Title: Trends in the incidence of Merkel Cell Carcinoma in Victoria, Australia between 1986-2016

Running title: Incidence of Merkel Cell Carcinoma

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Abstract

Background/Objectives: Merkel cell carcinoma (MCC) is a highly invasive cutaneous malignancy. The objective of this study was to investigate the incidence and trends of MCC in Victoria, Australia between 1986-2016.

Methods: Population-based, descriptive analysis of Victorian Cancer Registry (VCR) data. The de-identified records of patients with MCC were obtained from Victoria residents diagnosed between 1986 and 2016. Age-standardised incidents of MCC; trends were examined using joinpoint analysis.

Results: A total of 1,095 cases were found. Incidence of MCC was 3.9 per 100,000 for men and 1.5 per 100,000 for women. The incidence of MCC in men 66-85 is increasing the fastest at an annual rate of 4.2% (2.8-5.8%, 95% CI). However, since 2002 the incidence in women in the same age-group has been decreasing. While there is an overall stabilisation in the incidence of MCC, incidence of MCC for males is increasing. For MCC in males 85 years old and over incidence of MCC was 26.8 per 100,000 between 2012-2016. Relative five-year survival for patients diagnosed between 2008 and 2012 is 50%.

Conclusion: MCC remains an aggressive cancer, especially among older men. Differences in trends seen in local data can help target preventative and early intervention management strategies in specific groups.

Key words: Gender differences, Merkel cell carcinoma, incidences, Australia

Learning points: The incidence in Merkel cell carcinoma has increased in some groups in recent years, especially among older men. Incidence of Merkel cell carcinoma is increasing at the fastest rate in men aged between 66-85 whereas for women in the same age group has the rate decreased. Merkel cell carcinoma is an aggressive cancer and understanding trends in local data can help to target prevention and early intervention strategies.

Intro

Merkel cell carcinoma (MCC) is a primary cutaneous neuroendocrine carcinoma most often found in the head and neck region in older individuals.¹ MCC is frequently found in men.² They can often resemble basal and squamous cell carcinoma or amelanotic melanoma which means they can be clinically misdiagnosed. Risk factors include ultraviolet light exposure, advanced age and immunosuppression. The association between the polyomavirus and MCC has been established but its causative role is still unclear. However in populations with chronic ultraviolet light exposure as occurs in Australia, the causal role of the polyomavirus is thought to be less likely.^{3,4}

The incidence of MCC is increasing, although it varies with geographical location. In countries with increasing incidence of skin cancer in general, the incidence of MCC is seen to be the highest. Over a 20-30 year period, research suggests that there has been an increase mortality of MCC in the United States of 300% (correlated with the increased incidence).⁵ Of those with MCC receiving standard treatment regimens at that time, 30-40% will die from the disease.⁵ Clinical trials of immunotherapy for metastatic MCC are ongoing and have shown durable response in patients (discussed later). The rates of mortality from MCC is far higher than for those individuals diagnosed with melanoma.¹ Given the aggressive nature of the disease, understanding the trends and incidences of MCC could help improve detection at an earlier stage of the disease. This is important because diagnosis at earlier stages of the disease corresponded to improved overall survival.⁶

Methods

Data

We undertook a population-based, descriptive analysis of VCR data. The de-identified records of patients with MCC were obtained for Victoria residents diagnosed between 1986 and 2016, including deaths to end 2017. Data identifying MCC as the cause of death was only available from 2007 onwards. The Cancer Council Victoria approved for the release of and use of these data. Mid-year population estimates were obtained from the Australian Bureau of Statistics.⁷

Statistical analysis

Incidence rates were calculated on an annual basis and stratified by gender and age-group. Age-standardised incidences were calculated, standardising to the 2001 Australian Standard Population. Joinpoint analysis⁸ was used to assess the changes in MCC incidence. Joinpoint regressions evaluate changes in trends, meeting at “joinpoints”. In our analysis, models were constrained to have a minimum of four years between each joinpoint.

Survival was evaluated for the most recent five-year period which allows a complete five years of follow up. This comprised patients diagnosed between 2008 and 2012. Relative survival and MCC specific survivals were calculated along with age and gender specific expected survival was calculated with reference to the Australian population.⁹

Results

From the VCR between 1986 and 2016 there were 1,095 cases of MCC diagnosed, with 49% of these cases diagnosed in the last ten years. 59% of cases were in men and the median age at diagnosis was 79.5 years (Table 1).

In Victoria between 2012 and 2016 the average age-standardised incidence rate of MCC was 2.5 per 100,000 population (Figure 1). During the same period the incidence of MCC was 3.9 per 100,000 for men and 1.5 per 100,000 for women. The incidence of MCC in men 66-85 is increasing the fastest at an annual rate of 4.2% (2.8-5.8%, 95% CI) whereas the incidence in women in the same age-group has been decreasing since 2002, stabilising the overall incidence. The incidence of MCC in males 85 years old and over was 26.8 per 100,000 between 2012 and 2016 (Table 2). Since 2007, there have been 205 deaths in Victoria where MCC was identified as the cause (Table 1). In the deaths from MCC in patients diagnosed in 2007 or later, the median survival after diagnosis was eleven months.

Relative five-year survival for patients diagnosed between 2008 and 2012 was 50%, being negatively correlated with age (Table 3). Relative five-year survival was 83% for patients aged 46-65 and 23% for patients aged over 85 years. Survival curves decreases rapidly in the first two years before flattening (Figure 2). The survival of males aged 66-85 years declined more quickly than females over the fifth year resulting in the relative five-year survival being lower for males than females in this age group. A similar observation can be made for males and females aged 46-65 years, however there were too few female cases in this age-group to draw proper comparisons. MCC specific five-year survival rate was 56%.

Discussion

From international studies the incidence of MCC was 0.2 per 100,000 in Denmark,¹⁰ Finland and 0.3 per 100,000 population in Sweden 2012,¹¹ whereas it was 0.7 per 100,000 in United States in 2009.¹² Not only are these rates far less than studies reported in Australia, the incidence in Nordic countries remain stable. In contrast, the incidence of MCC in Australia was 0.8 per 100,000 in Western Australia (between 1993 and 2007)¹³ and in Queensland (between 2006 and 2010) it was 1.6 per 100,000 population.¹ Given the incidence of MCC in Victoria, Queensland and Western Australia, this research suggests that Australia has some of the highest rates of MCC in the world. Further, the rates of MCC were higher in men than women¹³ and the age of diagnosis tends to be >65 years of age. In Australia this difference in incidence between genders could represent differences in sun protective measures between these groups.¹⁴

The increase in incidence over time could also be attributed to improved cancer registration of patients with MCC and improved histological diagnosis with the use of immunohistochemistry. Another possible cause for the increasing global incidence of MCC could be the greater number of individuals being treated with immunosuppression for organ transplants, inflammatory diseases or human immunodeficiency virus.¹⁵

Some epidemiological similarities that have been noted between Melanoma and MCC.¹ Although there is a lower incidence of MCC than melanoma (46.0 per 100,000 population age standardise incidence of invasive melanoma in Victoria 2015) there are similar trends in increase in the older population and higher rates among men.¹⁶ As with other skin cancers like squamous cell carcinoma and melanoma, the link between UV radiation in the development of MCC is well noted.²

The rates on MCC were correlated with melanoma regardless of geographical latitude.¹⁷ A review of the incidence of MCC worldwide found that white males in Northern America have higher rates of MCC and melanoma the closer they lived to the equator. However, this study reported that these results were not evident in Northern American women or European countries studied. The UV index is generally higher in Queensland than Victoria and this could contribute to the differences in incidence seen between the two Australian states.^{18,19}

Besides chronic ultraviolet light exposure, the Merkel cell polyomavirus (human polyomavirus 5) is also thought to play a role in the formation MCC. The polyomavirus clonally integrates into the genome of cells which allows for virally induced transformation into MCC.² Primary infection by polyomavirus is common and has no signs or symptoms. A majority of people become seropositive (40-80%) at an early age.²⁰ Studies of Merkel cell polyomavirus rates in Australia varies from 23% to

70%.^{21, 22} Even with these high rates of infection, MCC is still rare. The influence of polyomavirus on survival is controversial and needs further investigation.²

The trends in the survival rates of Victorian patients with MCC are in line with those seen in other states of Australia (41-64%),¹³ Europe (59-64%)^{23, 24} and United States (54%).²⁵ An Australian study found the five year relative survival rate was 93% for melanoma²⁶ compared to 41% for MCC. This outcome could be attributed to the poorer health of patients with MCC with MCC having a worse stage-specific survival for localised and regional disease compared to melanoma.² In addition, this difference in comparative results could also attributed to the development of new therapies for melanoma that have seen the overall survival dramatically improved over the previous years.²⁷ Given the ongoing low survival rates for MCC, further work is being conducted to find agents that can optimise survival rates. Current studies of immunotherapy for the treatment of MCC have shown promise. MCC is thought to be an immunogenic cancer given the incidence in the immunosuppressed individual. Related studies have shown that MCC have the expression of PD-L1 on infiltrating macrophages and tumour cells, and PD-1 on infiltrating lymphocytes pointing to the possibility of drugs targeting these receptors.²⁸ Avelumab (PD-L1 monoclonal antibody) has shown a progression free survival at one year of 30% and an overall survival of 52% in patients with stage IV disease that have received one or more lines of chemotherapy in a phase 2 trial.²⁹ Pembrolizumab (PD-1 monoclonal antibody) has shown a progression free survival at two years of 48% and an overall survival of 68% in patients with stage IV disease who were treatment naïve in a phase 2 trial.³⁰ These studies highlight the growing role for immunotherapy in the treatment of MCC.

The locations of MCC were not recorded in the VCR during the time period observed. From other studies MCC tend to be on the face ears, scalp, head and neck and limbs in countries with high UV exposure whilst countries with less exposure have a high proportion of MCC on found on the trunk. A Queensland study found a rate of distant metastasis at diagnosis of 15%.¹ Other studies have found rates of 6-12%.² This highlights the need for early detection, as stage of disease is associated with prognosis.

A strength of this study is the larger sample size of patients from a population based cancer registry rather than a single institute series. Limitations of the study were that the stage, polyomavirus and immunosuppression status and site of lesions were not recorded in the registry. Further work to analyse the characterisation of immunosuppression status for patient to further assess trends and incidence in this population would be of benefit. The results from this study indicate that the incidence of MCC is increasing and in particular in the elderly population and with a male

predominance. Given the aggressive nature of MCC and ever increasing incidence, this is an important disease for clinicians to familiarise themselves with.

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Figure legends

Figure 1: Merkel cell carcinoma – Victoria 1986-2019, incidence trends. A: age standardised incidences for patients older than 45 years. B: Age group incidences. Trends fitted with joinpoint regression.

Figure 2: Merkel cell carcinoma – Victoria survival of patients diagnosed 2008-2012. A: Survival by sex. B: Survival by age-group and sex.

Tables

Table 1: Merkel cell carcinoma - Victoria 1986-2016

	Males	Females	Persons
Total cases (1986-2016)	649	446	1095
Age at diagnosis			
0-45	3 (0.5%)	6 (1.3%)	9 (0.8%)
46-65	115 (17.7%)	42 (9.4%)	157 (14.3%)
66-85	398 (61.3%)	271 (60.8%)	669 (61.1%)
85+	133 (20.5%)	127 (28.5%)	260 (23.7%)
Median age at diagnosis (yrs)	79	80	79
Total deaths (since 2007)	124	81	205
Age at death			
0-45	0 (0.0%)	0 (0.0%)	0 (0.0%)

46-65	8 (6.5%)	4 (4.9%)	12 (5.9%)
66-85	71 (57.3%)	40 (49.4%)	111 (54.1%)
85+	45 (36.3%)	37 (45.7%)	82 (40.0%)
Median age at death (yrs)	84	83	85

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Table 2: Merkel cell carcinoma - Victoria 1986-2016 incidences per 100,000 and annual percentage changes.

	Incidence	Cases	Incidence trend 1				Incidence trend 2			
	2012-16	2012-16	Period	APC	(95% C.I.)	P	Period	APC	(95% C.I.)	P
Persons										
Age-standardised (> 45yr)	2.5	308	86-'01	6.9	(3.8,10.5)	< 0.001	01-'16	0.3	(-1.8,2.4)	0.763
46-65	0.7	50	86-'16	3.3	(1.8,4.9)	< 0.001				
66-85	4.8	172	86-'01	7.9	(4.3,12.4)	< 0.001	01-'16	-0.7	(-3.1,1.8)	0.580
85+	17.3	86	86-'16	2.8	(2.0,3.7)	< 0.001				
Males										
Age-standardised (> 45yr)	3.9	207	86-'16	3.3	(2.2,4.5)	< 0.001				
46-65	1.0	35	86-'16	3.4	(1.8,5.1)	< 0.001				
66-85	7.5	125	86-'16	4.2	(2.8,5.8)	< 0.001				
85+	26.8	47	86-'16	0.6	(-0.8,1.9)	0.380				
Females										
Age-standardised (> 45yr)	1.5	101	86-'02	6.2	(2.8,10.0)	< 0.001	02-'16	-2.9	(-5.9,0.4)	0.082
46-65	0.4	15		1.9	(0.0,4.0)	0.049				
66-85	2.5	47	86-'03	5.8	(2.4,9.6)	0.002	03-'16	-6.1	(-10.2,-1.3)	0.014
85+	12.1	39		6.2	(2.8,10.0)	0.001				

APC – annual percentage change. Trends identified through joinpoint analysis. Age- standardised to the Australian standard 2001 population (over 45).

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Table 3: Merkel cell carcinoma - Victoria 5-year relative survival of patients diagnosed 2008-2012

	Count	5yr Relative Survival
Persons	223	50%
Age at diagnosis (yrs)		
46-65	30	83%
66-85	127	52%
85+	64	23%
Males	131	51%
Age at diagnosis (yrs)		
46-65	23	86%
66-85	81	46%
85+	27	22%
Females	92	49%
Age at diagnosis (yrs)		
46-65	7	74%
66-85	46	61%
85+	37	22%

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