

Merkel Cell Carcinoma

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OHSU Radiation Oncology

Visiting Medical Student Presentation

CASE: DW

DW

- Bend, Oregon
- 54yo female presenting on 5/28/10 with painful 10cm R groin/thigh mass that had been growing rapidly for 2-3 weeks and new red-purple papule on R heel
- ROS: Positive for mild RLE edema, R groin discomfort, night sweats, mild flushing

DW: PMH

- 30-40 SCCa on b/l upper and lower extremities (3 invasive) removed over the past 5-6 years, one BCCa excised, one melanoma in situ excised
- Hashimoto's thyroiditis s/p RAI in 1990
- Kidney stones s/p cystoscopy x3, last in 1996
- Multiple ovarian cysts, one laparoscopy
- Reactive airway disease
- Chronic LBP
- Herpes Zoster-like episodes q6-8mo x 20 years since back surgery

DW: PSH

- Appendectomy in 1972
- L5-S1 lumbar laminectomy
- L5-S1 fusion in 1985
- L4-L5 diskectomy in 1996
- Vaginal hysterectomy in 1996
- B/l knee arthroscope
- Breast reduction in 2003
- L hip replacement in 2005
- L shoulder surgery 2/2 snowboarding accident

DW: Social Hx

- Respiratory therapist at St. Charles Medical Center in Bend, OR
- Single, two children, multiple grandchildren
- Active in outdoor sports
- Hx of **arsenic exposure** in water source in Cottage Grove, OR, 1982-1986
- Nonsmoker, rare EtOH, no h/o drug use

DW: Family Hx

- Adopted, family history unknown
- Has met 3 biological sisters
- 2 have died of malignancies, unknown type

DW: Allergies and Medications

- Allergies:

- Epinephrine (severe tachycardia)

- Tetanus toxoid (anaphylaxis)

- Iodine, IVP dye only (airway constrict)

- Thimersol (conjunctival bleeding)

- Medications:

- Alprazolam 0.5mg po BID

- Vicodin 7.5mg/3.25mg po q4h prn

- Levothyroxine 125mcg po QD

- Oxycodone po prn

- Oxycontin 10mg po QHS

- Protonix 40mg po QD

- Compazine po q6-8h prn

- Valacyclovir 1000mg po QD

DW: Physical Exam

- BP 133/72
- BMI: 26.26 kg/m²
- Skin: Shows multiple scars of previous excisions and a number of actinic lesions. The R foot notes **red-purple papule on heel**.
- Neck: w/o mass
- Nodal exam: Reveals a **single easily palpable R groin node, measuring about 5 x 2.5cm**
- Extremities: w/o edema

DW: Differential Diagnosis

- SCCa
- Amelanotic melanoma
- BCCa
- Lymphoma
- Metastatic carcinoma
- Sarcoma
- Pheochromocytoma
- Epidermoid cyst, lipoma, dermatofibroma

DW: Imaging

- CT Chest/Abdomen/Pelvis - 5/28/10
 - Enlarged and probably pathologic mass in **R proximal leg, distal to the R inguinal chain**
 - Small lymph nodes within the **R inguinal region**
 - Abnormal enlarged lymph node within the **R external iliac chain** at its border with the R inguinal region

DW: Pathology

- FNA Biopsy R groin mass - 6/15/10

- **Metastatic neuroendocrine tumor**

+ | Pankeratin, CD56, Chromogranin (dim),
Synaptophysin, TTF-1 (dim), CK5/6

- | CD45/LCA, S100, HMB45, MART01, CK7, CK20

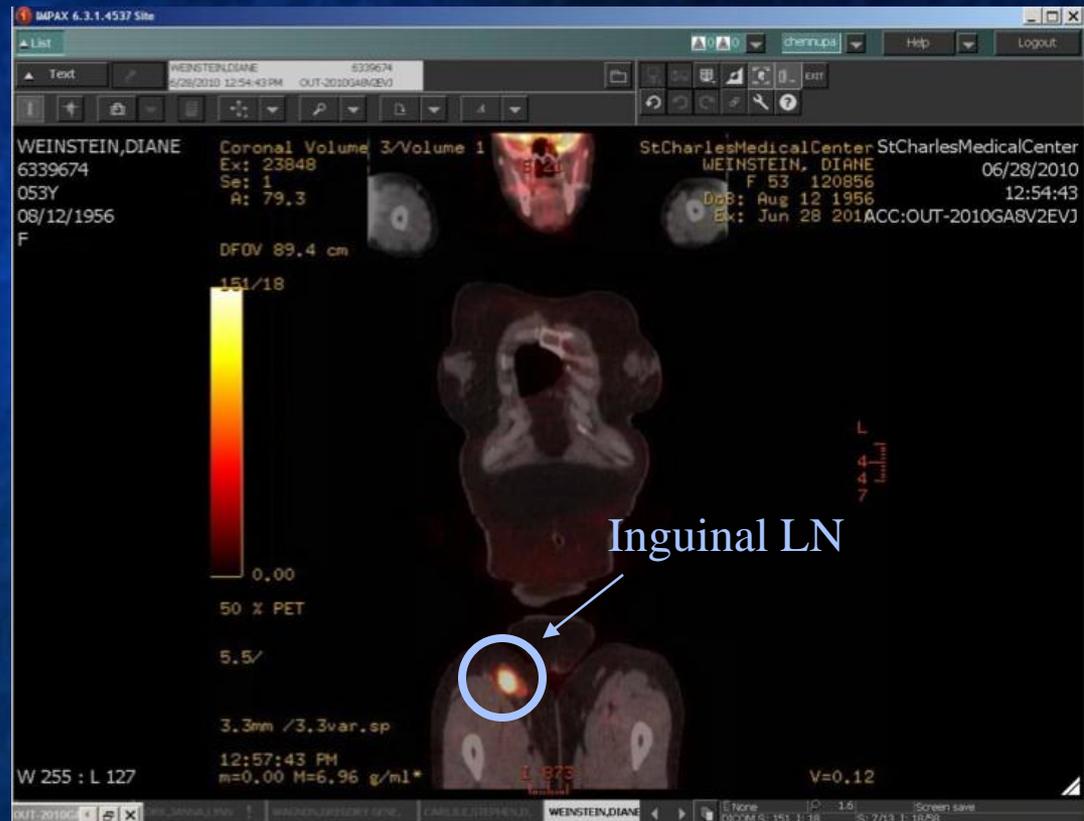
IHC consistent with metastatic carcinoma and rules out lymphoma and melanoma.

DW: Pathology

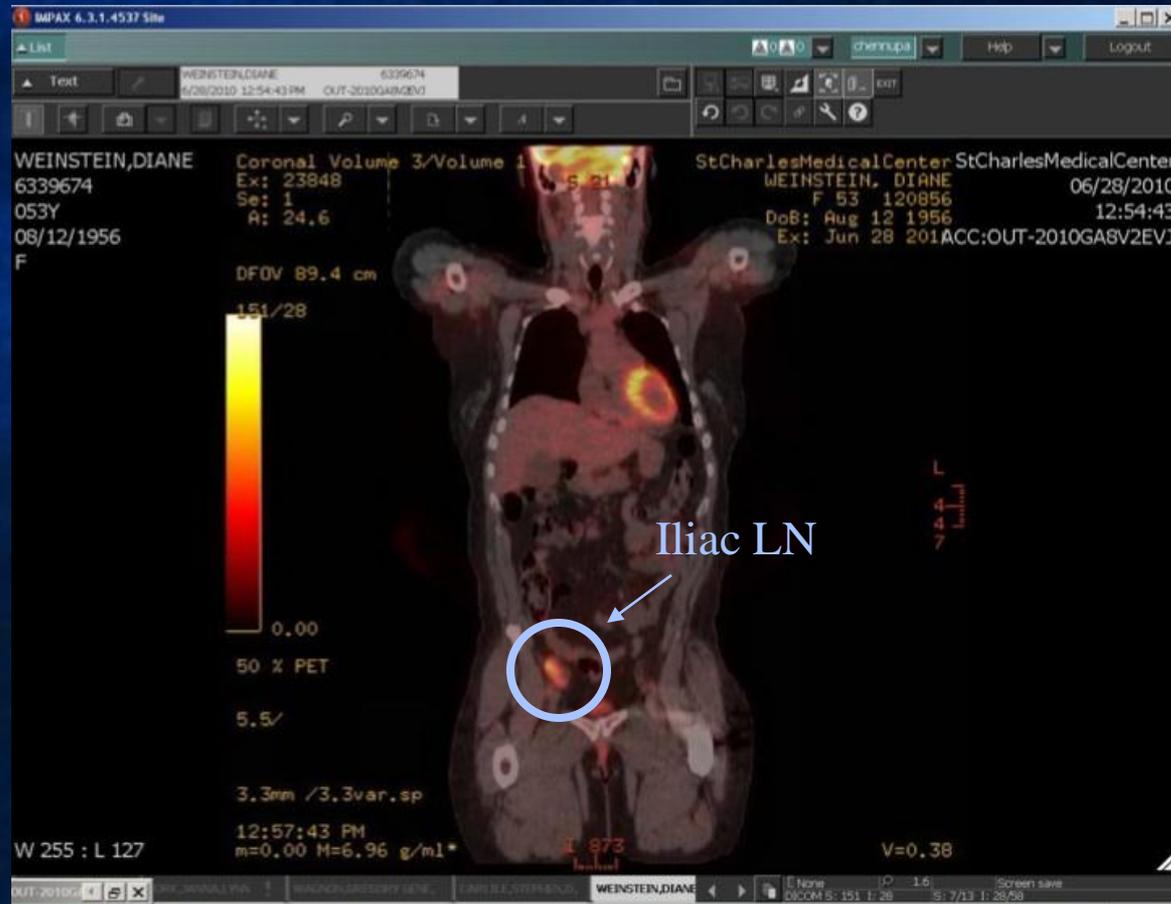
- Shave biopsy foot lesion - 6/18/10
 - Neuroendocrine (Merkel cell) carcinoma
 - Microscopic description: Aggregations and cords of small malignant cells with hyperchromatic nuclei. Mitotic figures and necrotic cells are conspicuous. Many aggregations are sizable. A juxtaposed lymphohistiocytic infiltrate is present concurrently.
 - Immunoperoxidase staining: There is avid expression of both neurofilament and CK20, both with a paranuclear “dot” pattern of positivity, and this staining combination is confirmatory of the above diagnosis. An S100 protein stain was also completed and proved to be negative, and thus there is no indication of melanoma.

DW: Further Imaging

- PET-CT - 6/28/10
 - Total of 5 abnormal R iliac chain and inguinal LN with increased metabolic activity and abnormal CT morphology indicative of metastatic disease
 - No convincing sites of distant metastatic disease



DW: Further Imaging



DW: Initial Treatment

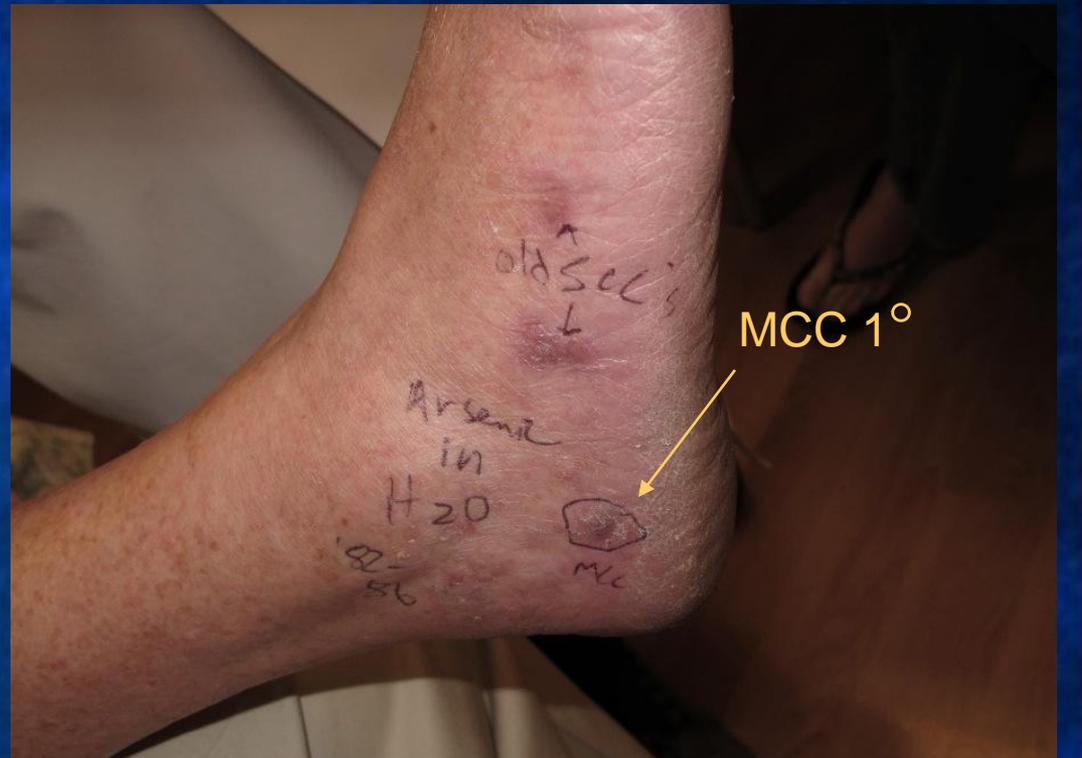
- Palliative approach:
 - Received one cycle cisplatin/VP-16
 - Poorly tolerated: severe nausea, fatigue, neutropenia, mild outbreak of herpetic disease in the L sciatic region, mild URI symptoms
 - Second cycle chemo with carboplatin/VP-16
 - Improved tolerance
- Transferred care to Dr. Paul Ngheim, dermatologist in Seattle, WA
- Now wishes to receive care from OHSU

DW: Physical Exam 9/3/2010

- Vitals: BP 137/71 HR 74 T 96.7 RR 16
- BMI: 24.78 kg/m²
- HEENT: Alopecia 2/2 chemotherapy, EOMI
- Extremities: Multiple scars on b/l upper and lower extremities from SCCa excisions. 2cm post-biopsy lesion on R lateral heel is red, flat, with some scaling.
- Groin: R groin mass approximately 8cm x 6cm on palpation, nontender and firm. No other femoral/inguinal lymphadenopathy palpated on exam. No lower extremity edema.

DW: Physical Exam

- Post-shave biopsy
- 2 cm flat reddish lesion on R lateral heel



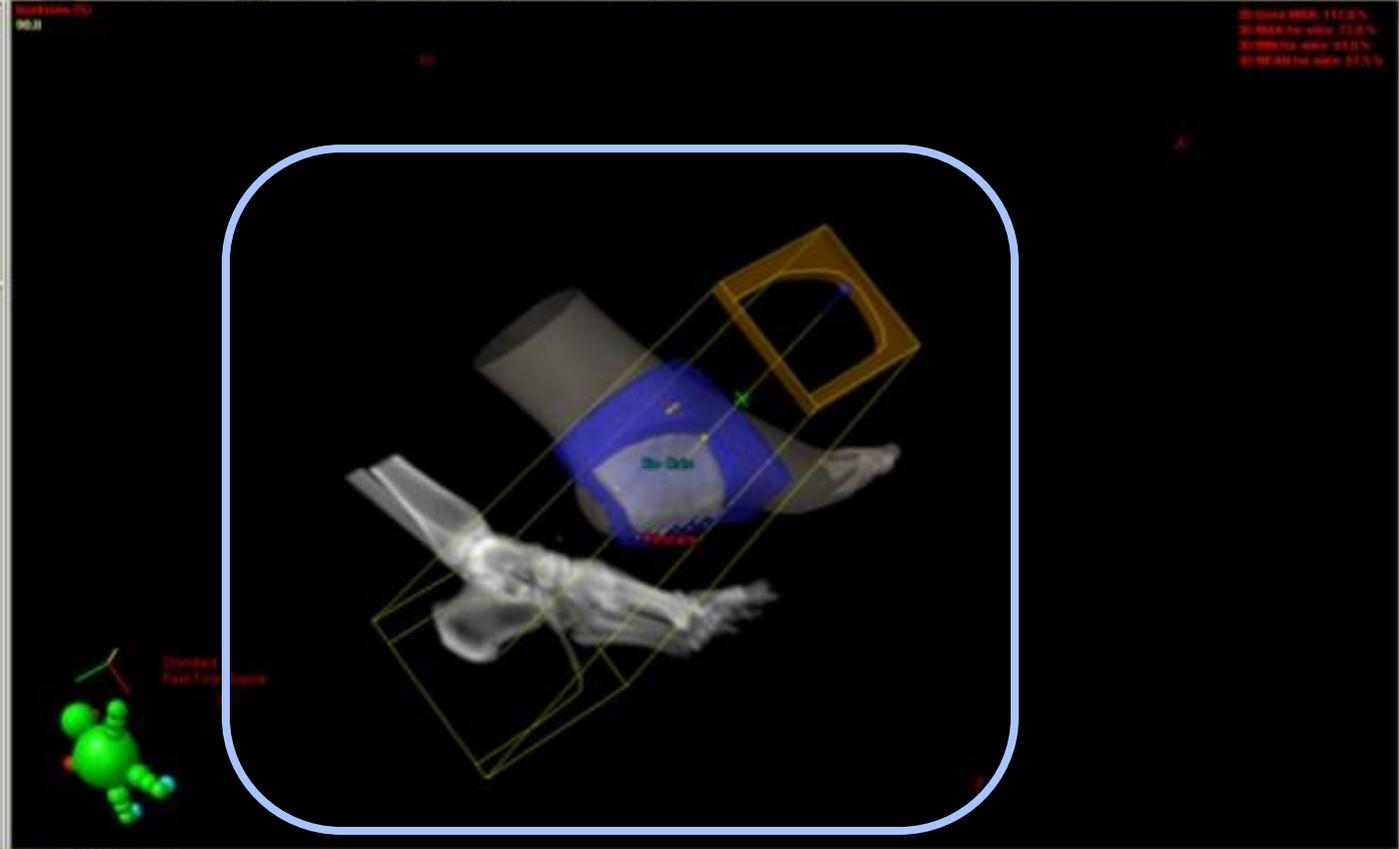
DW: Current Treatment

- Concurrent chemotherapy and radiotherapy
- Chemotherapy:
 - Carboplatin/VP-16 x 2 more cycles
- Radiotherapy:
 - R heel: En face electrons - 1.8 Gy x 28 fractions to 50.4 Gy
 - R pelvic/inguinal LN: EBRT AP/PA - 1.8 Gy x 25 fractions with boost to 50.4 Gy

RADIOTHERAPY PLAN

- 06339674
 - BOC4
 - Abdomen Sept10
 - Abdomen Sept10
 - FootPole Sept10
 - pekiLgrosLN
 - R Fast

- R Fast
 - R Sept10
 - Registered Images
 - CT_1
 - 1.0 CM Bolus
 - BOOY
 - LN
 - None
 - R kidney
 - Sigmoid
 - card
 - wire
 - User Origin
 - Reference Points
 - Sp Calc
 - wire
 - Dose
 - Fields
 - 1 on Face
 - 1 on Face-DRR
 - Block1
 - A30
 - 1.0 CM Bolus

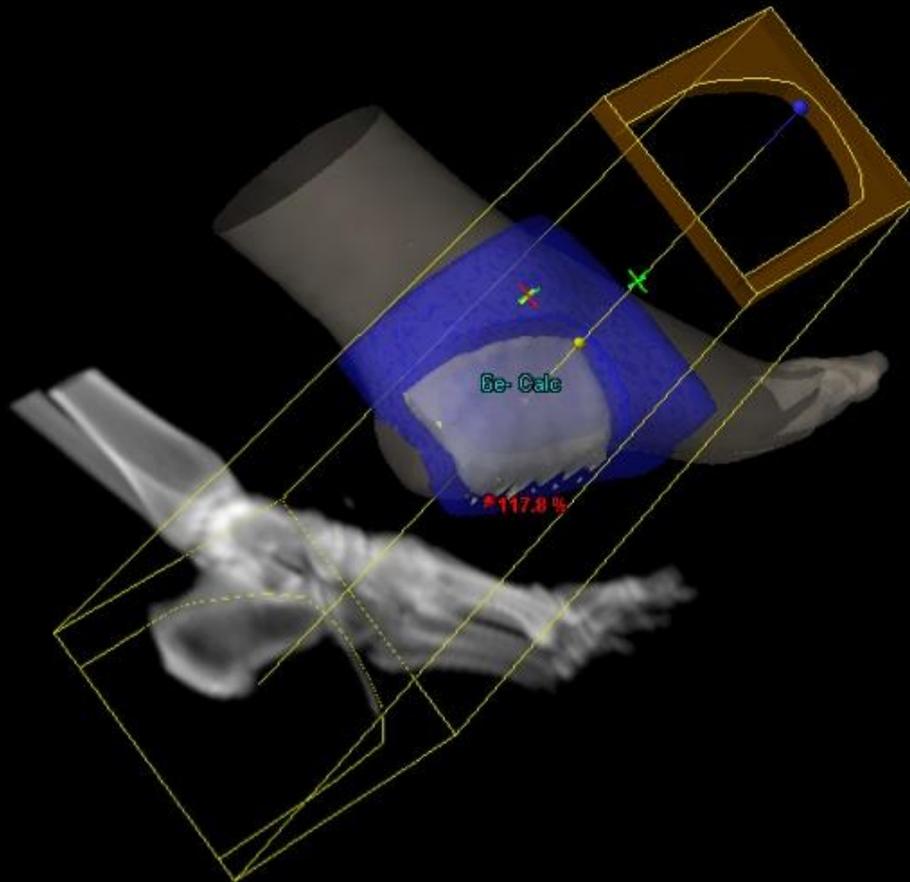


30 Gross Mean: 117.8%
 30 Mean for wire: 71.8%
 30 Mean for wire: 41.0%
 30 Mean for wire: 57.5%

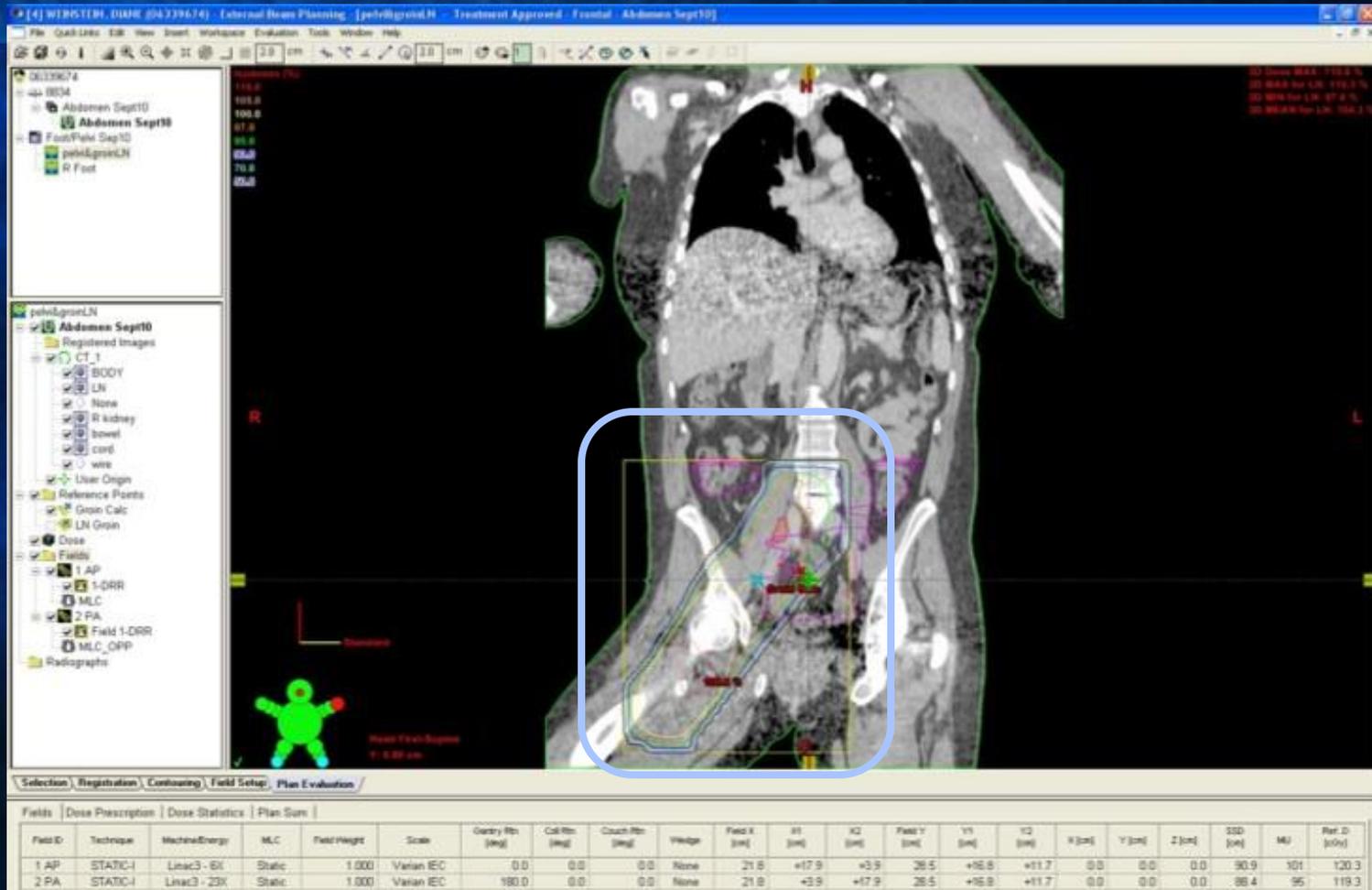
Selection Registration Contouring Field Setup Plan Evaluation

Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

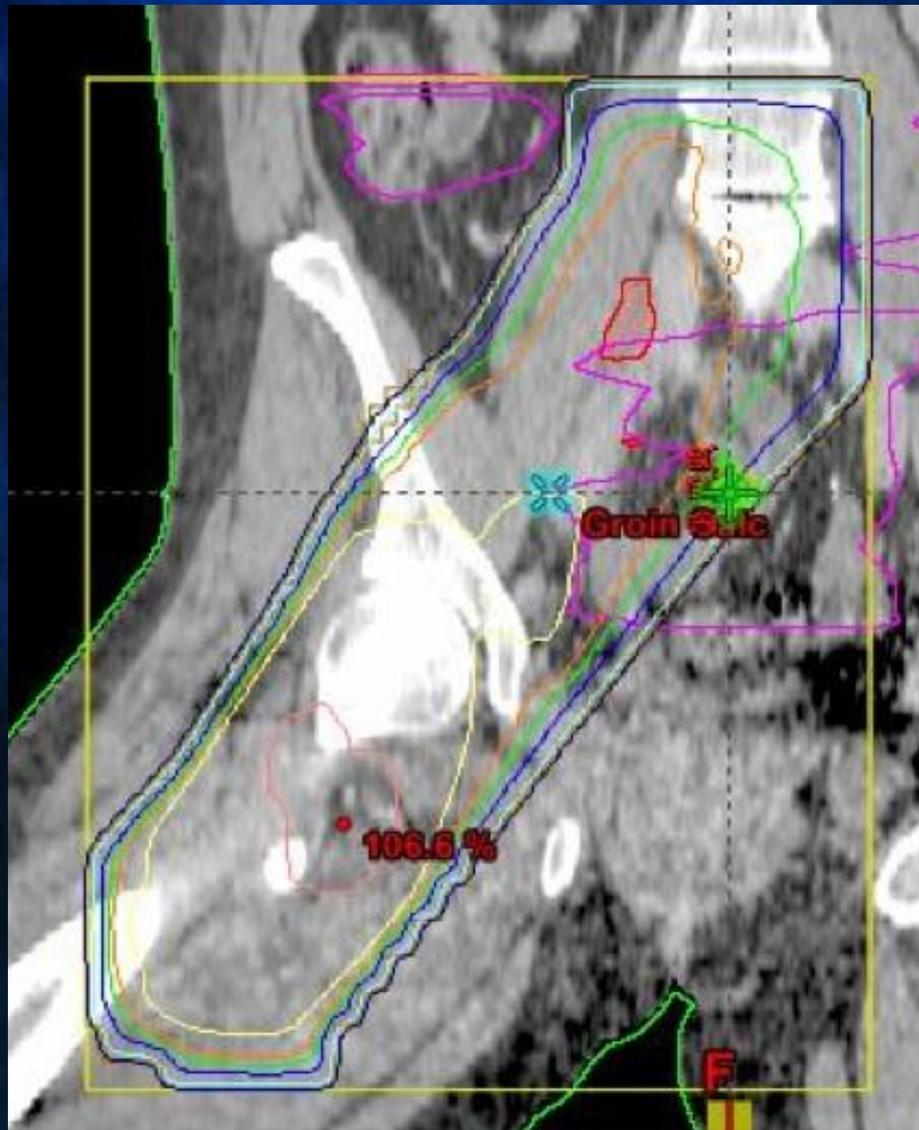
Group	Field ID	Technique	MechanEnergy	SLC	Field Height	Scale	Entry Rn [cm]	Cut Rn [cm]	Couch Rn [cm]	Weight	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	SSD [cm]	MU	Ref D [cm]
	1 on Face	STATIC-F	Linac3 - BE		1.000	Varian IEC	90.0	0.0	0.0	None	30.0	+10.0	+10.0	30.0	+10.0	+10.0	7.3	5.0	4.0	105.0	226	



- Electron en face field
- Planned total RT dose: 50-60 Gy for R heel; 1.8 Gy per fraction x 28 fractions to 50.4 Gy
- Energy: 6eMEV
- Beam Arrangement: en face electrons
- Isodose line: 90% IDL
- Position: R foot elevated, wire placed



- Critical structures: cord, kidneys, and bowel
- DVH parameters achieved: spinal cord dmax 4554cGy, R kidney dmax 154 cGy, bowel dmax 4822 cGy



- Photon field (R common iliac, external iliac, inguinal, and femoral nodal regions)
- Planned Total RT dose:
 - 45-50 Gy for pelvis
 - 50-60 Gy for femoral node
- 1.8 Gy per fraction x 25 fractions for initial plan, followed by boost to gross nodal disease to 50.4 Gy
- Energy: 6x/23x
- Beam Arrangement: en face electrons
- Isodose line: 97% IDL
- Position: frog-leg

MERKEL CELL CARCINOMA

MCC: Overview

- Merkel cell carcinoma (MCC) is a rare, **clinically aggressive neuroendocrine tumor** of the skin with a high propensity for local, regional, and distant spread
- Initially described by Toker in 1972
- Lethal in 33% of cases and therefore carries a worse prognosis than malignant melanoma (15%)

MCC: Biology

- The Merkel cell (MC) was first described by Friedrich Sigmund Merkel in 1875 as a nondendritic, nonkeratinocyte epidermal “tastzellen” or “touch cell” that functions as a tactile skin receptor
- MC are distributed in the skin, typically in the DEJ
- May function as slowly-adapting mechanoreceptors of epidermal origin to sense touch and hair movement

MCC: Etiology

- H/o sun exposure or concurrence of other sun-associated skin conditions, particularly SCCa
- Immunosuppression (solid organ transplant, HIV, radiation or chemotherapy)
- Chronic exposure to arsenic
- Autoimmune disease -- Rheumatoid Arthritis
- Co-incidence of other primary neoplasms
 - Multiple Myeloma
 - CLL
 - NHL
 - Malignant Melanoma

MCC: MCV

- Characterization of a new polyomavirus named **Merkel cell polyomavirus (MCV)** by Moore and Chang
- Polyomaviruses have a double-stranded, circular, supercoiled DNA genome and have been shown to have oncogenic potential
- Up to 80% of MCC tumors are positive for MCV
- In an *in vitro* assay, **UV irradiation** was shown to induce the MCV early promoter causing an increase in ST-antigen mRNA in a dose-dependent fashion

MCC: Molecular & Cytogenetics

- Frequent gain:
 - 1, 3q, 5, 6, 8q
- Frequent loss:
 - 3p, 4, 5q, 7, 10, 13, 17q
- Other common chromosomal abnormalities:
 - Trisomy of chromosome 6
 - Deletion of 5q12-21 in 26% of tumors
 - Deletion of 13q14-21 in 26% of tumors (containing tumor suppressor RB1)
 - Focal amplification at 1p34 in 39% of tumors (centers on L-Myc)
 - Deletion in the nearby region 1p35-36
- Tumors with fewer chromosomal abnormalities were associated with improved survival ($P = 0.04$)

MCC: Molecular & Cytogenetics

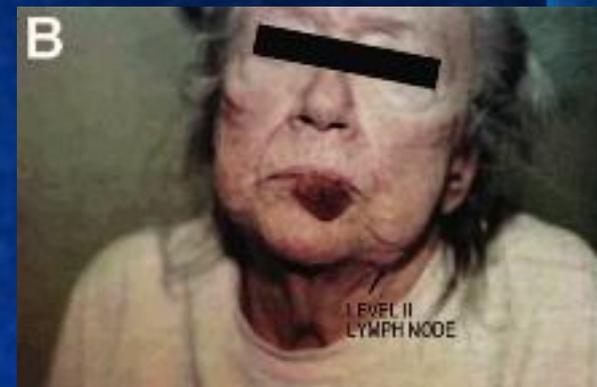
- Potential poor prognostic markers:
 - p63 ($p = 0.0003$), KIT, Ki-67, tyrosine kinase receptor c-kit (CD-117), Tenascin-C (Tn-C), MMP-26
 - Overexpression of MMP-7, MMP-10/2, tissue inhibitor of metalloproteinase 3, vascular endothelial growth factor (VEGF), P38, stromal NK-kappaB, and synaptophysin may also be associated with tumor spread
- Potential favorable prognostic markers:
 - MMP-21 and MMP-28

MCC: Epidemiology

- Overall incidence of first primary MCC in the US
 - 0.32 per 100,000 person-years (SEER data, 1992-2001)
- Incidence increased by 8% per year from 1986-2001
- Estimated annual incidence of 1300 cases
- Most common in elderly (dx 76yo F/ 74yo M) with only 4% of patients being 49 years or younger
- Incidence in whites ~8x that in blacks, and almost 2x that in other ethnic groups
- Male: Female = 2:1

MCC: Clinical Presentation

- Classically **painless** subcutaneous mass
- **Cystic or nodular**, sometimes plaque-like
- Tumor size ranges from 2-200 mm, but is most often **<20 mm**.
- **Vastly range in color** (red/pink, blue/violaceous, or skin-colored)
- Can exhibit overlying **telangiectasia** or a shiny surface
- 1/3 erythematous, 3/4 with intact epidermis
- More advanced tumors become ulcerative and hemorrhagic
- **Rapid growth** with mean 6.2 months (2 wks to 2 yrs) between the patient noticing the lesion and presenting for histologic diagnosis



Clinical Presentation

- Most common **primary sites** in decreasing order:
 - Head and neck (approximately 50% of cases), extremities, trunk, and buttock
- Occurrences in **sun-protected areas** have been reported:
 - Bartholin gland, vagina, vulva, bowel, parotid gland, and oral mucosa
- Spontaneous regression of the primary lesion has been documented
- 10% to 20% of cases will present with no obvious primary site

Clinical Presentation

- Stage I or II disease (clinically negative nodes)
 - 71-78%
- Stage III disease (regional nodal metastasis)
 - 19-24%
- Stage IV disease (distant metastasis)
 - 2-5%

Clinical Presentation

- Secondary sites of involvement:
 - skin (28%)
 - lymph nodes (27%)
 - liver (13%)
 - lung (10%)
 - bone (10%)
 - brain (6%)
- Rare metastases to:
 - testicle, heart, pancreas, stomach, conjunctiva, iris, leptomeninges, bone marrow

MCC: Differential Diagnosis

Benign

Epidermoid cyst
Acneiform lesion
Lipoma
Dermatofibroma/fibroma
Vascular lesion

Malignant

Amelanotic melanoma
BCCa
SCCa
Lymphoma
Sarcoma
Metastatic carcinoma

Misc. Cut. Lesions

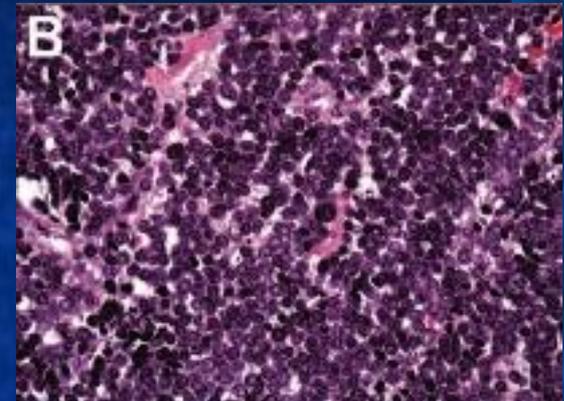
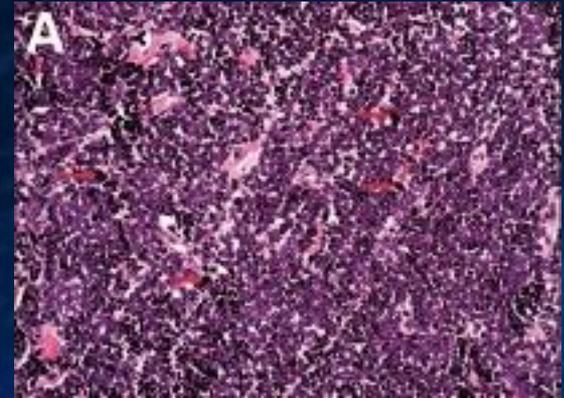
Adnexal Tumors
Pyogenic Granuloma
Carcinoid
Retinoblastoma
Neuroblastoma
Leukemia cutis

MCC: Differential Diagnosis

- In a study of 195 patients by Heath et al, the most common clinical features of MCC were outlined to aid in the diagnosis of MCC
- AEIOU:
 - Asymptomatic
 - Expanding rapidly (doubling in less than 3 months)
 - Immune suppressed
 - Older than 50 years
 - UV-exposed skin site, with a subcategory of fair skin
- In the 62 patients for which all 5 criteria were available, at least 3 criteria were fulfilled by 89% of patients, at least 4 by 32% of patients, and all 5 were seen in 6% of patients

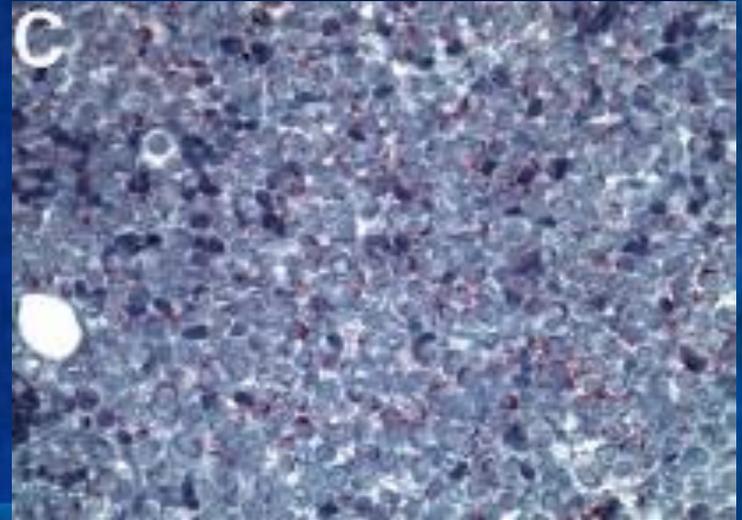
MCC: Diagnosis

- Small, basophilic cells (**small round blue cells**) with frequent mitoses
- Hyperchromatic nuclei, sparse cytoplasm
- **Cytoplasmic spinous processes**
- **Neurosecretory granules** (seen on EM, 100-200nm in diameter)
- Arranged in a vague trabecular pattern without defined acini
- Vascular and perineural invasion is common



MCC: Diagnosis

- 3 distinct histologic architectural patterns.
 - Classic trabecular pattern - irregular cords or ribbons of basophilic cells
 - **Intermediate cell or solid pattern** - nuclear molding with a distinct “ball-in-mitt” pattern
 - Small cell or diffuse pattern



MCC: Diagnosis

	MCC	SCLC	Melanoma	B-cell Lymphoma
→ CK20	+	-	-	-
S100	-	-	+	-
→ Thyroid Transcription Factor 1	-	+	-	-
→ Neurofilaments	+	-	-	-
Leukocyte Common Antigen (LCA)	-	-	-	+
Neuron-specific enolase (NSE)	+	+/-	-	-
Vimentin	-	-	+	+
Chromogranin A (CgA)	+/-	-	-	-
MASH1	-	+	-	-

MCC: Staging

- Multiple previous staging systems
- AJCC performed study of 5823 patients
- Found nodal status was important prognostic factor

MCC: Staging

T	N	M
<p>TX: Primary tumor cannot be assessed.</p> <p>T0: No evidence of primary tumor (e.g. nodal/metastatic presentation without associated primary).</p> <p>Tis: <i>In situ</i> primary tumor.</p> <p>T1: ≤2 cm maximum tumor dimension</p> <p>T2: >2 cm but ≤5 cm maximum tumor dimension.</p> <p>T3: >5cm maximum tumor dimension.</p> <p>T4: Primary tumor invades bone, muscle, fascia, or cartilage.</p>	<p>NX: Regional lymph nodes cannot be assessed.</p> <p>N0: No regional lymph node metastasis.</p> <p>cN0: Nodes negative by clinical exam (via inspection, palpation, and/or imaging, but no pathologic node exam performed).</p> <p>pN0: Nodes negative by pathologic exam.</p> <p>N1: Metastases in regional lymph node(s).</p> <p>N1a: Micrometastasis (diagnosed after sentinel or elective lymphadenectomy).</p> <p>N1b: Macrometastasis (clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy).</p> <p>N2: In transit metastasis (distinct from 1° lesion and located either between 1° lesion and draining regional LN or distal to the 1° lesion).</p>	<p>M0: No distant metastasis.</p> <p>M1: Metastases beyond regional lymph nodes.</p> <p>M1a: Metastases to skin, subcutaneous tissues, or distant lymph nodes.</p> <p>M1b: Metastasis to lung.</p> <p>M1c: Metastases to all other visceral sites.</p>

Merkel cell carcinoma. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 318-9.

MCC: Staging

- **NX**: Regional lymph nodes cannot be assessed.
- **N0**: No regional lymph node metastasis.
- **cN0**: Nodes negative by clinical exam (via inspection, palpation, and/or imaging, but no pathologic node exam performed).
- **pN0**: Nodes negative by pathologic exam.
- **N1**: Metastases in regional lymph node(s).
- **N1a**: Micrometastasis (diagnosed after sentinel or elective lymphadenectomy).
- **N1b**: Macrometastasis (clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy).
- **N2**: In transit metastasis (distinct from 1° lesion and located either between 1° lesion and draining regional LN or distal to the 1° lesion).

Stage	T	N	M
0	Tis	N0	M0
IA	T1	pN0	M0
IB	T1	cN0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	Any T	N1a	M0
IIIB	Any T	N1b/N2	M0
IV	Any T	Any N	M1

MCC: Diagnostic Codes

ICD Codes for Merkel Cell Carcinoma

209.31	Merkel cell carcinoma of the face
209.32	Merkel cell carcinoma of the scalp and neck
209.33	Merkel cell carcinoma of the upper limb
209.34	Merkel cell carcinoma of the lower limb
209.35	Merkel cell carcinoma of the trunk
209.36	Merkel cell carcinoma of other sites
209.75	Secondary Merkel cell carcinoma
V10.91	Personal history of malignant neuroendocrine tumor

MCC: Work-up

- Initial staging of patients with MCC is of critical importance
- History and Physical Exam
- Baseline labs (CBC, serum electrolytes)
- Patients with localized disease without physical or symptomatic evidence of regional or distant metastases (**clinical N0**)
 - SLNB or ultrasound (exception H&N)
- Lesions suspicious for regional LN involvement (**clinical N1b**)
 - FNA cytology w/wo US guidance

MCC: Additional Imaging

- Concannon et al: After FDG-PET results obtained,
 - staging was adjusted in 6/18 pts
 - treatment approach was altered in 8/18 pts
- Iagaru et al: FDG-PET clinically contributive in 6/6 pts
- Belhocine et al: FDG-PET clinically contributive in 10/11 pts
- High-resolution CT, MRI, and somatostatin analog (octreotide) scintigraphy

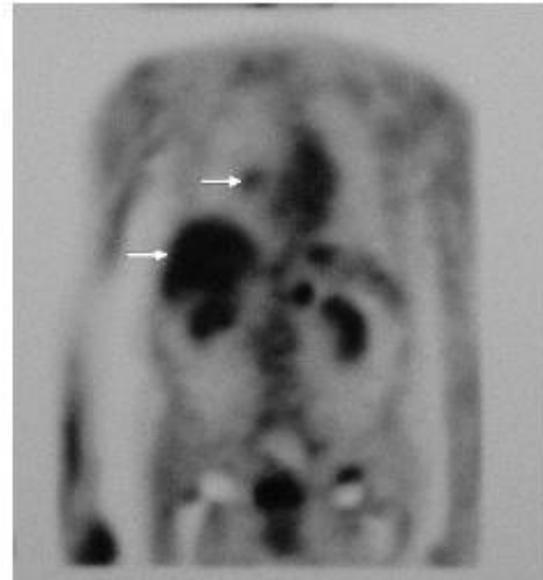


FIGURE 3. Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan illustrating liver and mediastinal metastases (arrows) in a patient with a mandibular primary MCC.

MCC: Prognostic Factors

- Survival at 5 years (relative to age- and sex-matched control/population data):
 - Stage I or II (local) - 64%
 - Stage III (regional nodal) - 39%
 - Stage IV (distant metastatic) - 18%
- Nodal Involvement:
 - Microscopic nodal involvement only - 42% survival
 - Clinically apparent nodal disease - 26% survival

Prognostic Factors

- Portend **poor** outcome
 - **Male sex**
 - **Age > 60 years**
 - Presence of co-morbid conditions
 - Immunocompromised state
 - Positive resection margin
 - High mitotic rate
 - Small cell size
 - Absence of an inflammatory infiltrate
 - Site of primary disease (head/neck, trunk, perineum, lower extremities)
 - **No adjuvant radiotherapy**
 - +/- Tumor thickness
- Growth Pattern:
 - Diffuse growth pattern associated with poor outcome
 - Nodular growth pattern associated with increased survival

□ TREATMENT

MCC: Surgery

- Allen et al
 - Memorial Sloan-Kettering Cancer Center
 - 102 patients with MCC
 - Treated over a 27-year period
 - Found no association between width of margins and either recurrence rate or survival
- O'Connor et al
 - Wide local excision (n = 41) vs. Mohs surgery (n = 12)
 - WLE: local persistence in 31.7% and regional metastasis in 48.8%
 - Mohs surgery: local persistence in 6.8% and regional metastases in 33.3%

PRINCIPLES OF EXCISION

Goal:

- Clear surgical margins when clinically feasible

Varied Approaches:

- 1- to 2-cm margins to investing fascia of muscle or pericranium with clear pathologic margins, when clinically feasible.
- Mohs technique¹
- Modified Mohs = Mohs technique with additional final margin for permanent section assessment
- CCPDMA = Complete circumferential and peripheral deep-margin assessment

Reconstruction:

- Immediate reconstruction in most cases
- It is preferable to delay reconstruction involving extensive undermining or flaps until negative surgical margins are assessed and certified pathologically clear
- When primary closure is not possible, consider split-thickness skin grafting to monitor for recurrence

- The National Comprehensive Cancer Network (NCCN) recommends 1-2 cm margins when clinically feasible and Mohs techniques to ensure clear margins, as well as to spare tissue

MCC: Chemotherapy

- SCLC regimens
- Utility very controversial
- Voog et al
 - 107 patients treated with first line chemotherapy
 - 61% response rate
 - 7.7% risk of toxic death due to neutropenia
- Tai et al
 - 204 patients treated with chemotherapy
 - Cyclophosphamide, doxorubicin/epirubicin, and vincristine w/wo prednisone
 - Response rate of 75.7%
 - Etoposide and cisplatin/carboplatin
 - Response rate of 60%
 - 3.4% toxic death rate

MCC: Chemotherapy

- Experimental agents:
 - Natural tumor necrosis factor (TNF)
 - Imatinib (Gleevec)
 - G3139 (Genasense)
 - High-dose polychemotherapy followed by autologous stem cell transplant
 - Isolated limb perfusion regional chemotherapy

CHEMOTHERAPY AGENTS²

Local disease:

- Adjuvant chemotherapy not recommended unless clinical judgment dictates otherwise

Regional disease:

- Adjuvant chemotherapy not routinely recommended because adequate trials to evaluate usefulness have not been performed, but could be used on a case-by-case basis if clinical judgment dictates
- Cisplatin alone or combined with etoposide
- Carboplatin alone or combined with etoposide

Disseminated disease:

- Cisplatin plus etoposide
- Carboplatin plus etoposide
- Cyclophosphamide, doxorubicin (or epirubicin), and vincristine
- Topotecan has been used

¹Mohs technique is used primarily in MCC to insure complete removal and clear margins, and secondarily for its tissue-sparing capabilities.

²When available and clinically appropriate, enrollment in a clinical trial is recommended. The literature is not directive regarding the specific chemotherapeutic agent(s) offering superior outcomes, but the literature does provide evidence that Merkel cell carcinoma is chemosensitive, although the responses are not durable, and the agents listed above have been used with some success.

MCC: Radiotherapy

- Common features with SCLC have led to the use of doses of 45-60 Gy, depending on the presence or absence of gross disease

Author (Year)	n	Treatment	Radiation Dose (Gy)	Chemotherapy	Results	p	Conclusions
Fang et al. (2010)	50	S ± RT ± C	Unspecified	Cis/Carbo/Etop (10), Etop (1), Cyclophos 5FU/MTX (1), Etop/ Doxo (1), unknown (1)	2-yr RRFS 78% vs 73% 2-yr DSS 73% vs 59% RT vs CLND 2-yr OS 81% vs 61% Microscopic vs palpable nodes	0.8 0.9 0.05	Radiation monotherapy showed similar efficacy compared to CLND in regional control of lymph-node positive MCC.
Foote et al. (2010)	112	S ± RT ± C	25-62	Platinum based (15)	2-yr OS 72%. 2-yr local-regional control rate 75% Relapse rate lower with elective nodal RT	<0.05	Demonstrates dose-response of elective nodal RT for subclinical (≥50 Gy) and gross disease (≥55 Gy).
Poulsen et al. (2010)	60	S ± RT ± C	30-60 50 median	Carbo/Etop (9)	5-yr RFS 0% vs 28% S vs S + RT ± C.	<0.05	Study of MCC in lower limb. Elective RT to inguinal nodes reduces relapse.
Tai et al. (2010)	145	S ± RT ± C	50 (most common)	Etop, Cis, Carbo, Cyclophos, Adriamycin, vincristine, taxotere.	LN mets 17%, 39%, 60% Recurrence 30%, 52%, 77% In tumors <1cm, 1-2cm, and >2cm respectively.	0.002 0.007	Favorable factors include early stage of presentation, wide LE, LND and use of adjuvant RT (p<0.03)
Bajetta et al. (2010)	95	S alone	None	None	5-yr DSS 67% overall; 5-yr regional recurrence 0% vs 39% with ≤2 vs >2 metastatic LN	0.004	Results vary when surgery alone is used for MCC. >2 metastatic nodes increased regional and distant recurrence.
Veness et al. (2009)	43	RT alone	50 median	None specified	In-field control 75%, Relapse 53%. Nodal status assoc with RFS	0.005	RT can achieve high chance of local control. Recommend 50-55 Gy.
Lawenda et al. (2008)	36	S ± RT ± C	51-72 Median 52.5	Not specified	LC 69% vs 95% S alone vs S + RT	0.02	RT to primary tumor site improves LC and shows trend toward LRC.
Clark et al. (2007)	110	S + RT vs RT or S alone	9-70 50 median	Platinum-based (8), Etop (5), alkaloids (3).	5-yr LC 84%, 5-yr LRC 69% S + RT had better DSS on univariable analysis	0.013	S + RT improves DSS for tumors >1cm even if node negative head and neck MCC
Mojica et al. (2007)	1665	S ± RT ± C*	Not specified	Not specified*	Median OS 45mo vs 63mo S alone vs S + RT	<0.001	Analysis of SEER registry data supports adjuvant RT to improve survival.
Lewis et al. ¹⁰ (2006)	1254	S ± RT	Not specified	None specified	Local recur 24.5% vs 9.6% S only vs S + RT Regional recur 44.8% vs 13.2% S only vs S + RT	<0.001 <0.001	Meta-analysis study supports local adjuvant RT to reduce local and regional recurrence.
Allen et al. ¹¹ (2005)	251	S + RT ± C	38-61	Carbo/Etop, Vincristine, Cyclophos, Doxo (25)	5-yr DSS 64% Stages I-IV: 81%, 67%, 52%, 11%. LR 10% vs 8%	0.001	Pathologic stage predicts long-term survival. Recommend negative margins and nodal staging. RT does not reduce

					Nodal relapse 13% vs 26%	0.76	LR.
					Adjuvant RT vs no RT	0.13	
McAfee et al ¹² . (2005)	34	S ± RT vs C + RT (2)	30-74.4 (Median 60)	Carbo, Cis (9)	5-yr LC 94%; LRC 80%; free DM 60%; CSS 52%; OS 37%		If treated aggressively with S + RT, about 50% chance of cure. Recommend adjuvant RT
Veness et al ¹³ . (2005)	86	S ± RT ± C	18-70	Platinum-based (6)	Total relapse 55% Nodal relapse 18% vs 37% Adjuvant RT vs no RT 5-yr OS 47%; 5-yr DFS 25%	<0.001	Recommend adjuvant RT for improvement of regional control rates.
Eng et al ¹⁴ . (2004)	85	S ± RT ± C	50-60	Mostly S ± Etop (16)	Recurrence 48% Persistent disease 12% 5-yr actuarial survival 55% Stage 1 survival 68%	<0.01	Adjuvant R ± C decreased recurrence. Predictors of good outcome were female sex, early stage
Poulsen et al ¹⁵ . (2003)	53	S + RT/C	50	Carbo/Etop (53)	RFS 65%; 3-yr OS 76%; LRC 75%; overall distant control 76%.		Phase II study of high risk patients shows good results with combined therapy.
Boyer et al ¹⁶ . (2002)	45	S (Mohs) ± RT	45-50	Unspecified (3)	LR 16% vs 0% S vs S + RT 5-yr OS 79% vs 80% S vs S + RT	0.12 0.74	RT does not improve OS. Recommend adjuvant RT when S incomplete, tumor large or recurrent.
Gillenwater et al ¹⁷ . (2001)	66	S ± RT	46-66	None	LR 12% vs 44%; RR 27% vs 85% S vs S + RT	<0.01	Patients receiving adjuvant RT had improved disease control but no difference in ODSS or DM.

S, surgery; RT, radiation therapy; C, chemotherapy; Cis, cisplatin; Carbo, carboplatin; Etop, etoposide; Cyclophos, cyclophosphamide; 5FU, 5-fluorouracil; MTX, methotrexate; Doxo, doxorubicin; RRFS, regional recurrence free survival; DSS, disease specific survival; CLND, completion lymphadenectomy; OS, overall survival; RFS, relapse free survival; LN, lymph node; LE, local excision; LC, local control; LRC, locoregional control; LR, local recurrence; RR, regional recurrence; DM, distant metastasis; CSS, cause specific survival.

*SEER Database does not provide information about chemotherapy or about sentinel lymph node biopsy.

Adjuvant Radiation Therapy Is Associated With Improved Survival in Merkel Cell Carcinoma of the Skin

Pablo Mojica, David Smith, and Joshua D.I. Ellenhorn

- 1665 pts (SEER, 1973-2002)
- Stage I 55%, Stage II 31%, Stage III 6%
- 89% surgery
- 40% surgery + adjuvant XRT
- Median survival w/XRT 63mo vs 45mo ($p < 0.001$)
- Improved OS in all stages

STUDY

Adjuvant Local Irradiation for Merkel Cell Carcinoma

Kevan G. Lewis, MD, MS; Martin A. Weinstock, MD, PhD; Amy L. Weaver, MS; Clark C. Otley, MD

- 1254 pts (Ovid)
- Metanalysis of 333 reports
- Individual- and aggregate-level studies
- Surgery vs Surgery + XRT
- LR: 24.5% vs 9.6% ($p < 0.001$)
- Regional Recurrence: 44.8% vs 13.2% ($p < 0.001$)

ORIGINAL ARTICLE

**MERKEL CELL CARCINOMA: IMPROVED OUTCOME WITH ADJUVANT
RADIOTHERAPY**

MICHAEL J. VENESS,* LAKMALIE PERERA,* JUNIE MCCOURT,* JENNIFER SHANNON,* T. MICHAEL HUGHES,†
GARY J. MORGAN* AND VAL GEBSKI*

**Head and Neck Cancer Service, Westmead Hospital and †Surgical Oncology Service, Westmead Hospital, Sydney, Australia*

- 86 pts (Sydney, Australia, 1980-2002)
- 36pt surgery alone
- 38pt surgery + XRT (median 50 Gy, range 18-70 Gy)
- Surgery alone vs Surgery + XRT:
 - Nodal Relapse 37% vs 18%
 - DFS 4mo vs 10.5mo (p<0.01)

Principles of Radiation Therapy

Dose Recommendations for Radiation Therapy:

Primary site:

- Negative resection margins 50-56 Gy
- Microscopic (+) resection margins 56-60 Gy
- Gross (+) resection margins or unresectable 60-66 Gy

Nodal bed:

- No SLNB or LN dissection
 - Clinically (-) but at risk for subclinical disease 46-50 Gy
 - Clinically evident adenopathy: head and neck 60-66 Gy
 - Clinically evident adenopathy: axilla or groin¹ -- 1
- After SLNB without LN dissection
 - Negative SLNB: axilla or groin Radiation not indicated²
 - Negative SLNB: head and neck, if at risk for false-negative biopsy 46-50 Gy²
 - Microscopic N+ on SLNB: axilla or groin 50 Gy³
 - Microscopic N+ on SLNB: head and neck 50-56 Gy
- After LN dissection
 - Lymph node dissection: axilla or groin 50-54 Gy⁴
 - Lymph node dissection: head and neck 50-60 Gy

- All doses at 2 Gy/d standard fractionation. Bolus is used to achieve adequate skin dose. Wide margins (5 cm) should be used, if possible, around the primary site. If electron beam is used, an energy and isodose line (e.g., 90%) should be used to deliver adequate lateral and deep margins.
- Extremity and torso MCC: after negative SLNB and WLE, in most instances, radiation therapy is given to the primary site only. SLNB dictates the need for regional irradiation. If SLNB is negative, then regional nodal basins can be observed. If SLNB is not performed, consider irradiating nodal beds for subclinical disease. Irradiation of in-transit lymphatics is usually not feasible unless the primary site is close to the nodal bed.
- Head and neck MCC: risk for false-negative sentinel node biopsy is higher, because of aberrant lymph node drainage and frequent presence of multiple sentinel node basins. The radiation field to treat the primary site is often overlying the draining lymph node beds. Treatment options for clinically node negative MCC of the head and neck include:
 - Perform SLNB and WLE. If SLNB is negative, options are to irradiate the primary site ± nodal beds and in-transit lymphatics or observe.
 - OR
 - Perform WLE without performing SLNB and irradiate the primary tumor site, in-transit lymphatics, and regional nodal sites.

MCC: Treatment Summary

- Early Stage (Stage I/II disease, N0)
 1. WLE
 2. SLNB (+) :
Tumor Board Consultation; LND + XRT
 3. SLNB (-) : XRT
- Early Stage with Head/Neck Primary
 1. WLE
 2. XRT

MCC: Treatment Summary

- Advanced Disease (Stage III Disease)
 1. FNA LN
 2. FNA (+) : Additional Imaging
 1. M0 : LND + XRT, chemo in special cases
 2. M1 : Tumor Board Consultation; supportive care with a combination of surgery, chemotherapy, XRT
 3. FNA (-) : Open biopsy
 1. Bx (+) : Additional Imaging --> M0/M1
 2. Bx (-) : Treat as appropriate N0 disease

MCC: Treatment Summary

- Metastatic Disease (Stage IV Disease)
 - Tumor Board Consultation
 - Supportive care
 - Combination of chemotherapy, radiotherapy, and surgery

MCC: Conclusion

- MCC is a rare neuroendocrine tumor of the dermis with mortality rate that is $>2x$ higher than that of melanoma (33% vs. 15%)
- With advances in diagnostic techniques, coding, and staging, larger, more uniform studies can be performed to answer the many unanswered questions that still exist regarding the biology and treatment of MCC

MCC: Future Directions

- Larger clinical trials
- Prospective randomized trials
- Role of MCV in the etiology of MCC
- Significance of molecular markers and chromosomal abnormalities in predicting prognosis
- Establishing best therapeutic approach

□DW

THANK YOU