

Merkel Cell Carcinoma of the Extremity

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Patient Presentation

80 year old man: noted a new skin lesion on his right forearm

- It was removed by his dermatologist without pathologic analysis.
- The lesion returned within 1 month, growing to 1-2cm in size.
- Biopsy showed Merkel cell carcinoma.

Physical Exam

* = Mapping
Bx Sites

- Physical exam: Right dorsal forearm has 3x3 cm round erythematous papule, bleeding with bandage removal, on a background of diffuse erythema & induration ~16cm proximal to distal and 5-7cm medial to lateral, extending to the ventral surface of the forearm.



Workup

- Consider MRI of the primary site to assess for deep invasion
- PET/CT for regional and distant staging
- Biopsy of primary and sentinel node biopsy

Imaging

- PET/CT showed FDG-avid disease in the right forearm and right axilla.
- *Note: diffuse lymphadenopathy elsewhere from advanced Mantle Zone lymphoma*



Pathology

- Right axillary LN biopsy/ excision in which multiple matted nodes are removed:
 - Metastatic Merkel cell carcinoma with ECE, largest focus 21mm.
- Punch biopsies around the lesion in the area of erythema & induration:
 - All consistent with Merkel cell carcinoma.

General Principals

Merkel cell is a primary neuroendocrine malignancy of the skin, which is typically rapidly progressive with marginal, regional, and distant recurrence.

General Principals: Surgery

Primary management consists of wide local excision (1-2cm margin) and sentinel node biopsy \pm adjuvant radiation

- Best in cN0 patients
- Relative indications for adjuvant primary irradiation: LVSI, immune suppression, positive margin
- If cN+: lymph node dissection or FNA bx + RT
- Relative indications for adjuvant nodal irradiation: multiple positive nodes, ECE, SLNBx +, high risk of false SLNBx (H&N regions have multiple basins or aberrant drainage, risk of false neg up to 20% [Tai 2013, Ridge 2007])
 - No RT after full node dissection without adverse features
- Observation after complete resection for <1cm and N0

General Principals: Adjuvant RT

Evidence for adjuvant radiation

- Large population databases:
 - SEER: Mojica JCO 2007, Kim JAMA Derm 2013
 - NCDB: Bhatia JNCI 2016, Vargo 2016 JNCI
- Meta-analysis:
 - Pooled 1254 patients from non-randomized studies:
Lewis Arch Derm 2006

General Principals: Definitive RT

- Definitive radiation can be used for unresectable disease
 - Doses $> 50\text{Gy}$ indicated, consider 60-66Gy
 - Margins 3-4cm around the primary to account for lymphovascular spread and in-transit metastases
 - Treat primary and lymph nodes in continuous field if possible (defined as less than 20cm by TROG 9607)

Dosing Summary

Primary		Regional Nodes	
R0	50-56Gy/ 25-28fx	SLN Bx negative	Axilla/ Groin: Observe H&N: 46-50Gy
R1	56-60Gy/ 28-30fx	cN+, no dissection	60-66Gy
R2 or definitive	60-66Gy/ 30-33fx	Microscopic pN+	50-56Gy Observe if 1 node
		ECE	56-60Gy

Definitive Therapy

- Wide margins around the tumor bed are recommended, 3-4cm if possible, to account for in-transit metastases and lymphovascular spread

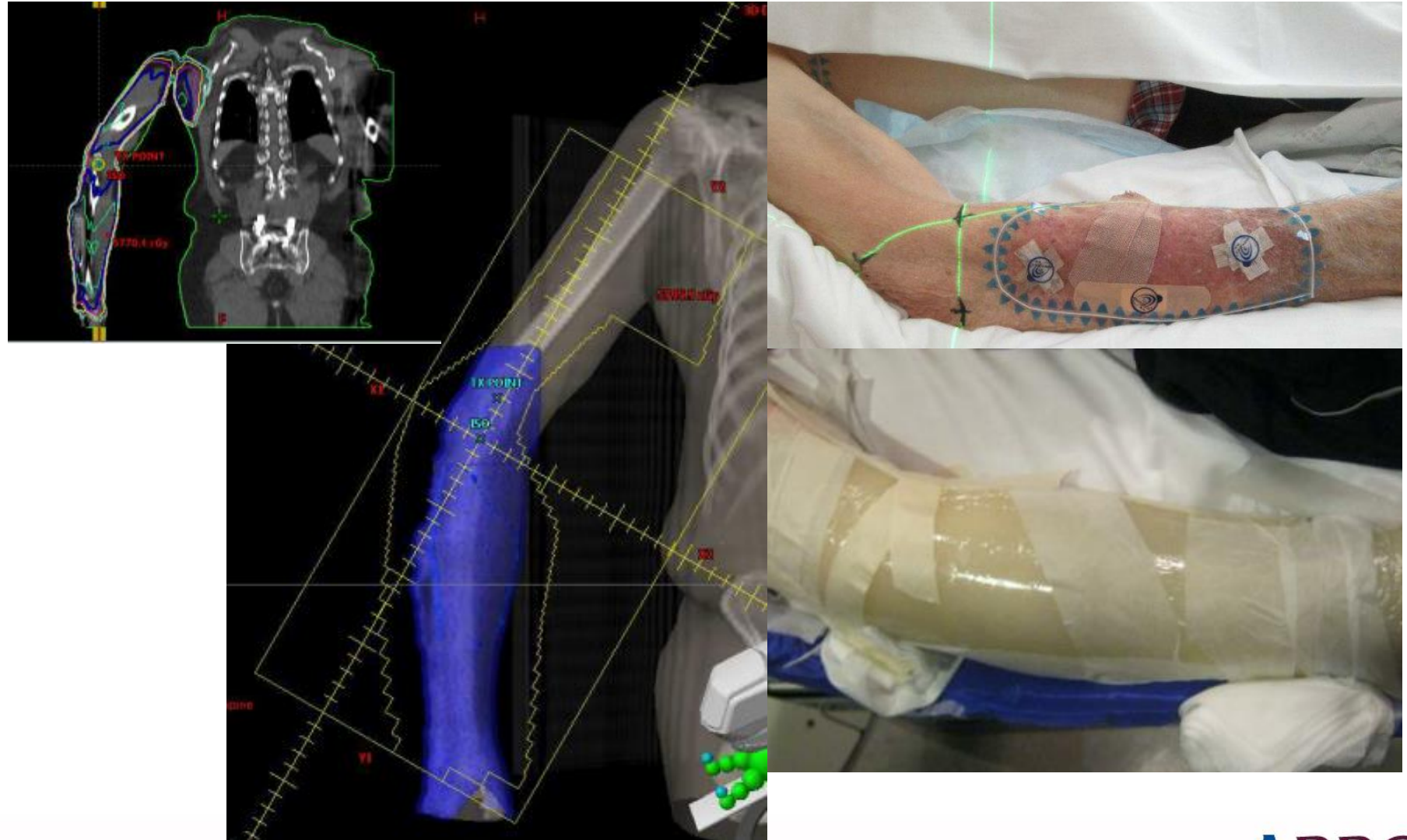
Our Patient

- Definitive primary radiation
- Adjuvant axillary radiation indicated for multiple nodes with ECE

Radiation Plan

- Setup: supine, arm slightly akimbo, stabilized in a cast, wire induration, BB sites of biopsy, wire scar (if present), margin ≥ 4 cm around induration, 0.5cm superflab bolus
- 50Gy/25fx to arm and axilla, 6MV AP/PA
 - Arm (64Gy): 14Gy/7fx boost, 12MeV enface
 - Axilla (60Gy): 10Gy/5fx boost, 6MV AP/PA

Radiation Plan 1



Our Patient

1 week post-RT:

- Radiation resolved pain at the primary site
- Expected skin desquamation
- New area of erythema at the distal field margin (wrist) at 1 month after treatment:
treatment related versus marginal failure?



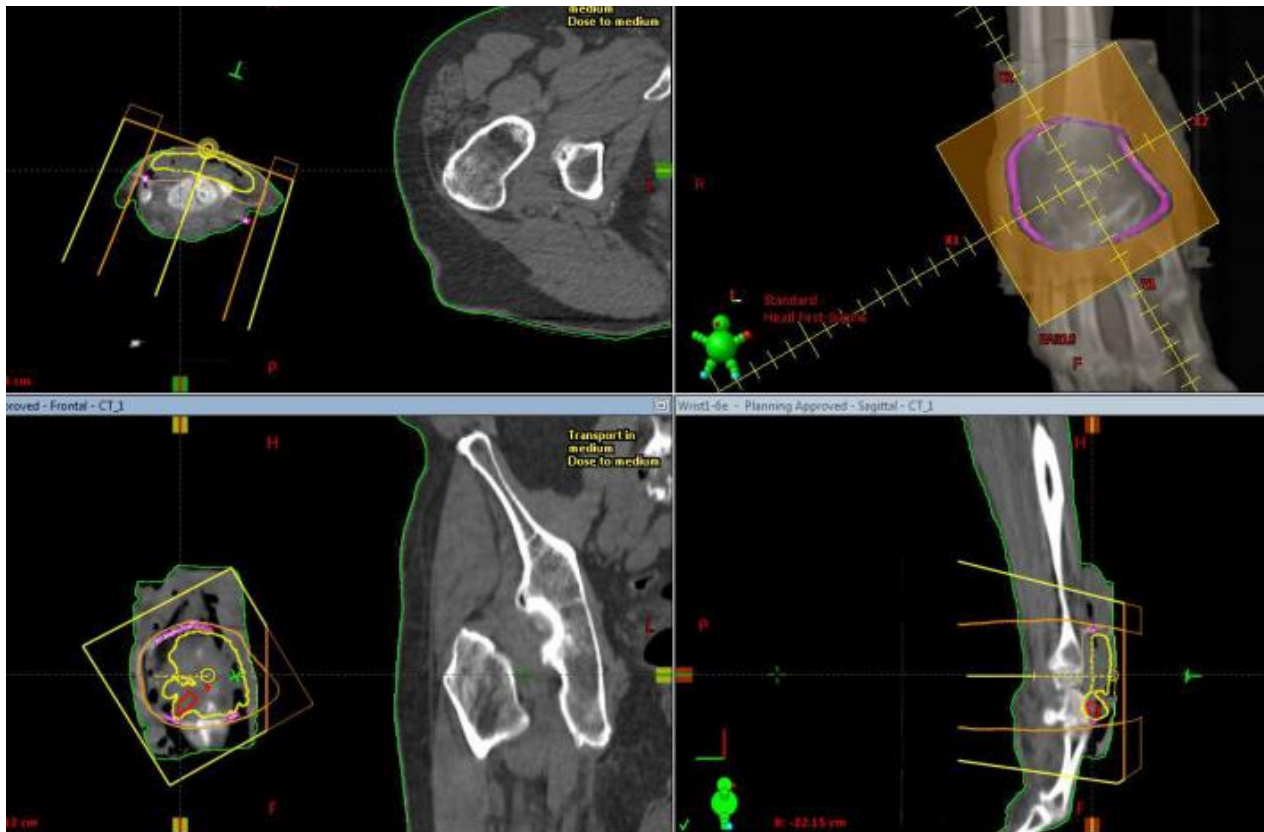
Our Patient

- 4 weeks post-RT:
 - Worsening erythema and developed discrete nodule
 - Biopsy proven MCC



Radiation Plan 2

- 30Gy/5fx to right wrist



Our Patient

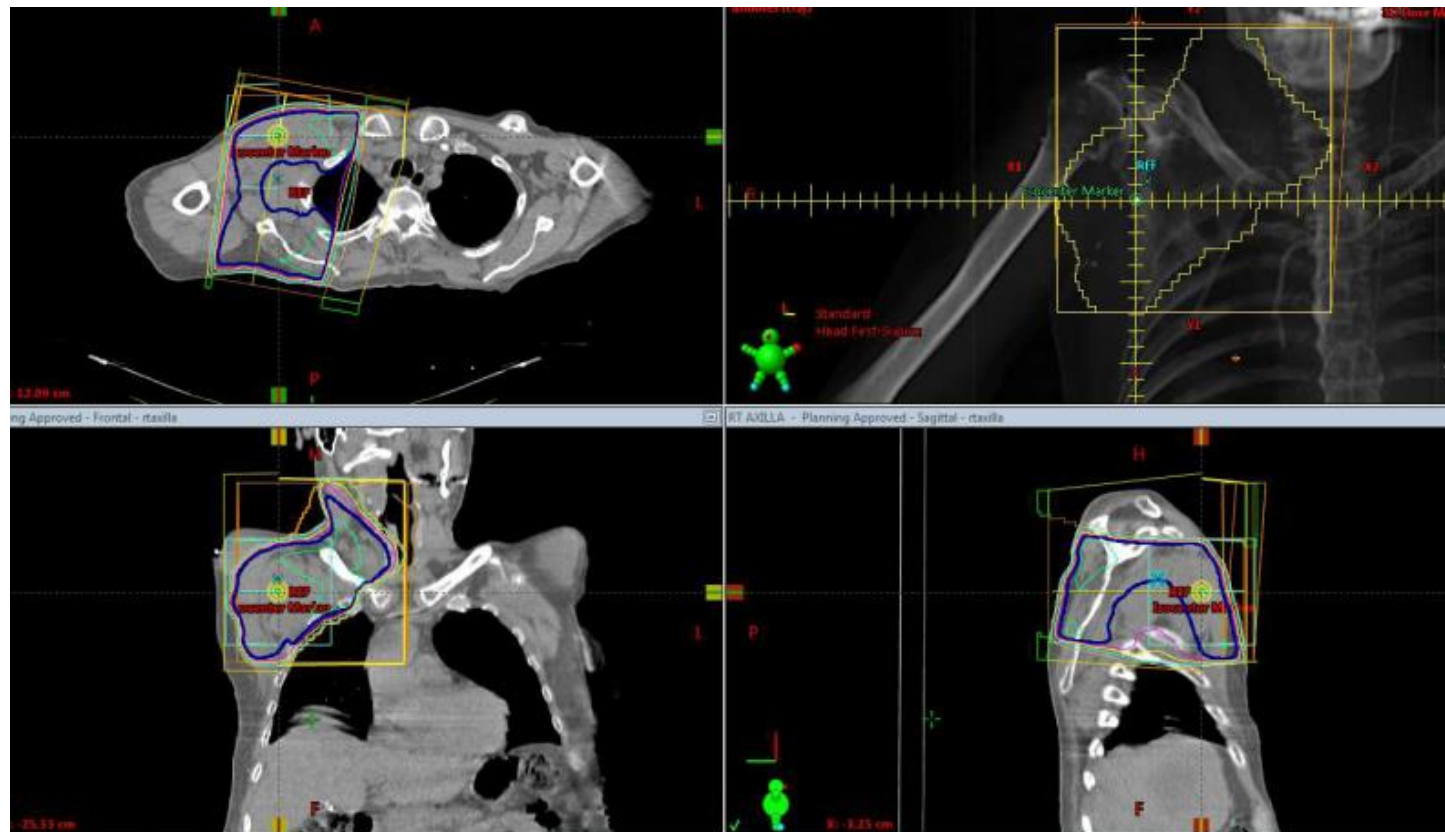
4 months after initial radiation course:

- Increasing pain in the right axilla, imaging showed increased right axillary and supraclavicular adenopathy



Radiation Plan 3

- 30Gy/10fx to right axilla/ supraclav regions



Systemic Therapy


- Currently reserved for the metastatic setting with checkpoint immunotherapy showing promise
 - Avelumab is approved for patients with metastatic MCC irrespective of prior therapy based on the results of the JAVELIN study (Kaufman J Immunother Cancer, 2018)
 - Pembrolizumab and Nivolumab also show antitumor activity in metastatic disease
- Adjuvant and neoadjuvant immunotherapy with checkpoint inhibitors is currently being studied
 - ADMEC-O (NCT02196961) is studying adjuvant Nivolumab (previously had Ipilimumab arm, now closed) in completely resected MCC
 - ADAM (NCT03271372) is studying adjuvant Avelumab for patients with nodal disease from MCC after surgery +/- RT
 - CheckMate 358 looked at neoadjuvant Nivolumab, preliminary results at ASCO 2018 showed major pathologic response in 65% of patients

Conclusions

- This case illustrates the **high risk of marginal and regional failures** in Merkel cell carcinoma.
- Adjuvant or definitive radiation is an important tool in the management of MCC.
- Immunotherapy (avelumab, pembrolizumab) are emerging systemic therapies.


Another Case

- See experts weigh in on another case featured in “The Gray Zone,”
 - Int J Radiation Oncol Biol Phys, Vol. 100, No. 1, pp. 12e13, 2018



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The Touchy Topic of the Touch Cell: A Case of Merkel Cell Carcinoma 

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- Checkmate 358 <https://clinicaltrials.gov/ct2/show/NCT02488759>

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