

Treatment

The management of local disease, irrespective of location, consists of surgical resection, with complete resection providing the highest chance for cure. [9] Though based on retrospective small studies, the existing evidence in MM, does not support wider pathological or surgical margins to benefit OS or recurrence-free survival (RFS). [75] As more extensive surgery in an often challenging location, in close relation to vital organs, is mutilating and can negatively affect quality of life, further research on this topic is warranted. [76] Also, as the course of disease is aggressive with high risks of local or distant recurrence, (extensive) surgical procedures should be weighed carefully against these risks and complications of surgical intervention.

As there is a high rate of regional spread in MM, close follow-up of clinically negative nodes is required. Although the evidence is limited, sentinel node biopsy in locally confined VMM, HNMM, and anorectal MM may be valuable for identifying patients who might benefit from adjuvant treatment. [40, 77] Elective lymph node dissection is no part of standard treatment as there is no proven survival benefit and has high complication rates. [40, 78] In HNMM and anorectal MM adjuvant radiotherapy may improve local control and reduce the risk of local recurrences but does not prolong survival, in part because of the high rate of systemic relapses. [28, 79, 80] The treatment plan of locally advanced and unresectable MM should be individualized depending on age, involvement of adjacent tissue/organs, feasibility, and the patient's preference. Whilst evidence is still awaiting, neoadjuvant therapy is of interest in bulky MM, as it may reduce tumor load ensuing complete resection. [81] An investigational approach, in which immunotherapy is given in neoadjuvant setting, is of interest in MM. Those treated with neoadjuvant/adjuvant immunotherapy in a phase II trial including resectable stage III/IV melanoma, less often had disease progression or recurrence, when compared with those treated with adjuvant immunotherapy only. [82] Yet, in this trial only four patients with MM were included, all of them received the same treatment strategy and OS was not evaluated. Given the high recurrence rates and challenges associated with achieving tumour-free surgical margins, neoadjuvant immunotherapy presents itself as a viable option in MM treatment. Currently, clinical trials (NCT03313206 and NCT02519322) are ongoing, investigating the use of neoadjuvant immunotherapy in MM.

The optimal clinical management for patients with positive lymph node(s) has not been established. In HNMM, therapeutic lymph node debulking (LND) is thought to optimize regional control without improving OS. [26, 78, 83] Some advocate LND in VMM and anorectal MM, but most studies emphasize the high complication rate of LND in the groin without survival benefit. Therefore nodal treatment should be individualized and outcomes should be monitored. [77] Despite not prolonging survival, it may identify patients who are in need of intensified treatment. Radiotherapy of (bulky) lymph nodes only has a role in improving local control and complaints, but does not improve OS. [28, 77]

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For metastatic disease, guidelines are lacking, and therefore treatment choices are often made on case-by-case basis and relying on expert opinion. Radiotherapy can be offered as palliative treatment to relieve symptoms and improve quality of life, whilst chemotherapy is not part of treatment as response rate and duration are low and does not improve survival. [77] The overall response rate (ORR) of various chemotherapeutic agents in MM is slightly lower than in CM (0-20% vs 15-30%), but most importantly survival benefit in both CM and MM is very limited, whilst toxicity rates are high. [84-86] Hence, research focusses on novel systemic therapies, which, since the introduction in 2011, have drastically improved OS of advanced CM. [87] In particular the immune-checkpoint inhibitors (ICI) nivolumab, pembrolizumab and ipilimumab have revolutionized the therapeutic field in immunogenic cancers. These agents target CTLA-4 and PD-1 which are immune checkpoints located on activated T-cells, normally suppressing immune response against cancer cells. By blocking the CTLA-4 and PD-1 pathway, the suppression is released, and the cancer cells are recognized and attacked providing a boost in immune response. [88] In advanced CM, single agent ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) both have superior efficacy over chemotherapy. The combination of both yields even better ORR, though is accompanied with concomitant toxicity. [87] The Checkmate 238, a randomized phase 3 trial assessing adjuvant nivolumab vs ipilimumab in resected stage IIIB-C and stage IV melanoma reported that nivolumab is a more efficacious drug with a higher 4-year RFS respectively 41.2% vs 51.7%. [89] Similarly, the CheckMate 067 trial, demonstrated the benefit of ipilimumab, nivolumab and combined nivolumab/ipilimumab in advanced CM, with a median OS after 6.5 years of follow-up of 19.9, 36.9 and 72.1 months. [90]

In MM anti-CTLA-4 blockage has shown only a minor survival benefit, with an ORR of 0-17% and progression-free survival (PFS) of less than 5 months. [91] As in CM, anti-PD1 blockage and in greater degree the combination of anti-CTLA-4 and anti-PD1 blockage are more promising. A pooled analysis of six clinical trials report that in advanced MM, nivolumab and nivolumab combined with ipilimumab have an ORR of 23% and 37% and a median PFS of 3 and 6 months, respectively. [92] However, whilst only little comparative data is available, MM seems less immunogenic than CM with on average 30% lower ORR of combined anti-CTLA-4 and anti-PD-1. [91] Unfortunately, patients with rare types of melanoma as MM and uveal melanoma (UM) are often excluded from clinical trials, and therefore evidence is limited. Therefore, though having distinct clinical behaviour and a different genetic profile, treatment of metastatic MM follows the insights of CM.

Pathogenesis and tumour biology

Together with acral melanoma, Spitz melanoma, and a melanoma in a blue or congenital naevus, MM is classified as a distinct entity by the World Health Organization, all lacking a

relation with chronic sun damage. [19] MM arise from melanocytes which are specialized cells derived from neural crest cells, producing melanin. Melanin is pigment that gives our skin color but most importantly protects the DNA in the cell from UV light. [93] The purpose of melanocytes located at sun shielded locations as the vulva or anus or head and neck is not clear. It is hypothesized that cells may have migrated during neural crest migration. [94] In contrast to its cutaneous counterpart, which has a high mutational load caused by UV mutagenesis, MM has a lower mutational burden, endorsing that UV light exposure does not play a role in the pathogenesis of MM. [19] In CM the UV-induced BRAF mutation and the NRAS mutation is found in 35-50% and 43% of the patients, whilst in MM this is seen in respectively 6% and 8% of the cases. [93] However, MM harbour a KIT mutation and NF-1 mutation in 13% and 20% of the cases, both being infrequent in CM. [93]. Thus, as BRAF mutations are lacking in MM, the KIT mutation is the only mutation for which targeted therapy is available (Imatinib). Furthermore, in the era of immune and targeted therapy, studies in CM have demonstrated that a higher tumor mutational load is predictive for a better and more durable response to ICI. [95, 96] The low mutation rate in MM explains that this entity seems less immunogenic and highlights the need for translational research in this field. [97] Besides unraveling the genetic landscape, efforts are made to understand the pathogenic role of well-known carcinogenic factors as smoking and human papilloma virus. Although both are risk factors for squamous cell carcinoma of the vulva and head and neck, they have not been associated to MM. [98] Up to today, no hereditary genetic predispositions for MM have been identified.

Prognosis

Survival of patients with MM is poor, and regardless of stage of disease, is worse than CM (Table 1). [99] 5-year OS of patients with MM is only 27.6% compared with 76.3% in CM. [5] Also, MM has high recurrence rates and time to recurrence is relatively short. [100] Unlike CM, in which a 6.4% annual decline in mortality was seen between 2013 and 2017, survival rates for MM have not improved over the last decades. [101] The rapid decrease in mortality in CM is largely attributed to better preventive measures and early diagnosis, leading to a higher proportion of patients with localized disease and a lower Breslow thickness at diagnosis. [87] In contrast, MM is often diagnosed at an advanced stage and effective preventive measures do not exist. Moreover, the introduction of immune and targeted therapy has improved 5-year OS in advanced CM from less than 10% to 40-50%, which has lower efficacy in MM. [87] As MM is rare, and patients have only recently been included in trials, the effect of the novel systemic therapies on OS in MM is not well studied.

The knowledge gap in MM

Whilst research in CM has accelerated, the rarity of this tumour kept MM from being investigated at the same pace. Unfortunately, studies assessing incidence and survival covering the last decades are limited. While 20% of the patients with CM develop metastasis, this percentage is rigorously higher in patients with MM, highlighting the need for better treatment strategies for advanced MM. The evaluation of novel systemic treatment on survival of MM and research focusing on the pathogenesis and tumour environment are crucial to guide the way forward.

Thesis outline

The main aim of this thesis is to give an overview of clinical behavior, incidence, survival, and predictors of survival of rare melanomas of which mucosal melanoma (MM). Second, to analyze if survival has changed against the background of recently introduced immune and targeted therapies. In this thesis we highlight an important subgroup of MM, those located at the vulva, by presenting a full-spectrum overview of a large cohort of patients with vulvar melanoma (VM).

Using data from the nationwide cancer registry, we were able to accurately evaluate incidence and survival of MM over time in the Netherlands. The Dutch Melanoma Treatment Registry (DMTR) adds specific value by registering treatment data combined with survival and recurrence data. In light of the rapidly evolving treatment landscape this gives valuable data of fairly new treatment in a real-world setting.

In **part 1** we evaluate incidence and survival of mucosal melanoma in the Netherlands. [Chapter 2](#) gives an overview of MM over a thirty-year time period (1990-2019) in the Netherlands using data from the National Cancer Registry. Nationwide incidence rates, clinical characteristics, primary treatment strategies and survival for all stages of MM are analysed. Moreover, we evaluate if survival of MM has improved over the last decades.

The last two decades are marked by the introduction of immune- and targeted therapy, and population-based research has confirmed that the introduction of these therapies resulted in survival benefit for CM and therefore has changed perspectives for these patients dramatically. In [Chapter 3](#) data from the DMTR is used to investigate the survival benefit of MM treated with immune and targeted therapy as compared to with those who received no treatment or conventional therapies. Furthermore, we analysed if survival of MM has improved as much as CM over the same time period. [Chapter 4](#) includes data from the same DMTR database in which we assess the response and toxicity rates of patients with MM and UM treated with the combination of ipilimumab and nivolumab.

In **part 2** we take a detailed look at a subgroup of MM, located at the vulva. Due to the low numbers evidence is limited and there are no guidelines comprising the management of this disease. Chapter 5, presents a comprehensive overview of the literature, discussing the clinicopathological and genetic characteristics of VM. Furthermore, we evaluated the predictive value of these factors in terms of survival and recurrence. As a translation to the clinical practice, we established a flowchart including the diagnostic process and therapeutic strategies that can be used in clinical management. In Chapter 6 we describe a large international retrospective cohort of VM's and assess the clinicopathological characteristics, mutation status and treatment of 198 cases. In addition, recurrence rates, survival curves and prognostic factors of survival and recurrence are presented.

In the general discussion in **part 3** a summary of this thesis is given and implications for future research are discussed.

Table 3. Seventh edition of the AJCC staging (2009) for cutaneous melanoma [66]

T category	Thickness	Ulceration status/ mitoses	
T0: No evidence of primary tumour	Not applicable	Not applicable	
Tis (melanoma in situ)	Not applicable	Not applicable	
T1	≤1.0 mm	a: without ulceration and mitosis < 1/mm ² b: with ulceration or mitosis > 1/mm ²	
T2	>1.0–2.0 mm	a: without ulceration and mitosis < 1/mm ² b: with ulceration or mitosis > 1/mm ²	
T3	>2.0–4.0 mm	a: without ulceration and mitosis < 1/mm ² b: with ulceration or mitosis > 1/mm ²	
T4	>4.0 mm	a: without ulceration and mitosis < 1/mm ² b: with ulceration or mitosis > 1/mm ²	
N category	Number of metastatic nodes	Nodal metastatic burden	
N0	No regional metastases detected	No	
N1	One tumour-involved node	a: micrometastasis b: macrometastasis	
N2	Two or three tumour-involved nodes	a: micrometastasis b: macrometastasis c: in transit or satellite metastasis without metastatic nodes.	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)	No	
N2b	Two or three, at least one of which was clinically detected	No	
N2c	One clinically occult or clinically detected	Yes	
N3	Four or more tumour-involved nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes		
M category	Anatomic site	LDH level	
M0	No evidence of distant metastasis	Not applicable	
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not elevated	
M1b	Distant metastasis to lung	Not elevated	
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not elevated	
M1d	Any distant metastasis	Elevated	
Stage	Primary tumour (T)	Lymph node (N)	Metastases (M)
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0

Table 3. (Continued.)

Stage	Primary tumour (T)	Lymph node (N)	Metastases (M)
IIC	T4b	N0	M0
IIIA	T1- 4a	N1a	M0
	T1- 4a	N2a	M0
IIIB	T1- 4b	N1a	M0
	T1- 4b	N2a	M0
	T1- 4a	N1b	M0
	T1- 4a	N2b	M0
	T1- 4a	N2c	M0
IIIC	T1- 4b	N1b	M0
	T1- 4b	N2b	M0
	T1- 4b	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

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