Characteristics and clinical outcomes of mucosal melanoma

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Appendices

Summary

Part I Mucosal melanoma

In Chapter 1 of this thesis, a comprehensive overview of the epidemiology, biology, treatment, and clinical outcomes of mucosal melanoma (MM) is provided. This rare tumour comprises 1.4% of all melanomas and has an incidence of 2.2 cases per million with approximately 850 new cases per year in Europe. MM arise from the mucosal lining of which the majority is located at the head and neck region, gastrointestinal tract, and female genital tract. The latter comprises 15-20% of all MM, explaining the higher incidence in females as compared to males. For local spread MM, wide local excision aiming for R0 resection is the primary treatment. For higher stages of disease, optimal treatment strategy is not well-established. Studies assessing the treatment strategy for nodal disease are limited and the reported outcomes of advanced MM treated with any type of systemic treatment are disappointing. Therefore, whilst MM is distinct from cutaneous melanoma, treatment for regional and distant spread MM follows the guidelines of its well-studied cutaneous counterpart.

In Chapter 2 we analyzed incidence and survival of MM over a thirty-year period (1990-2019) in the Netherlands. We emphasized on assessing trends in treatment and survival over time, by comparing the timeperiod 2014-2019 with all other years. The Dutch population was analysed using the nationwide population-based database registering all clinical, tumour and treatment characteristics together with survival of all newly diagnosed cases with cancer in the Netherlands. In this thirty-year period 1496 patients were diagnosed with MM and incidence over time remained stable. We confirmed the poor prognosis with 5-year overall survival (OS) of 24% and a median OS of 1.7 years. OS improved significantly when comparing patients diagnosed between 2014-2019 with all other years. We identified, diagnosis in 2014-2019, MM located at the female genital tract and primary treatment with immune- or targeted therapy as independent predictors for better survival and MM located at the respiratory tract, higher age, and higher stage at diagnosis as predictors for worse survival.

Next, Chapter 3 focusses on patients with advanced stage mucosal and cutaneous melanoma. Using data from the Dutch Melanoma Treatment Registry (DMTR), we investigated clinicopathological characteristics and survival of 120 MM and 2960 CM diagnosed between 2013-2017. In this cohort the median OS in advanced stage MM was lower than CM (8.7 months vs 14.5 months). Whilst OS improved for patients with CM when comparing those diagnosed between 2013-2014 with those diagnosed between 2015-2017, for MM survival did not improve when comparing the same time periods.

To take a closer look to the efficacy of immunotherapeutic agents in rare melanomas, in Chapter 4 we assessed 46 patients with MM and 13 patients with UM treated with combined

ipilimumab/nivolumab treatment. Approximately half of the patients had clinical benefit, but median OS was short. Moreover, as seen in CM, toxicity rates were high leading to discontinuation in most of the cases. The results of Chapter 3 and Chapter 4 demonstrate, that whilst immunotherapeutic agents have revolutionized the therapeutic landscape in CM, in MM, the efficacy is low and survival has not improved. This emphasizes the need for trials specifically focusing on novel (combination) of treatment strategies in MM.

Part II Vulvar melanoma

Part 2 of this thesis shifts toward an important subgroup of MM, those located at the vulva. Vulvar melanomas (VM) account for 60% of the female genital tract MM, which together with the head and neck region and the gastrointestinal tract are the most common locations of MM. Chapter 5 provides a general review including clinical characteristics, pathological characteristics, treatment, and survival of VM. This disease presents with an itching or bleeding pigmented lesion at the labia majora, labia minora or clitoris and is characterized by low survival rates and high recurrence rates. As in CM higher age, advanced Breslow stage and lymph node involvement are predictors for survival. Due to the anatomical challenging location in close relation to vital organs, local treatment of VM can be mutilating and affect quality of life. Unfortunately, as in MM, the efficacy of radiotherapy, chemotherapy, and immunotherapy are low, and the optimal management of regional and distant spread disease is still being investigated.

In Chapter 6 an international cohort of 198 VMM's was retrospectively analysed. Median age at diagnosis was 72 years, and most of the patients were symptomatic. Still, median time from symptoms to diagnosis was four months, which is partly ascribed to patient's delay. At presentation, 75.8% had had locally spread disease, 12% had regionally disease, 8% had distant spread disease and in 4% stage at presentation was unknown. However, pathological analysis demonstrated that more than half of the patients had a Breslow thickness > 4 mm (i.e. highest T stage). The aggressive course of VM was demonstrated by 2 and 5-year OS of respectively 48% and 31%. Moreover, recurrence occurred in two third of the patients of which the majority were regional or distant recurrences with a median time to recurrence of 11 months. We found that higher age and larger tumour diameter were independent predictors for survival. In conclusion, this study shows that even whilst the majority of the patients presents with early stage disease, recurrence rates are high and prognosis is poor.