Characteristics and clinical outcomes of mucosal melanoma

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General introduction and outline of this thesis

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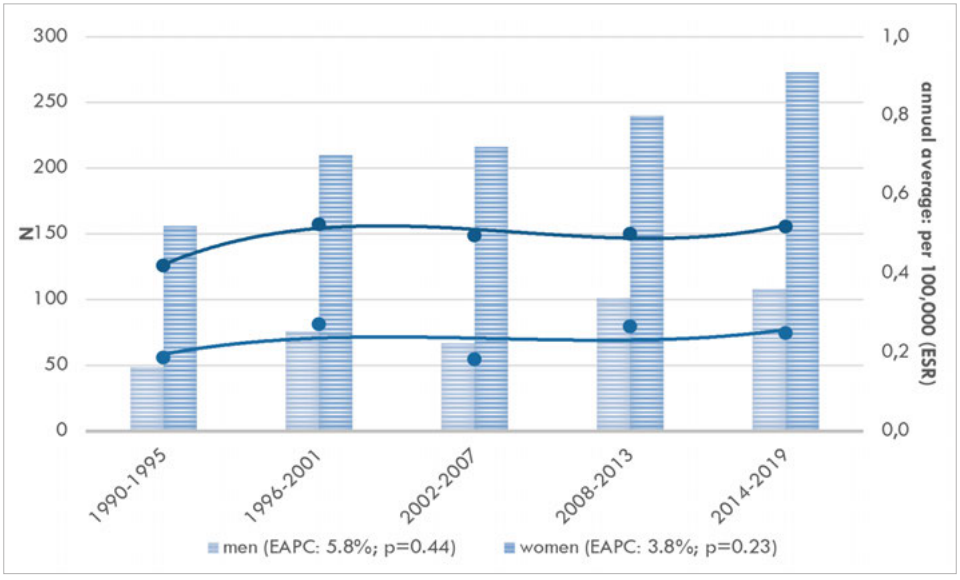
Mucosal melanoma and uveal melanoma: rare types of melanoma

Mucosal melanoma (MM) is a rare type of tumour that arises from melanocytes located in the mucosal lining. [1] MM represents 1.4% of all melanomas and has an age-adjusted incidence of 2.2 cases per million, which remained stable over time (Figure 1). [2-6] The RARECARE network, a large collaboration between population-based cancer registries across Europe, estimated approximately 850 new cases per year in Europe. [7] In the Netherlands, 1496 patients were diagnosed with MM between 1990-2019, corresponding with an age adjusted incidence of 3.5 cases per million. [8]

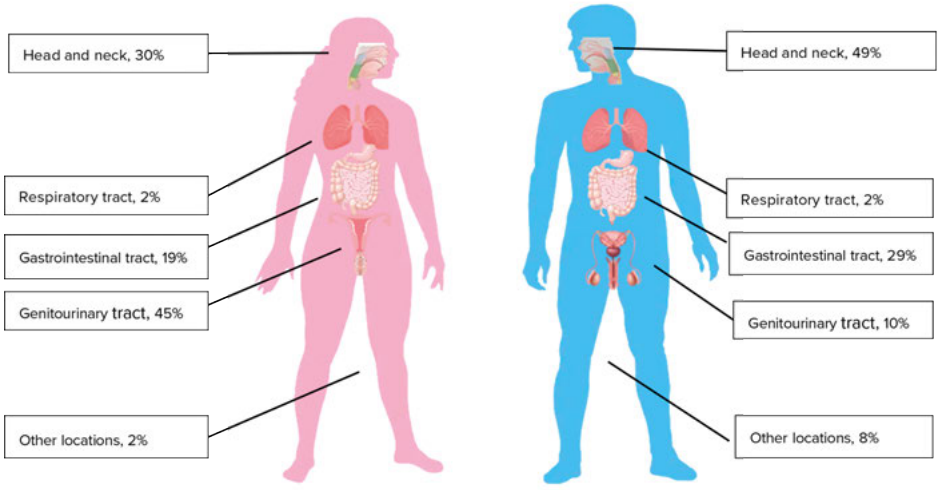
Figure 1. Crude numbers (bars, left axis) and annual averaged, age-adjusted incidence rates (line, right axis) for patients with mucosal melanoma by sex in the Netherlands.



MM is more common in females than in males, with an incidence of 2.8 cases per million and 1.5 cases per million, respectively. Among females, the genitourinary tract and head and neck region are the most commonly affected sites, whereas in males, MM is predominantly seen in the gastrointestinal tract and head and neck region (Figure 2, Table 1). [9, 10] The higher incidence in females can be attributed by the high percentage of MM located in the female genital tract, particularly the vulva and vagina. [2, 9, 11] Similar to cutaneous melanoma (CM), MM exhibits a large geographic and racial variation, but in contrast with CM has a higher prevalence in non-Caucasians. [12, 13] In particular, the Asian population has a higher proportion of melanomas located in the mucosal lining (23-38%) compared

to the Caucasian population (<1%). [2, 13, 14] Whilst in CM, geographical differences are related to the amount of UV-radiation exposure and type of skin-color, the rationale of the geographic and racial differences in MM is not clear. [13] Unfortunately, due to a low number of population-based studies, the epidemiology of this disease is poorly understood.

Figure 2. Distribution of mucosal melanoma in men and women



This figure is based on six population-based studies ([2, 6, 9, 15-17]) Other locations consists of MM located at the gallbladder, prostate, brain, spinal cord

Like MM, uveal melanoma (UM) is a rare subgroup of melanoma which develops from the iris, ciliary body, or choroid of the eye. The incidence of UM is 4.4 cases per million in Europe and comprises 3-5% of all melanomas. [7, 18, 19] Despite their common origin, both MM, UM and CM display extreme differences in their biological behavior. [20] Whilst, in all, metastatic disease is the leading cause of mortality, the metastatic pattern is distinct. Disease spreads hematogenously in UM, resulting in metastasis in the liver in 90-95% of the cases, whilst in CM disease spreads lymphatically, thus metastasis are seen in the lungs, brain, lymph nodes and soft tissue. [20, 21] In MM the metastatic pattern is not fully understood and large variations exist between anatomical locations. [22] Moreover, the rapid disease progression and concomitantly poor prognosis of UM, together with the comparable lower efficacy of immunotherapy as compared to CM, has resulted in a liver-directed treatment approach in metastatic UM. [20]

Table 1. Overview of clinical characteristics and survival and recurrence rates in total and in subgroups of mucosal melanoma.

	Proportion of total (%)	Median age at diagnosis (years)	Gender (%) Male	Female	2-year OS (%)	5-year OS (%)	Median OS (months)	Recurrence rate (%)
Total [1, 8, 15, 23, 24]	-	55-72	44	56	44.4	14-27.6	**11**	**83**
Tumour site								
Head and neck [25-32]	50-60	64	50-54	42-50	64	20-44	54	81
Oral [1, 25, 28, 29, 33]	20-24	58	55	45	55.7	28, 33.1-45	24	41
Sinonasal [5, 29, 32, 34-37]	14.5	60/70	44	56	45	21, 23-43	21	50-70
Larynx [38, 39]	4-15	59.7	77.3	20.5	46	12	-	88
Anorectal tract [8, 40-43]	24	62-75	61	39	30.2	7-17	8-19/17	65
Rectum [8, 42-44]	39.7	67	22-39 [1]	61-78	23.5	18	16-22	70
Anus [8, 42, 43]	60.3	61	39	61	38.4	11	27	59
Upper gastrointestinal tract [5, 15, 45, 46]	5/6.7-12	53	56	44	-	21	34	-
Female genital tract [8, 40, 47-51]	15-20/18	66	0	100	50-57	27.8	24	56
Vulva [8, 40, 47, 49]	68-75	62	0	100	0-63	45	45	38, 42-70
Vagina [8, 40, 49-51]	5-25/ 19	73	0	100	26.1	13-32	11-17	-
Urinary tract [8, 15, 45, 52]	3-5	57-63	32	68	63	31	25-34	71-92

This table consists of studies including a minimum of ten patients. OS: Overall survival

Clinical presentation and subtypes of mucosal melanoma

MM typically presents in the seventh decade of life, though also younger cases, particularly in the head and neck region and female genital tract, have been reported. [9, 53] As this disease is heterogenous with various primary locations, clinical presentation is diverse. Regardless of the primary location, common symptoms are a painful or itching sensation and (oral, nasal, vaginal or rectal) bleeding. [54] MM located at more visible locations, such as the vulva, vagina, penis and some sublocations of the head and neck region, may present with a brown, black or blue lesion which changes over time. However, approximately 40% of the MM are amelanotic which make them difficult to identify and hard to distinguish from benign or premalignant lesions. [55] The lack of visibility and late or aspecific symptoms result in a substantial delay in diagnosis, with patients being diagnosed at an advanced stage in approximately 40-60% of the cases. [40, 45, 56] Yet, even in patients who present with local disease, the course of disease is aggressive with eventually 79% developing regional or distant metastasis, of which many in the first year. [40, 57]

Most common are head and neck mucosal melanoma (HNMM), which predominantly arise from the sinonasal and oral cavity, and less frequently are located in the pharynx or larynx (Figure 20). [28] The vast majority of all HNMM (90-95%), do not have distant metastasis at presentation, leading to a better prognosis compared to other locations. [26, 27] Yet, oral MM still have a high risk of nodal involvement (25-43%) as compared to sinonasal MM (<10%). [27] Within the HNMM, patients generally are diagnosed at a younger age which may be attributed to the more visible and accessible location, leading to earlier detection. [27] The female genital tract is the second most prevalent location of MM, of which the vulva comprises three quarter of the cases. [58] Unlike other locations, the vulva consists of both hairy (cutaneous) skin which gradually transitions to glabrous (mucosal) skin. Due to the fact that melanoma can develop from both cutaneous and mucosal skin in the vulvar region, determining the origin of the melanoma can be challenging. [59] Like many other vulvar or vaginal issues, reluctance to get gynecological examination can often lead to a delay in seeking medical attention, leading to a more advanced disease at diagnosis. The third largest group of MM is found in the anorectal region. Like in the female genital tract, metastasized disease is common in patients with anorectal MM, resulting in lower 5-year OS rates of 47%. [60, 61]

Staging

Although various staging systems have been proposed, a universal staging system for MM does not exist (Table 2). The challenge in developing a staging system suitable for all locations lies in the heterogenous course of disease, the pathological differences and

surgical considerations which heavily depend of the site-specific anatomy. [62] Additionally, the low number of patients make it difficult to validate staging systems. The Ballantyne staging system was introduced in 1970 to stage HNMM, classifying patients based on the extent of the disease as local, regional, or distant spread (Table 2). [63] The American Joint Committee of Cancer (AJCC) developed a staging system including depth of invasion (i.e. TNM classification), which proved to be more predictive for survival in HNMM than the Ballantyne staging system (Table 2 and 3). [28, 64] In 2009, the AJCC updated the staging system for MM by removing T1 and T2 but keeping T3 and T4 as categories for tumour invasion, resulting in at least AJCC stage III disease, indicating the aggressiveness of MM (Table 2). [65] For other locations than the head and neck, there is no site-specific staging system. The AJCC staging system for CM is proven to predict OS in anorectal and vulvar MM and therefore is commonly used in clinical practice (Table 2). [45, 61]

Table 2. Staging systems for head and neck, female genital and anorectal melanoma [67]

	Staging system	Important characteristics of the current staging system	Previously proposed staging system(s)
Vulvar MM			
	AJCC for CM [66]	See Table 3 for the entire staging system.	Macrostaging: FIGO staging [67] Microstaging: Clark [68], Breslow[69], Chung staging [70]
Vaginal MM			
	Ballentyne staging system for head and neck MM (I/II/III) [63]	Stage I Local disease Stage II Regional disease Stage III Distant metastasis	
Head and Neck MM			
	AJCC MM head and neck [71]	T3: Epithelium/submucosa T4a: Deep soft tissue, bone, overlying skin T4b: Brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, mediastinal structures, cartilage, skeletal muscle, bone	Ballentyne [63], Modified Prasad/Ballantyne staging [72], Thompson staging [73]
Anorectal MM			
	Adapted AJCC for CM [66, 74]	T1 Thin (≤ 1 mm) T2 Intermediate (2-4 mm) T3 Thick (>4 mm)	
	Ballentyne staging system for head and neck MM [63]	Stage I Local disease Stage II Regional disease Stage III Distant metastasis	

MM: Mucosal melanoma, CM: Cutaneous melanoma, FIGO: The International Federation of Gynecology and Obstetrics, AJCC: The American Joint Committee on Cancer, T stage: the T describes the extent of the primary tumour.

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]

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 hereditable 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 asses 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 T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 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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