

New Zealand Merkel Cell Carcinomas present with body laterality ~~potentially~~ linked to sun exposure probably not

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Background/Objective

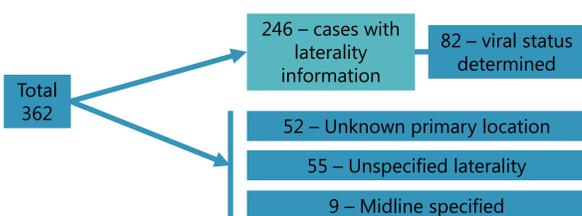
Merkel Cell Carcinoma (MCC) is an uncommon but very aggressive skin cancer, and NZ has one of the highest rates in the world. MCC is initiated by two etiologies; Merkel Cell Polyomavirus (MCPyV) which interferes with the Retinoblastoma Rb tumour suppressor, and a virus-negative (likely UV-mediated) form which show many oncogenic mutations and a UV-linked mutational signature.

Asymmetric lateral distribution (left-sidedness) has been found in MCCs in studies from the United States¹, Finland² and Germany³, with a hypothesis offered of unequally distributed UV exposure due to vehicle driving side. To our knowledge, this is the first study reporting on MCC laterality in Australasia, where there is a much higher proportion of MCCs with the UV-linked etiology.

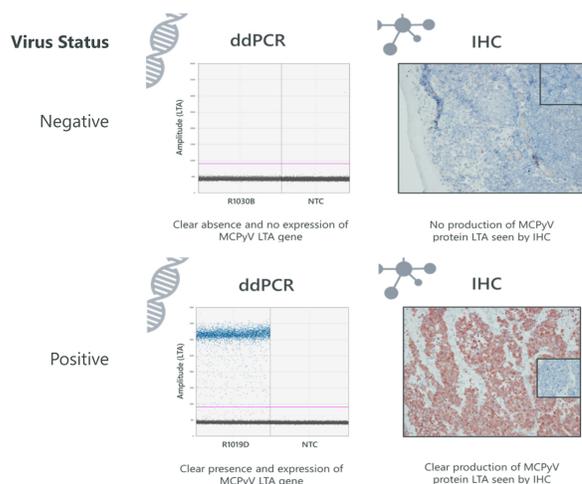
We aim to analyse the distribution of MCC primary tumours in a NZ cohort and test the hypothesis that UV-mediated virus negative tumours would asymmetrically present on the right side due to unequal UV exposure during driving.

Methods

This cohort was extracted from the NETwork! NZ neuroendocrine registry. 362 total cases were identified in NZ (diagnosed between 1994 and 2016). Laterality was established from the histopathology report, with clinical notes accessed for those cases in the Auckland region.



Virus status was determined using a multimodal method including droplet digital PCR for RNA and DNA and immunohistochemistry (IHC).⁴



Results

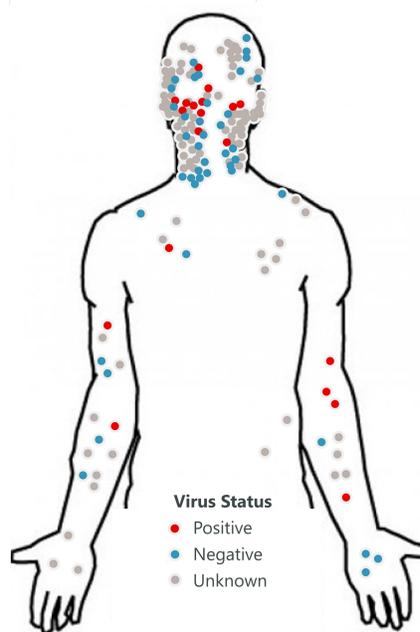
Tumour Location

MCC most commonly presents on the head and neck region, in both virus positive and virus negative tumours.

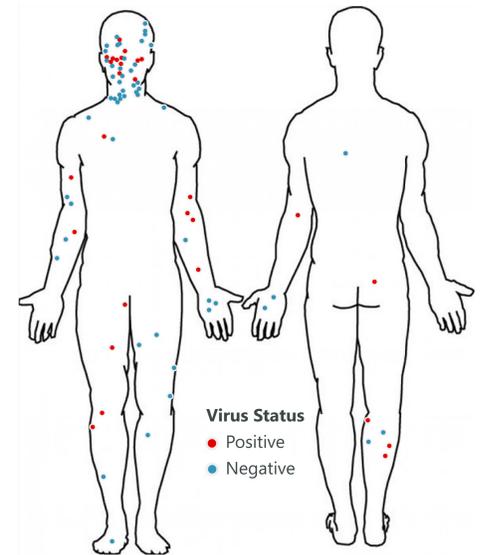


Laterality

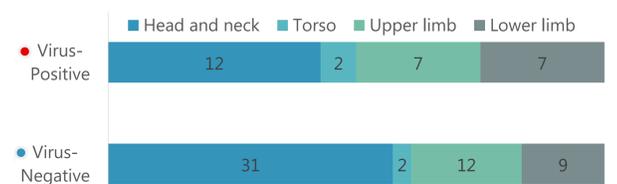
Right sided laterality is seen on the head and neck region and appears to be unaffected by viral status. Notably, right sided asymmetric presentation is not seen in the upper limb.



Virus Status	Head and Neck		Upper Limb	
	L	R	L	R
Positive	3	9	5	2
Negative	12	19	7	5
Unknown	38	44	12	14
Total	53	72	24	21



82 primary tumours with viral status assessed and laterality information.



Discussion

Despite observing right-sided laterality for head and neck primary tumours, other body regions did not appear to show this. Notably the right arm, which is expected to receive the highest asymmetric UV exposure while driving in NZ on the right side, did not show any convincing laterality. This is possibly due to a high ambulant and all year round UV exposure in NZ, during daily activities not limited to driving a vehicle. It could also be that the NZ climate allows for clothing that protects from UV-radiation, exposing the head and neck, but covering the arm. Another possibility is that this laterality is not due to UV radiation and may be attributed to some other unknown factor.

Perhaps the biggest limitation in this study is the small sample set for each body location, particularly when limiting the analysis to those tested for virus, making the ability to draw statistical conclusions difficult.

With right-sidedness seen in head and neck for virus positive in addition to virus negative (UV-linked), this introduces more hesitancy about the driving side hypothesis. It would be reasonable to expect that the UV-mediated form would be preferentially lateralised to the increased UV-exposure, when compared to the viral-mediated etiology. Although, recent studies suggest a potential influence of UV in viral-mediated tumorigenesis also, where perhaps a DNA-damaging event such as UV promotes linearization and integration of the viral genome into the host⁵.

Conclusions and Future Work

- Unequal distribution of MCCs is seen in the head and neck in NZ patients, presenting more often on the right side for both virus positive and negative tumours.
- Sidedness is not convincingly seen in other body regions analysed, including the upper limb, despite disproportionately increased UV exposure while driving.
- It therefore appears that vehicle driving in NZ is unlikely to influence the asymmetric presentation of MCC, possibly due to high daily ambulant UV exposure.
- Future work might include a broader study with other UV-linked skin cancers such as melanoma, BCC and SCC to assess laterality and support for right-sided head and neck data.

1. Paulson et al. (2011) PMID 21514002

2. Koljonen et al. (2013) PMID 22741742

3. Gambichler et al. (2017) PMID 27778198

4. Woodhouse et al. (2018) PMID 29928756

5. Colunga et al. (2018) PMID 29217527