



# Gender and immunosuppression impact Merkel Cell Carcinoma diagnosis and prognosis. A population based cohort study.



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## Introduction

Merkel cell carcinoma (MCC) is an aggressive cutaneous neuroendocrine skin cancer. While rare, MCC is increasing in incidence. It has a worse prognosis than malignant melanoma<sup>1</sup>, with more than one third of patients dying from metastatic disease. It is recognised that merkel cell polyoma virus (MCPyV) is implicated in many of these tumours, while others demonstrate signature ultraviolet radiation (UVR) mutations with a higher mutational burden. Recent data on survival suggests better outcomes for women than men diagnosed with MCC<sup>2</sup>. There is a marked increased risk of MCC in immunosuppressed individuals, with aggressive tumour behaviour, increased metastases and poorer disease specific survival<sup>3</sup>. This study examines epidemiological, clinical and outcome data for MCC within the Irish population, including organ transplant recipients (OTR) over a 20 year period.

## Methods:

All cases of MCC in Ireland are reported to the National Cancer Registry Ireland (NCRI). Cases of MCC between 1994 and 2014 were identified. Covariates of interest including age, anatomical location of MCC, period of diagnosis, deprivation status, risk of other keratinocyte skin cancers (KC) were examined relative to gender and compared in OTR with non-transplanted patients. The standardised incidence ratio (SIR) was calculated for MCC in transplant recipients as compared to the general population.

## Results:

In total 314 cases of MCC were identified between 1994 and 2014, with a female predominance (53.8%). The number of cases diagnosed between the first and second periods reviewed showed over a 100% increase for both genders. There was a particular increase in incidence for males in the most recent periods (figure 1). The average age at diagnosis was 77.6 years (males 75.1 years vs. females 79.7 years). Male patients were more likely to present under the age of 65 years (15.9% males vs. 7.1% females), while female patients were more likely to present over 80 years of age (57.4% females vs. 42.8% males). In total one male patient presented under the age of twenty.

Overall, the majority of MCC cases presented on the head and neck (54.1%). Males were more likely to present with MCC in this location (60.7% male vs. 48.5% females). A statistically significant difference was noted between genders in terms of anatomical location of MCC (p value <0.001) (figure 2). Forty percent of patients had a history of other KCs (73 males, 53 females). One hundred and six patients were alive at the censoring date (31/12/2014) (56 male, 50 female). One hundred patients died from MCC (31.8%). Of these, 46 were male and 54 were female. Of those who died from MCC, average survival time was 3.5 years (males 3.4 years, females 3.5 years).

Ten MCC cases were identified in OTR, all were male (9 renal transplant recipients, 1 heart transplant recipient). The number of MCC cases diagnosed in OTR more than doubled between the first and second periods examined. The standardised incidence ratio for MCC in OTR was 59.96. The average age at diagnosis in OTR was 65.1 years compared to 79.0 in the non-transplanted patients. The average time from transplantation to the development of MCC was 14.07 years. Seventy percent of MCC cases in OTR developed on the head and neck. All of the OTRs in this study also had been diagnosed with a KC, with 70% of OTR having had had 2 or more KCs. Seventy percent of OTR diagnosed with MCC died from this disease. Median survival for OTR who died from MCC was 0.14 years.

In the multivariate all-cause survival analysis OTR, older patients, and patients with MCC's on sites other than the head and neck, were all at greater risk of dying. In competing risks regression, gender was not significantly associated with the risk of dying from MCC, with females having a non-significantly higher hazard of dying from MCC. OTR and less deprived patients were at significantly increased risk of dying from MCC.

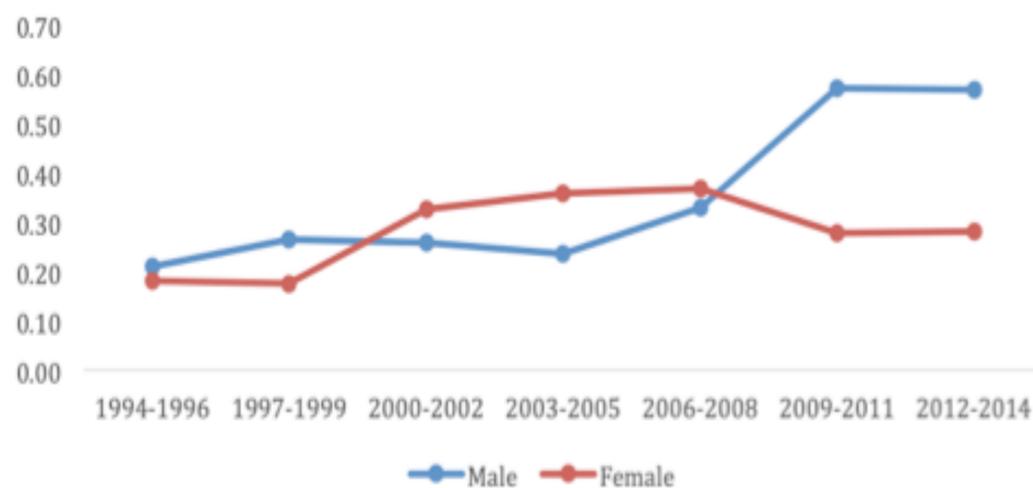


Figure 1. Incidence rate of MCC across genders over twenty year period, 1994-2004.

## Conclusions:

In this review females were shown to develop MCC at an older age, more frequently on sites less typically sun exposed, are less likely to have had prior keratinocyte cancers, and have a longer survival time than their male counterparts. This study suggests that there are a cohort of MCC patients who tend to be younger males, with MCC that is more likely to occur on the head and neck in association with a history of previous KCs. Further studies correlating MCPyV status and UV mutational load of tumours in these groups are required. We further demonstrate a significantly increased incidence of MCC in male OTR, with an earlier age at presentation, association with other KC and significantly reduced median survival.

This population based analysis provides epidemiological, clinical and outcome data for MCC over a twenty-year period, providing a comparison between genders, suggesting that while females had a reduced risk in all cause survival analysis compared to males, this difference was not significant. In cause specific analysis, females had a higher risk of dying from MCC, which was non significant. This, supports epidemiological trends around increasing MCC incidence but also identifies a number of gender related patterns that warrant further investigation.

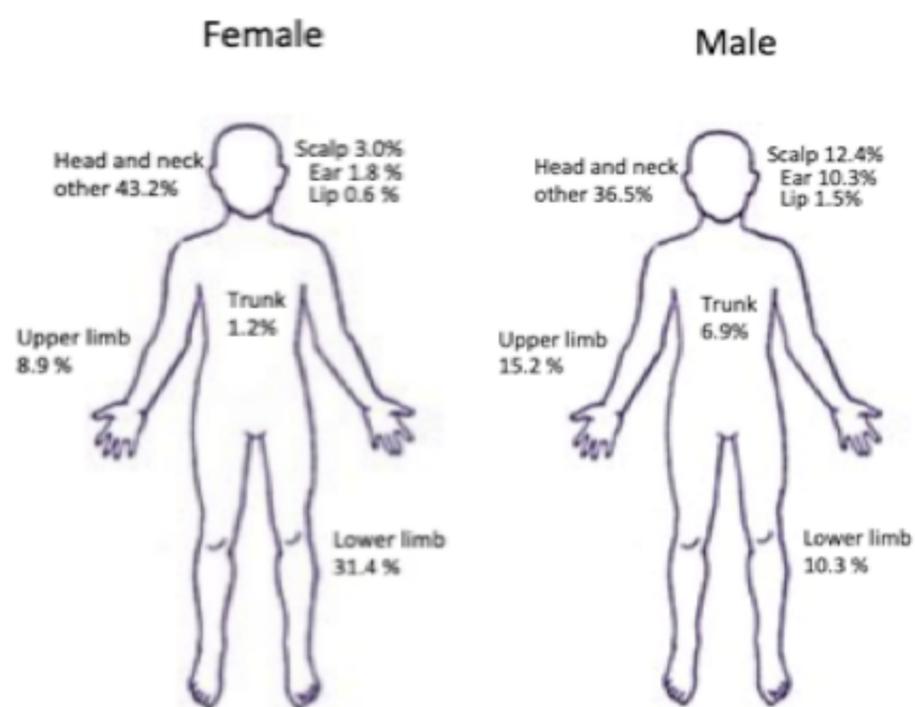


Figure 2. Variation in anatomical location of MCC by gender.

## References:

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