WHAT'S NEW IN MOHS SURGERY FOR LENTIGO MALIGNA AND MERKEL CELL CARCINOMA?

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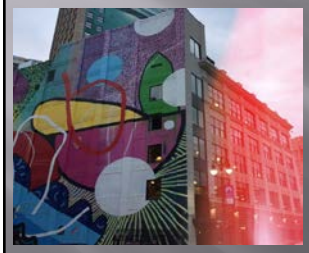
Disclosure

None

Henry Ford Department of Dermatology

- 24 Senior Staff Physicians
- 18 Residents/3 Research Fellows
- Basic Science and Clinical Research Labs
- 120 total Employees

Detroit – The Motor City



Downtown "Techno Music" Festival

Detroit – The Motor City

A total of 110 top 10 hits were recorded at this small house in Detroit

Across the street from Henry Ford Hospital is the Home where "Motown" records recorded in the 1960's

Outline

- Lentigo Maligna
  - Use of Confocal
  - Clinical and pathologic features as predictors for subclinical extension of MIS and invasive melanoma
  - Staged Excisions
  - MITF vs MART1
- Merkel Cell Carcinoma
  - PD-1 Blockade
  - CTLA4 blockade

In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons

- Confocal Microscopy: modern imaging device offering quasi-histologic view of a given skin tumor
- Use in tumor margins assessment
  - reflectance mode (in vivo on skin patient)
  - fluorescence mode (on freshly excised specimen)
- In vivo reflectance confocal microscopy (RCM) has been used as an add-on tool for bedside lentigo maligna and basal cell mapping and monitoring

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

Basal Cell Carcinoma

- Cancer margins marked out utilizing dermoscopy, then rechecked using RCM
- RCM showed BCC outside of pre-surgical mark in 30% of lesions
  - Deep tumor margin could not be assessed due to limited depth laser penetration
    - Not as useful for sclerosing or infiltrative BCC
- Rapid detection of residual tumor in a surgical wound
  - Useful
  - Need a smaller microscope head with an automated approach for imaging the entire wound in a rapid and controlled manner

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

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Lentigo Maligna

- Subtype of melanoma in situ, defined by a predominant lentiginous growth pattern of melanocytes as solitary units at the DEJ in chronically sun-damaged skin
- Ill-defined borders with the potential for significant subclinical extension
- Delineating LM preoperatively can be challenging due to several factors
  - Background sun-damaged skin
  - Intrinsic early changes of tumor composed of single atypical melanocytic proliferation

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

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Lentigo Maligna

- Margins were clinically, with dermoscopic exam, marked and RCM was then obtained in 4 radial directions (no more than 4 d/t time constraints)
- 29 patients
  - 4 false positives of RCM diagnosing LM, but not consistent histologically
  - 5 false negatives (LM histologically, without RCM evidence)
- Conclude this is reliable and easy method for presurgical margin assessment of LM

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

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Lentigo Maligna

- RCM used to monitor response of LM to nonsurgical treatment (imiquimod)
- Identified 70% of all responders with no false-negative results
- When compared with histopathology, no significant difference in evaluating the response to imiquimod

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

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Ex Vivo Fluorescent Confocal Microscopy (FCM)

- FCM used on freshly excised tumors
- Different fluorophores can be used at different wavelengths
  - Acridine orange is most common given excellent contrast
- Basal cell carcinoma
  - FCM correlates very well with frozens with more info
    - Analyzes fat tissue and other structures that can be altered in frozen Mohs processing
  - Sensitivity 88%, Specificity 99%
  - Reduces time invested compared with frozen sections by 2/3
- Limitations
  - Difficult to recognize cords and strands of infiltrative BCC and distinguish from stroma
  - Sebaceous glands confused as basaloid islands

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

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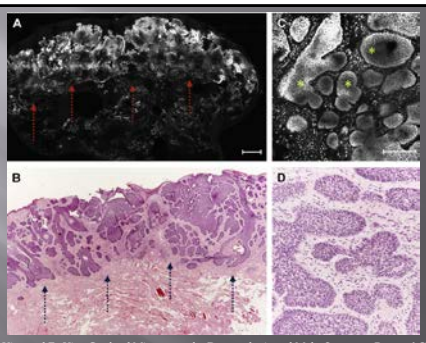


Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

Table 1
Comparison of FCM studies

Study	Mosaics Evaluated, N	Confocal Technique	Se	Sp	PPV	NPV	Scanning Time (min) for 12 × 12 mm	Staining Time (min)	Staining Technique
Patel et al,[7] 2007	—	FCM	—	—	—	—	9	0.5–5	Acetic acid
Rajadhyaksha et al,[7] 2001	—	RCM	—	—	—	—	3.5	0.5	Acetic acid
Gareau et al,[11] 2009	30	RCM	—	—	—	—	9	0.5–5	Acetic acid
Schüle et al,[12] 2009	284	FCM	0–89	29–89	—	—	—	2	Citric acid
Ziefle et al,[13] 2010	312	FCM	82	61	66.7	78	3	3.5	Acetic acid + toluidine blue
Al-Arashi et al,[16] 2007	37	FCM, RCM	—	—	—	—	—	2	Toluidine blue, methylene blue
Gareau et al,[17] 2008	50	FCM	—	—	—	—	9	0.5	Acridine orange
Gareau et al,[18] 2009 Karen et al,[19] 2009	48	FCM	96.6	89.2	93	94.7	9	0.3	Acridine orange
Larson et al,[25] 2013	17	FCM strip	94	94	—	—	<2	0.3	Acricine orange
Bennassar et al,[29] 2014	150	FCM	88	99	98	97	3	0.3	Acridine orange
Longo et al,[30] 2014	35	FCM	94.9	96.8	—	—	3	0.3	Acridine orange

Abbreviations: NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

Longo C, et al. In Vivo and Ex Vivo Confocal Microscopy for Dermatologic and Mohs Surgeons. *Dermatol Clin.* 2016 Oct;34(4):497-504

Clinical factors associated with subclinical spread of melanoma

- In situ melanoma
- Invasive melanoma

Clinical factors associated with subclinical spread of in situ melanoma

Shin TM, et al. *J Am Acad Dermatol.* 2017 Jan 7. [Epub ahead of print]

Clinical factors associated with subclinical spread of in situ melanoma

- Background: Subclinical spread of MIS occurs at wide frequency, ranging from 12-71%
- Subclinical spread = microscopic extension of tumors beyond the visible margin

Shin TM, et al. *J Am Acad Dermatol.* 2017 Jan 7. [Epub ahead of print]

Methods

- Retrospective, cross-sectional study of 674 melanomas
- Treated with Mohs and MART-1 immunostaining
- Visible melanoma and margins of 2-3mm of normal skin removed with debulking excision and sent for formalin-fixed paraffin-embedded, bread-loaf sectioning for tissue archiving and staging confirmation
- Mohs layer then taken w/ 2-3mm margin for frozen H&E and mart-1 immunostain
  - Positive margins → additional stages
- All tumors had ≥5mm margins

Results

Table II. Frequency of subclinical spread relative to clinical characteristics of study cohort

Variable	Frequency of subclinical spread
All cases	215/674 (31.9%)
Location	
Head, neck, acral, genitalia, pretibial leg	197/586 (33.6%)*
Trunk and proximal extremities	18/88 (8.4%)
Recurrence status	
Primary in situ melanoma	171/591 (29%)
Recurrent in situ melanoma	44/83 (53%)**
Preoperative size	
≤1 cm	64/259 (24.7%)
>1 cm	151/415 (36.4%)**
Age	
<60 years	51/195 (26%)
≥60 years	164/479 (34%)*
Sex	
Male	129/403 (32.0%)
Female	86/271 (31.7%)
Immunosuppression status	
Immunocompetent	211/662 (32%)
Immunosuppressed	4/12 (33%)

*$P < .05$.
**$P < .01$ compared to reference group.

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 7. [Epub ahead of print]

Limitations

- Academic center with referral sfor large, ill-defined melanomas
- Initial smaller margins taken in cosmetically sensitive areas like the eyelids
- Histologic subtype omitted due to lack of categorization
- Not all risk factors included
  - Fitzpatrick type, ethnicity, photoaging degree, % of clinically visible tumor remaining after biopsy, tumor color

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 7. [Epub ahead of print]

Conclusion

- Subclinical spread of MIS associated with:
  - Location on head, neck, acral sites and pretibial leg
  - Recurrence after previous treatment
  - Preoperative size > 1cm
  - Increasing age (>60 years, increasing by 2% each year)
- Risk of extensions increases with each additional risk factor
- Important to consider these risk factors when triaging surgical treatment of MIS for standard excision vs a more exhaustive microscopic margin assessment

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 7. [Epub ahead of print]

Clinical and pathologic factors associated with subclinical spread of invasive melanoma

- More rigorous margins assessment techniques can be used to identify and remove subclinical tumor prior to reconstruction
- Indications to use these techniques are not defined for invasive melanoma
- NCCN restricts consideration of exhaustive margin assessment to large lentigo maligna cancers

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 28. [Epub ahead of print]

Methods

- MMS with frozen-section bread-loaf processing of the debulking excision with complete margins assessment of the Mohs layer with H&E and MART-1 immunostain
- T1a tumors: minimum of 5-6mm margin was excised
- T1b and above: minimum of 1cm excised
- If diagnostic biopsy met criteria for SLNB, patients underwent procedure prior to MMS
  - If T1a upstaged to SLNB eligibility during frozen section evaluation of residual tumor, patients offered SLNB prior to reconstruction
- After MMS, debulking excision sent for paraffin-embedded sectioning to confirm staging and archive primary tumor

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 28. [Epub ahead of print]

Methods

- Retrospective, cross-sectional study
- 216 melanomas
- Subclinical spread: requiring ≥2 stages of MMS to clear margins

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 28. [Epub ahead of print]

Results

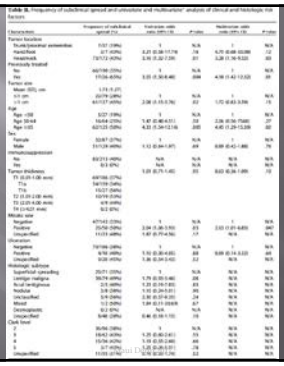
Subclinical spread in 83/216 melanomas

Subclinical Spread associated with:

Clinical Predictors
- Head and neck
- Recurrence after previous treatment
- Size > 1cm
- Age ≥ 65 years

Histologic Predictor
- Presence of mitoses

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 28. [Epub ahead of print]



Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 28. [Epub ahead of print]

Conclusion

- Comparable indications for MMS and other techniques with rigorous microscopic margin assessment prior to reconstruction might apply to both invasive and in situ melanoma.

Shin TM, et al. *J Am Acad Dermatol*. 2017 Jan 28. [Epub ahead of print]

Efficacy of Staged Excision with Permanent Section Margin Control for Cutaneous Head and Neck Melanoma

- Observational cohort study Oct 1997 through Dec 2006
- 806 patients with melanoma of the head and neck
- Assessed local recurrence rates and margin to clearance end points

Moyer JS, et al. *JAMA Dermatol*. 2017 Mar 1;153(3):282-288.

Methods

- Patients underwent staged excision with initial excision margins as below:
  - MIS: 0.5cm margins
  - Invasive melanoma: 1.0cm
- Sent for formalin-fixed permanent section comprehensive margin control
  - Immunohistochemistry not used
  - Subsequent areas of positivity determined by dermatopathologist were subsequently excised with additional 0.5cm margin
    - Margins in cosmetically sensitive areas had tissue sparing margins

Moyer JS, et al. *JAMA Dermatol*. 2017 Mar 1;153(3):282-288.

Results

- 806 patients
- Median potential follow up: 9.3 years; observed median time of last follow-up was 8.4 years
- 834 staged excisions
  - 17 local recurrences
  - 1.4% at 5 years, 1.8% at 7.5 years, and 2.2% at 10 years

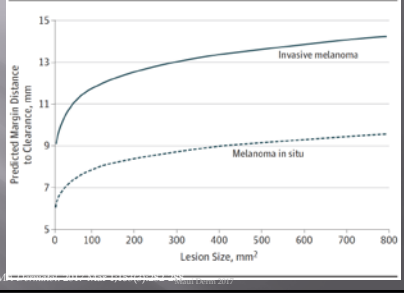
Moyer JS, et al. *JAMA Dermatol*. 2017 Mar 1;153(3):282-288 Maui Derm 2017

Results

- Lesion size, cutaneous tumor site, and immunosuppression affected local recurrence rate
  - For each 50mm² increase in size of the clinical lesions, there was a 9% increase in rate of local recurrence
  - Periocular had 12.5x increase risk as c/w scalp, forehead, cheek, or neck
  - No immunosuppressed patients had recurrence
- Greater margins needed for invasive vs in situ melanoma
  - Mean margin
  - MIS = 9.3mm
  - Invasive Melanoma = 13.7mm

Moyer JS, et al. *JAMA Dermatol*. 2017 Mar 1;153(3):282-288 Maui Derm 2017

Figure 2. Predicted Margins Required for Clearance of Melanoma In Situ and Invasive Melanoma Based on Clinical Lesion Size



Moyer JS, et al. *JAMA Dermatol*. 2017 Mar 1;153(3):282-288 Maui Derm 2017

Conclusions

- Staged excision with comprehensive permanent section margin control of melanoma arising in chronically sun-damaged skin on the head and neck has favorable recurrence rates when melanoma margins are difficult to assess, and recurrence rates are higher with traditional techniques
- Longer follow up is necessary to monitor these patients as 36% of recurrences developed after 5 years
- Factors a/w greater margin for clearance:
  - Increased lesion size
  - In situ vs invasive disease

Moyer JS, et al. *JAMA Dermatol*. 2017 Mar 1;153(3):282-288 Maui Derm 2017

Comparison of MITF and Melan-A Immunohistochemistry During Mohs Surgery for Lentigo Maligna-Type Melanoma In Situ and Lentigo Maligna Melanoma.

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75 Maui Derm 2017

Immunohistochemistry During Mohs Surgery for Lentigo Maligna-Type Melanoma In Situ and Lentigo Maligna Melanoma.

- Melan A: cytoplasmic melanocytic immunostain useful on frozen section, may lack specificity
  - Binds melan-A antigen, 22-kDa cytoplasmic melanosome-associated glycoprotein
  - Decreased sensitivity in chronically sun-damaged skin (CSDS)
  - May lead to false positives
    - Ex: pigmented keratinocytes and melanocytic dendritic processes
- Microophthalmia transcription factor (MITF): more specific nuclear melanocytic immunostain

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75 Maui Derm 2017

Study Design

- 16 patients with LM or LMM
- Initial debulking of clinical tumor on Wood's lamp exam, sent for permanent sections to assess further tumor invasion
- Periphery treated with MMS
  - Margin size and # of stages recorded

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75. Hawaii Derm 2017

Study Design

- Clinically residual tumor, a central section sent for frozen tissue processing
- CSDS also taken from ipsilateral side that was clear of lentigo, nevus or keratosis and clearly distinct from LM and/or LMM
- Neg Mohs margin obtained for frozen section and stained with H&E, MITF, and melan-A
- Examined by a board-certified dermatopathologist/fellowship-trained Mohs surgeon and at least 1 fellowship-trained Mohs surgeon
  - Melanocyte densities and nonspecific dermal staining noted as mild, mod, significant

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75. Hawaii Derm 2017

Results

- In CSDS: melan-A mean melanocyte counts (MMC) were significantly higher than MITF MMC (13.7% vs 9.8%, p<.001).
- In negative margin skin: melan-A MMC was significantly higher that MITF MMC (14.1 vs 8.8, p<.001)
  - The MMC for each stain approximated the retrospective CSDS control
- Tumor Samples: no difference in MMC with melan-A and MITF

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75. Hawaii Derm 2017

Results

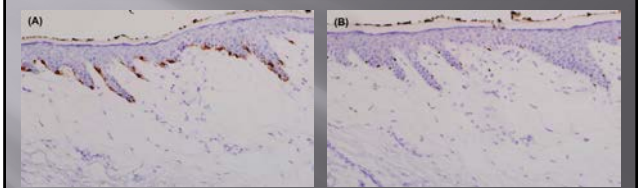
TABLE 3. Summary of Results

	Control CSDS		Negative Margin		Tumor	
Stain	MITF	Melan-A	MITF	Melan-A	MITF	Melan-A
Patients	16	16	16	16	12	12
Mean	9.8*	13.7*	8.8*	14.1*	63.5	62.4
SD	3.5	5.9	4.2	5.0	17.7	14.9
MAX	15.2	24.3	17.7	21.7	97.5	86.2
MIN	3.5	5.2	2.7	6.7	41.0	41.8

*Statistical significance (p < .001).
MAX, maximum; MIN, minimum.

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75. Hawaii Derm 2017

Staining of MMS negative margin



Melan-A –stained negative margin tissue with dendritic processes clear outlined

MITF stain is localized to the nucleus and fewer cells appear to be highlighted

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75. Hawaii Derm 2017

Discussion

- Authors present a 45-minute MITF staining protocol for frozen sections
  - Consistently and reliably stain melanocytes in CSDS, negative margins, and tumors (LM and LMM)
- There is significant non-melanocyte epidermal staining by melan-A in negative margins and CSDS c/w H&E and MITF
- Assessment of melanocyte morphology, density, and pattern in frozens remained largely dependent on H&E slides with immunostains as adjunct
- MITF: efficient, effective alternative stain to melan-A
  - Enhances nuclear size and pleomorphism and is convenient quantification of melanocytes
  - Cost, stain time, tissue processing are similar to melan-A

Christensen KN, et al. *Dermatol Surg*. 2016 Feb;42(2):167-75. Hawaii Derm 2017

Updates in Merkel Cell Carcinoma

Merkel Cell Carcinoma

- Merkel Cell Carcinoma (MCC) Risk Factors
  - Ultraviolet light
  - Merkel cell polyomavirus (MCPyV)
- Advanced Merkel Cell Carcinoma
  - Transient response to chemotherapy
  - Median progression-free survival ~ 3 months
  - Progressive disease in 90% within 10 months

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.

Background

- Programmed death 1 (PD1) immune inhibitory pathway
- Merkel Cell Carcinoma often express PD-L1
- Merkel Cell polyoma virus (MCPyV)-specific T cells express PD-1
- Pembrolizumab: Humanized monoclonal IgG4 Ab that blocks PD-1

It "Blocks the blocker" so tumor death can occur

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.

Study Design

- Multicenter, phase 2, non-controlled study
- Adults with advanced Merkel-cell carcinoma
  - Distant mets or recurrent locoregional
- Not amenable to definitive surgery or radiation
- Have not received prior systemic therapy
- Normal organ and bone marrow function
- Eastern Cooperative Oncology Group performance status 0 or 1
  - Relative functional
- Additional exclusion: immunosuppressed, autoimmune disease, second cancer, active CNS mets

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.

Study Design

- Pembrolizumab at dose of 2mg/kg IV q3 weeks
  - Max of 2 years or until complete response or dose-limiting toxic effects or disease progression
- All underwent CT of abdomen/chest + CT of other areas in which target lesions occurred
  - Screening, 12 weeks after therapy then q9 weeks up to 1 year
  - After 1 year, q12weeks
- Pre- and post-treatment tumor specimen for PD-L1 immunohistochemistry
- Blood analysis at time of CT scan
  - Serum antibodies or circulating T cells specific for MCPyV oncoproteins

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.

Study Design

- Primary end point: objective response rate
  - As defined by Response Evaluation Criteria in Solid Tumors, version 1.1
  - Complete response: Disappearance of all target lesions
    - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
  - Partial response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.
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Results

- 25 pts w at least one tumor evaluation
  - overall response rate is 56% (14/25) (95% CI 35-76)
    - 4 pts complete response
    - 10 pts partial response
    - 1 w stable disease
    - 9 w progression
    - 1 unconfirmed partial response
    - Most response at wk 12

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.
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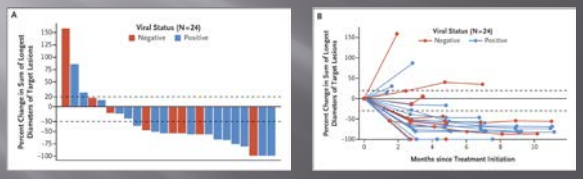
Results



Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.
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Results

- Objective response vs MCPyV status
  - 10/16 (62%) + MCPyV
  - 4/9 (44%) – MCPyV
- Median follow up 33 weeks (7-53 weeks)
  - 2/14 relapse later with CNS mets
  - Response duration ranged from 2.2 months to 9.7 months

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.
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Results

- Rate of estimated progression-free survival at 6 months was 67% (95% CI 49-86%)
- Median progression-free survival = 9 mos
- PD-L1 more frequent in MCPyV + tumors (71% vs 25%, P= 0.049)
  - Neither expression of PD-L1 on tumor cells nor infiltrating immune cells correlate w clinical response to pembrolizumab

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.
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Adverse Events

- Treatment-related AEs of any grade occurred in 77% of patients
- Most common: fatigue and lab abnormalities
- Grade 3 or 4 AEs were observed in 4/26 patients (15%)
  - Two grade 4 reactions: myocarditis and transaminitis
  - Both had reduction in AEs upon discontinuation of pembrolizumab and initiation of glucocorticoids

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med.* 2016 Jun 30;374(26):2542-52.
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Conclusion

- First-line therapy with pembrolizumab in patients with advanced MCC was associated with an objective response rate of 56%
  - Standard chemotherapy: median progression-free survival is 3 months w/ progressive disease developing in 90% of patients within 10 months
- Responses were observed in both MCPyV positive and negative tumors
- PD-L1 expression should not be used as a guide to make clinical decision regarding whether or not to treat MCC patients w PD-1 blocker

Nghiem PT, et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med*. 2016 Jun 30;374(26):2542-52.

Ipilimumab has efficacy in metastatic Merkel Cell Carcinoma: a case series of five patients

- Immunotherapy with immune checkpoint blockers such as the CTLA-4 antibody ipilimumab and PD-1 antibodies has revolutionized oncological treatment options
- MCC is an immunogenic tumor and the efficacy of PD-1 blockade has recently been demonstrated
- Retrospective analysis of five patients with metastatic MCC individually treated with ipilimumab between 2012 and 2015
- Administration of four cycles (3 mg/kg q3 weeks) was planned
- All patients had received previous surgical and radiation therapy before initiation of ipilimumab

Winkler JK, et al. Ipilimumab has efficacy in metastatic Merkel Cell Carcinoma: a case series of five patients. *J Eur Acad Dermatol Venereol. 2017 Mar 3. doi: 10.1111/jdv.14193. [Epub ahead of print]*

Patient	Sex	Age at first diagnosis (years)	First diagnosis	Initial tumor localization	Therapies before Ipilimumab	Start of ipilimumab	Adjuvant /additive	Number of cycles	Best response	PFS (months)	Therapies following Ipilimumab	OS (months)
1	M	55	07/13	Left inguinal lymph nodes	Left inguinal lymph node dissection and radiation, right inguinal lymph node dissection and radiation	03/14	No	4	PD	2.8	None	3.5
2	M	70	07/12	Right thigh	Right inguinal/iliac/paraaval lymphadenectomy and radiation to the iliac lymph nodes	01/14	No	4	SD	12.0	Radiation to cervical lymph nodes, nivolimumab, radiation to left paraaortal lymph node, etoposide	>36.2
3	M	81	12/10	Right lower leg, inguinal sentinel lymph node	Right inguinal lymph node dissection and radiation, excision right thigh and radiation	01/12	Additive (surgery)	3	SD	4.8	Radiation to right retro peritoneal lymph nodes, radiation to right renal bed	15.8
4	M	61	07/13	Left inguinal lymph nodes	Left inguinal lymph node dissection, left iliac lymph node dissection, radiation to left pelvis, low-dose interferon radiation to paraaortal lymph node	08/14	Adjuvant (radiation)	4	CR	12.6	Radiation to paraaortal lymphatic pathways, ipilimumab	>28.6
5	F	50	02/11	Left knee, inguinal sentinal lymph node	Right inguinal lymphadenectomy, radiation to the knee and right inguinal	01/15	Additive (radiation)	4	CR	>23.5	None	>23.5

Ipilimumab has efficacy in metastatic Merkel Cell Carcinoma: a case series of five patients

- Patient 1: Ipi started when imaging revealed suspicious nodes.
  - Re-evaluation s/p 2 cycles of Ipi revealed increased F-FDG uptake on PET-CT and increased LDH → developed increased retroperitoneal mets
- Patient 2: disease relapse twice prior to Ipi which was initiated due to enlarged cervical nodes.
  - Progression free disease for one year
  - Cervical mets enlarged and radiotherapy performed
  - Nivolimumab started due to new paraaortal node

Winkler JK, et al. Ipilimumab has efficacy in metastatic Merkel Cell Carcinoma: a case series of five patients. *J Eur Acad Dermatol Venereol. 2017 Mar 3. doi: 10.1111/jdv.14193. [Epub ahead of print]*

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- Patient 3: received Ipi s/p surgical resection of inguinal and iliac lymph node mets
  - Ipi stopped s/p 3 cycles due to elevated pancreatic enzymes
  - Progression occurred a few months latera → radiation to retroperitoneal and pelvic lymph nodes
  - Rapid disease
- Patient 4: radiotherapy of a growing paraaortal lymph node before adjuvant therapy with ipilimumab
  - PFS x 1 year then increased F-FDG uptake in the retrocrural area
  - Radiation and 4 cycles of Ipi
  - Thereafter, PT/CT scans were without evidence of disease

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- Patient 5: disease recurred and radiation performed to the right iliac lymph node metastases and PET scan revealed persistent uptake
  - Ipi administered
  - Since then, no tumor recurrence

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Ipilimumab has efficacy in metastatic Merkel Cell Carcinoma: a case series of five patients

- Potential role for ipilimumab within a multimodal therapeutic approach
- Estimated median progression-free survival was 12.0 months
- Favorable treatment response in pts who received Ipi after radiotherapy
  - Synergism of immunotherapy and radiotherapy is a known phenomenon
- Adjuvant Ipi after resection is under clinical trial investigation in Europe
- Worthwhile to study combined therapy of Ipi with anti-PD-1

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CME Question

Subclinical extension of melanoma in situ can be predicted by which of the following?

A. Location on the back
B. Dark brown to black color on initial presentation
C. Size > 1cm
D. Immunosuppressed patient
E. Male patient

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Explanation: Clinical factors that can predict subclinical extension of MIS include:

- location on the head, neck, acral skin, genitalia, and pretibia
- recurrent MIS
- preoperative size >1cm
- age ≥ 60
- Color of preoperative lesion was not assessed. Sex and immunosuppression status were not significant

Reference: Shim et al. Clinical factors associated with the subclinical spread of in situ melanoma. *J Am Acad of Dermatology.* 2017 Jan 7. pii: S0190-9622(16)31162-8. doi: 10.1016/j.jaad.2016.10.049. [E-pub ahead of print]