947-5-35>
25. Seaman B, Brem S, Fromm A, Staller A, McCardle T, Jain S. Intracranial spread of Merkel cell carcinoma to the cerebellopontine angle. J Cutan Med Surg 2012;16(1):54–60.
26. Barkdull GC, Healy JF, Weisman RA. Intracranial spread of Merkel cell carcinoma through intact skull. Ann Otol Rhinol Laryngol 2004;113(9):683–687.
27. Basu S, Ranade R. Favorable Response of Metastatic Merkel Cell Carcinoma to Targeted 177Lu-DOTATATE Therapy: Will PRRT Evolve to Become an Important Approach in Receptor-Positive Cases? J Nucl Med Technol 2016;44(2):85–87.
28. Salavati A, Prasad V, Schneider C-P, Herbst R, Baum RP. Peptide receptor radionuclide therapy of Merkel cell carcinoma using (177)lutetium-labeled somatostatin analogs in combination with radiosensitizing chemotherapy: a potential novel treatment based on molecular pathology. Ann Nucl Med 2012;26(4):365–369.
29. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. J Clin Oncol 2015;33(16):1855–1863.

**Thank you for your
attention!**