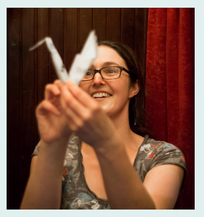
Merkel Cell Carcinomas in New Zealand: Virus or Ultraviolet?



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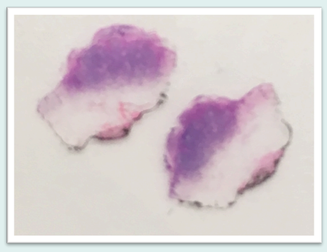
Merkel Cell Carcinoma (MCC) is an uncommon but aggressive cancer originating from sensory cells in the skin. Globally, it is most common in elderly males and is associated with immunosupression, such as seen in transplant or leukemia patients.



Clinically, the tumour can present with an aggressive course, with surgery and radiotherapy the main stay of treatment. Chemotherapy is uncommon and immunotherapy is in trials with good success rates.

Histologically, MCCs have a distinct small cell architecture and diagnosis is confirmed by a panel of immunohistochemical markers including chromogranin A, synaptophysin and cytokeratin 20.

Virus or Ultraviolet? In 2008 a groundbreaking study identified the presence of a novel polyoma virus in four MCCs, subsequently named Merkel Cell Polyoma Virus (MCPyV)[1]. This commensal dsDNA virus increases in incidence on the skin with age. MCCs are initiated by the integration and mutation of MCPyV into the cells own genome. A class II mutagen, MCPyV proteins are oncogenic, interfering with the Retinoblastoma Rb tumour suppressor.

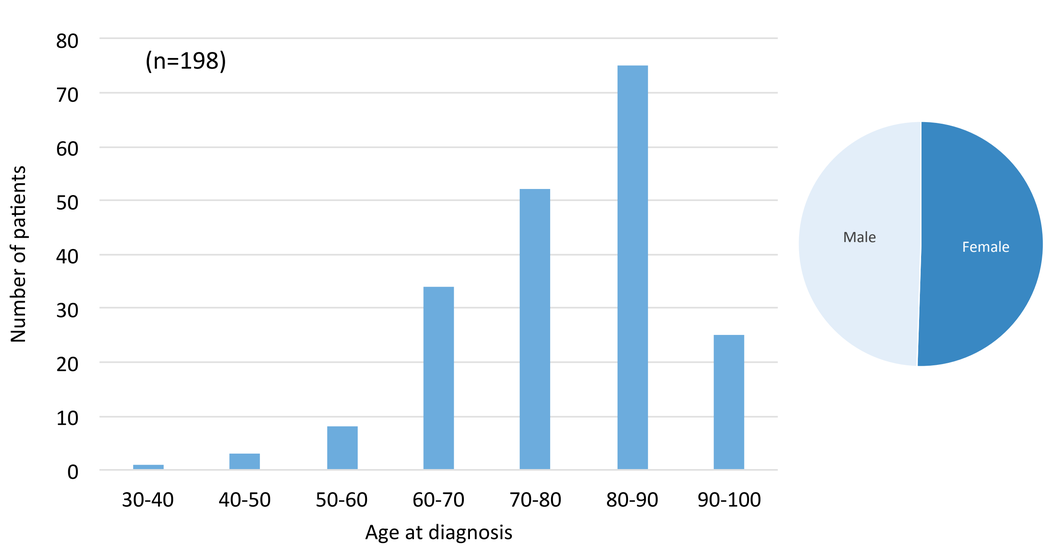
Multiple epidemiological studies from across the world have reported the presence of MCPyV in ~80% of MCCs[2, 3, 4]. However, in Australia, where rates of MCC are high, MCPyV was detected in only 24% of cases[4]. MCCs were also in sun exposed sites on the body.

Analyses of MCPyV negative cases have identified a UV-linked mutational signature with C-T substitutions plus a multitude of mutations in oncogenes including *TP53* and *RB1*[5].

The two etiologies, Virus and UV, are linked by common gene pathways so a question remains whether they're a single disease or two distinct diseases.

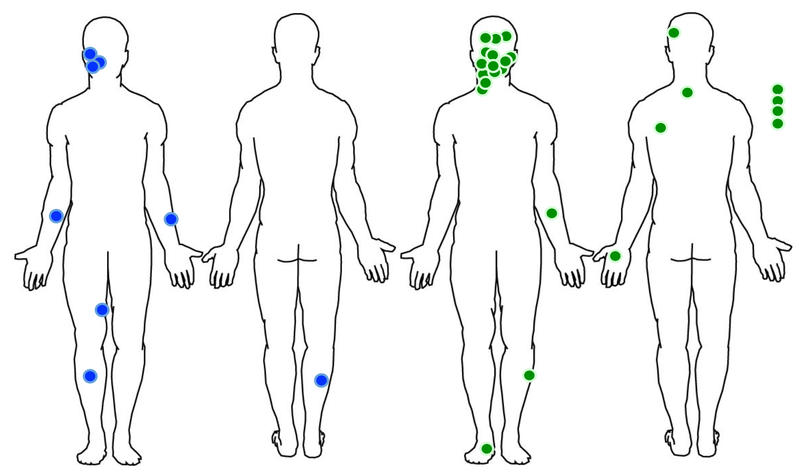
Methods: MCC patients were identified using the NETwork Registry which spans 1996-2012 for the Auckland region and 2008-2012 for New Zealand. 161 patients were identified in Auckland and archived formalin fixed paraffin embedded (FFPE) tissue blocks were recalled from the three DHBs and from private Anatomical Pathology Service who obtain the majority of primary skin biopsies. Where possible skin primary plus nodal and distant metastases were accessed. ~150 individuals have been identified with suitable tissue for analysis. FFPE tissues were reviewed as MCC, based on morphology and pathology records and regions of tumour and matched normal were extracted for DNA/RNA using macrodissection. Tumour and stromal cellularity were recorded for all cases. A bank of well-annotated tissues with DNA, RNA and slides has been collated for 80 individuals. These will be used for pathological review, immune cell staining and genomic analyses. Thirty-five MCC patients have been screened for Virus status using droplet digital PCR on DNA.

Who are the MCCs in NZ? (2008-2012)



What is the viral positivity rate in NZ? 8/35 (**22.9%**) individuals are positive for MCPyV with status retained in locoregional recurrences and distant metastases.

Where on the body do the primary NZ MCCs occur?



	MCPyV Positive n=8	MCPyV Negative n=27
Head and Neck	3 (37.5%)	17 (63.0%)
Upper Limb	2 (25.0%)	2 (7.4%)
Lower Limb	3 (37.5%)	2 (7.4%)
Torso	0 (0%)	2 (7.4%)
Unknown	0 (0%)	4 (14.8%)

Does MCC virus status correlate with clinical features?

	Positive (n=8) n, %	Negative (n=27) n, %	Total (n=35) n, %
AGE AT DIAGNOSIS (years)			
median	85	75	79
range	69-97	46-98	46-98
GENDER			
Male	3 (37.5)	18 (66.7)	21 (60.0)
Female	5 (62.5)	8 (29.6)	13 (37.1)
Unknown	0	1 (3.7)	1 (2.9)
STAGE AT DIAGNOSIS			
Primary Skin	7 (87.5)	14 (51.9)	21 (60.0)
Node	1 (12.5)	9 (33.3)	10 (28.6)
Distant metastasis	0 (0.0)	2 (7.4)	2 (5.7)
Unknown	0 (0.0)	2 (7.4)	2 (5.7)

Conclusions: New Zealand MCCs are dominated by the non-viral form. As such, we question whether current guidelines for management and diagnosis that have originated in Europe and USA are valid for use in Australasia. Virus screens point to an association of negative status in younger males with nodal and distant metastasis at diagnosis.

Future work:

1. Combine NZ virus screen data + clinical data with studies from Australia and Europe to increase the numbers for better understanding of whether the virus positive and negative cases differ with disease course.

2. Histological screen of primary tumours for identification of new prognostic features, particularly for virus negative cases such as vascular invasion and immune cell infiltrates.

3. Genomic analyses of NZ-MCCs to identify 'druggable' mutations for use of targeted systemic therapies.

References:
1. Feng *et al* 2008 PMID: 18202256, 2. Kassem *et al* 2008 PMID: 18593898, 3. Becker *et al* 2009 PMID: 18633441, 4. Garneski *et al* 2009 PMID: 18650846, 5. Wong *et al* 2015 PMID: 26627015