State of the Art in Merkel Cell Carcinoma

Dr Jordi Rubió Casadevall
Medical Oncology Department
ICO-Girona

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Pathology

✓ First described by Toker in 1972

✓ Merkel cell are believed to function as mechanoreceptors

✓ Features of neuroendocrine tumor, expressing IHC features as neuron-specific enolasa, neurofilament, chromogranin, synaptophysin in addition to CK20

✓ Histologic variants: intermediate cell type, small cell type, trabecular type

✓ Over expression c-KIT, PDGFR $\alpha$ and $\beta$ and VEGFR
Epidemiology

Incidence  world age standardized incidence rate in different Population-based Cancer Registries (cases x 100,000 inhabitants-year)

<table>
<thead>
<tr>
<th>Cancer Registry</th>
<th>Men</th>
<th>Women</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand 2002-2011</td>
<td>1.05</td>
<td>0.74</td>
<td>0.88</td>
</tr>
<tr>
<td>Olmed County (Minnesota, USA) 1976-2011</td>
<td>0.69</td>
<td>0.1</td>
<td>0.35</td>
</tr>
<tr>
<td>Denmark 1995-2006</td>
<td>0.20</td>
<td>0.25</td>
<td>0.22</td>
</tr>
<tr>
<td>Girona (Spain) 2002-2012</td>
<td>0.37</td>
<td>0.26</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Expected cases in Spain: 145-150 each year

Trends in incidence:

USA (SEER ¹): 1986-2011, Incidence raised from 0.22 to 0.78 (p<0001)
Girona (1994-2012): APC 1.4 (-3.5;6.5), but in men APC 4.1 (1.3;9.8)

Etiology

- UV exposure
- “Clusters” in immunosuppressed patients
- Association with Merkel Cell Polyomavirus (MCPyV), described in 2008
  
  - In 80% of MCC (regional differences)
  - Production of MCPyV T-antigen specific T cells.
  - MCPyV positive patients higher titers of antibody than negative patients
  - LT-Ag high affinity binding for RB
  - PI3K/AKT/mTOR signaling pathway
  - MCC 70% PDL1 + correlated with CD8 lymphocyte infiltration

2 Afanasiev OK et al. Merkel Polyomavirus Specific T Cells fluctuate with Merkel Cell Carcinoma Burden and express therapeutically targetable PD1 and Tim3 exhaustion markers Clin Cancer Res 2013; 19: 5351-5360
Clinical characteristics

- **Asymptomatic**, indurated, solitary dermal nodule, erythematos-violaceous color
- Expanding rapidly with local infiltration via dermal lymphatics and producing satellite lesions
- Patients at risk, those Immune suppressed and Older than 50 years (median age of diagnosis 75-77 years-old)
  More frequent in UV-exposed skin

<table>
<thead>
<tr>
<th></th>
<th>Skin of face, scalp and neck (C44.0; C44.1; C44.2; C44.3; C44.4)</th>
<th>Skin of trunk (C44.5)</th>
<th>Skin of arm and shoulder (C44.6)</th>
<th>Skin of leg and hip (C44.7)</th>
<th>Overlapping lesion of skin or NOS (C44.8; C44.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEER 1 (1973-2006)</td>
<td>43.9%</td>
<td>10.6%</td>
<td>22.0%</td>
<td>14.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>New Zealand 2 (2002-2011)</td>
<td>48.8%</td>
<td>7.9%</td>
<td>16.3%</td>
<td>17.4%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Girona (1994-2012)</td>
<td>69.7%</td>
<td>6.1%</td>
<td>9.1%</td>
<td>15.1%</td>
<td>--</td>
</tr>
</tbody>
</table>

Prognostic markers

156 cases MSKCC ¹ (1980-2005)

Tumor thickness

Anatomic compartment

Lymphovascular invasion

Solar elastosis

Tumor necrosis

Ulceration

STAGE

High MCPyV viral copies/cell: better prognosis (non viral MCC with mutations TP53, worse prognosis)²

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>II vs I</td>
<td>2.05 (0.78-5.36)</td>
</tr>
<tr>
<td>III vs I</td>
<td>2.68 (1.12-6.41)</td>
</tr>
<tr>
<td>IV vs I</td>
<td>33.66 (10.3-109.4)</td>
</tr>
<tr>
<td>Tumor growth pattern (infiltrative vs nodular)</td>
<td>6.85 (2.11-22.19)</td>
</tr>
<tr>
<td>LIV (present vs absent)</td>
<td>3.84 (1.43-10.28)</td>
</tr>
</tbody>
</table>

² Bathia K et al. Merkel cell carcinoma subgroups by Merkel cell polyomavirus DNA relative abundance and oncogene expression. Int J cancer 2009; 126: 2240-2246.
### Staging: AJCC (7th edition)\(^1\)

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1:</td>
<td>(\leq 2) cm</td>
</tr>
<tr>
<td>T2:</td>
<td>(&gt; 2 \leq 5) cm</td>
</tr>
<tr>
<td>T3:</td>
<td>(&gt; 5) cm</td>
</tr>
<tr>
<td>T4:</td>
<td>primary tumor invades bone, muscle, fascia or cartilage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0:</td>
<td>no regional lymph nodes metastasis</td>
</tr>
<tr>
<td>N1:</td>
<td>regional lymph nodes metastasis</td>
</tr>
<tr>
<td>N2:</td>
<td>in transit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a:</td>
<td>skin, subcutaneous tissues or distant lymph nodes</td>
</tr>
<tr>
<td>M1b:</td>
<td>lung</td>
</tr>
<tr>
<td>M1c:</td>
<td>all other visceral sites</td>
</tr>
</tbody>
</table>

#### % diagnosis \(^2\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA:</td>
<td>T1pN0M0</td>
<td>44%</td>
</tr>
<tr>
<td>IB:</td>
<td>T1cN0M0</td>
<td>26%</td>
</tr>
<tr>
<td>IIA:</td>
<td>T2-3 pN0M0</td>
<td>24%</td>
</tr>
<tr>
<td>IIB:</td>
<td>T2-3 cN0M0</td>
<td>6%</td>
</tr>
<tr>
<td>IIC:</td>
<td>T4N0M0</td>
<td>18%</td>
</tr>
<tr>
<td>IIIA:</td>
<td>any T,N1a</td>
<td>42%</td>
</tr>
<tr>
<td>IIIB:</td>
<td>any T, N1b or 2 M0</td>
<td>60%</td>
</tr>
<tr>
<td>IV:</td>
<td>M1</td>
<td>79%</td>
</tr>
</tbody>
</table>

#### 5 years relative survival \(^3\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA:</td>
<td>79%</td>
</tr>
<tr>
<td>IB:</td>
<td>60%</td>
</tr>
<tr>
<td>IIA:</td>
<td>58%</td>
</tr>
<tr>
<td>IIB:</td>
<td>49%</td>
</tr>
<tr>
<td>IIC:</td>
<td>47%</td>
</tr>
<tr>
<td>IIIA:</td>
<td>42%</td>
</tr>
<tr>
<td>IIIB:</td>
<td>26%</td>
</tr>
<tr>
<td>IV:</td>
<td>18%</td>
</tr>
</tbody>
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\(^3\) Lyer J et al. Merkel Cell Carcinoma. ASCO educational book 2010
Staging

**Sentinel node biopsy:** rationale for routine use

- better staging: 20% positivity in T1; 45% in T2: Better outcome for patients with pathologically proven N0 than those clinically evaluated.\(^1\)

- prognostic information: 60% recurrence SLNB+ vs 20% SLNB- at 3 years.\(^2\)

- decision making regarding adjuvant treatment: 91% SLNB+ vs 36% SLNB- received adjuvant treatment.

12-17% false negative rate

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\(^1\) Lemos B et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: Analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol 2010;63: 751-761

\(^2\) Gupta SG et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana Farber experience and meta-analysi of the literature. Arch Dermatol 2006; 142: 685-690
Treatment:

*MCC considered a chemo and radio-sensitive tumor in which concepts of other neuroendocrine tumors are applied*

Problems in the interpretation of evidence:

- Lack of randomized trials
- Retrospective series with few cases and large periods of time
- Different criteria for the indication of adjuvant radiotherapy or chemotherapy

Key points:

- Benefit of the local RT
- Benefit of RT on nodes versus LND
- Benefit of chemotherapy
Treatment: local and adjuvant setting

Stages I and II

**Surgery:** 1-2 cm margin (no more local relapse with wider excision\(^1\))

**Radiotherapy:** Benefit of the local RT?

- SEER \(^2\) database 6908 MCC patients. Better OS in Stage I HR 0.75 [95% CI 0.67–0.83], \(p<0.0001\); Stage II HR 0.77 [95% CI 0.67–0.90], \(p=0.0006\).

**Benefit of RT on nodes?**
- no benefit in SLNB-, relapses 14% vs 4% (\(p 0.31\)) \(^4\)
- Randomized trial stopped \(^3\): 0% vs 16.7% LRR

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\(^2\) Bathia S et al. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: Survival analysis of 6,908 cases from the National Cancer Data Base. ASCO 2014 Abstract Nº: 9014


Treatment: local and adjuvant setting

Stages IIIA and IIIB

Benefit of RT on nodes?
3-years RFS 51% vs 0% using or not nodal adjuvant radiotherapy in SLNB+ ¹

RT after LND “always”?  NCCN guidelines: EC extension or multiple involved nodes (category 2A)

Nodal RT substitutes LND? No differences in 2-y RFS or OS in small cohort comparing RT alone vs LND+RT ²

² Fang et al. Radiation monotherapy as regional treatment for lymph node positive Merkel carcinoma. Cancer 2010; 116: 1183-90
Treatment: local and adjuvant setting
Treatment: adjuvant setting

Benefit of chemotherapy?
TROG 96:07, 53 patients high risk: primary size > 1cm, involved nodes, residual disease after surgery, local or node recurrence

Surgery+RT (50Gy)+Carbo (AUC=4.5)/Etoposide (80mg/m2 x 3d) weeks 1,4,7,10

Results: 76% 3y-OS ; 65% 3y-RFS

…but no benefit of CT comparing historical controls

To discuss in H&N tumors, >3cm and positive margin

Ongoing: Prospective randomized trial of an adjuvant therapy of completely resected Merkel Cell Carcinoma (MCC) with 3mg/kg BW Ipilimumab (Yervoy®) every 3 weeks for 12 weeks versus observation (EUDRACT-2013-000043-78)


Treatment: advanced disease. Chemotherapy

The literature on MCC metastatic patients is sparse and based in retrospective series with few cases

Chemotherapy regimens commonly used for the treatment of MCC¹,²:

- Cyclophosphamide + doxorubicine + vincristine
- Etoposide + cisplatin / carboplatin

Response rate 1ˢᵗ line: 57-70%
Response rate 2ⁿᵈ line: 23-25%
Median overall survival: 9-9.5 months
Median progression-free survival: 3.1-5.3 months

² Paul Nghiem et al. Systematic literature review of efficacy, safety, and tolerability outcomes of interventions in patients with distant metastatic Merkel cell carcinoma. ASCO 2016, abstract №: e21018
Treatment: advanced disease. Immunotherapy

26 patients received pembrolizumab 2mg/kg every 3 weeks for 2 years, or CR, toxicity or progression.

Enrolled from January 2015 to December 2015

Median age 68 years-old
35% MCPyV negative tumors; 65% positive

Results:

56% response rate (15% CR, 4 patients)
62% RR in virus positive (10 of 16); 44% RR in virus negative (4 of 9). Virus negative MCC: high mutational load and many predicted neoantigens.
67% PFS at 6 months, median PFS 9 months
Responses ongoing in 12/14 (86%) responders (7.6 months median follow-up)

15% (4 patients) grade 3-4 toxicity

88 patients received Avelumab 10 mg/kg IV Q2W
ORR was 29.5% Six pts (9.8%) had complete responses, 12 (19.7%) partial responses, and 7 (11.5%) stable disease.
Median PFS: 2.6 m; PFS rate at 6m: 36%
15/18 responses (83%) ongoing
Treatment: advanced disease. Targeted therapy

**A Phase II Trial of Imatinib Mesylate in Merkel Cell Carcinoma (Neuroendocrine Carcinoma of the Skin): A Southwest Oncology Group Study (S0331).** Samlowski W et al. Am J Clin Oncol 2010; 33: 495-499

23 patients. 1 partial response (4%), 1 month PFS and 5 months OS


16 of 17 patients evaluable. 3/16 PR (19%)+6 patients SD, clinical benefit in 9/16 (56%).
Median duration of treatment with pazopanib: 8.0 weeks
Median progression-free survival: 3.2 m.
Median overall survival: 6.4 m
CONCLUSIONS

-MCC is a rare cancer with an incidence of 3 cases x million inhabitants-year, which mainly affects older people.

-Merkel cell polyomavirus plays a role in its carcinogenesis

-Treatment is based in surgery, SLNB and adjuvant radiotherapy

-In advanced stage, chemotherapy and immunotherapy achieve good response rates

-More multi-institutional trials are needed
jrubio@iconcologia.net

(no conflict of interest)

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<thead>
<tr>
<th>ICO l'Hospitalet</th>
<th>ICO Badalona</th>
<th>ICO Girona</th>
<th>ICO Camp de Tarragona i Terres de l'Ebre</th>
</tr>
</thead>
</table>
| Hospital Duran i Reynals  
Av. Granvia de l'Hospitalet, 199-203  
08908 L'Hospitalet de Llobregat | Hospital Germans Trias i Pujol  
Ctra. del Canyet s/n  
08916 Badalona | Hospital Doctor Trueta  
Av. França s/n  
17007 Girona | Hospital Joan XXIII  
C. Dr. Mallafré Guasch, 4 43005 Tarragona  
Hospital Verge de la Cinta  
C. de les Esplanetes, 14 43500 Tortosa |

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