# Introduction and Outline of this Thesis

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## Introduction

### *Epidemiology*

Melanoma, while responsible for a minority of all new skin cancers, is certainly the most lethal, accounting for 90% of skin cancer associated deaths[1]. Incidence of this deadly disease has risen in the past decades, both on a global level[2, 3] , and on a national level[4, 5]. In the Netherlands, the number of newly diagnosed melanomas increased from 2,593 in 2005 to 5,926 in 2015[6], and the number of melanoma related deaths increased from 624 to 826 in the same time span. Globally, 230,000 melanomas were diagnosed and 55,489 melanoma related deaths occurred in 2012 [7, 8]. Melanoma incidence and mortality world adjusted standardized rates (WSR) in the Netherlands were the second highest of Western Europe[8]: in 2014 national incidence was 20.6/100,000 WSR, and mortality was 2.5/100,000 WSR[4].

Several attributable factors have been identified such as ultraviolet (UV) radiation and increased sun exposure in fair skin phenotypes, and a history of sunburn (as a child)[9], but still much is unknown about the development and progression of cutaneous melanoma, as not all melanomas are UV-radiation induced[10]. Classification systems have been brought into life to aid in stratifying patients according to their prognosis: which is currently accurately defined in the TNM melanoma staging system by the American Joint Committee on Cancer (AJCC) [11].

### *(History of) Nodal Staging*

For melanomas with a Breslow thickness of >1mm (or <1mm but presence of high risk features such as ulceration, high level of Clark invasion or a high mitotic rate), the risk of nodal metastases is substantial, warranting adequate nodal staging[1, 11-13]. Nodal status is one of the most powerful prognostic factors for primary melanomas with clinically negative nodes[11, 14]. Determination of nodal status is ideally performed based on histopathological proof of melanoma metastases in lymph node tissue, as physical examination and imaging techniques alone are not accurate enough[15-17]. Traditionally, elective lymph node dissections were carried out in order to determine nodal status, acquire adequate locoregional control, and potentially improve survival[3, 18]. While in theory a promising method, trial results turned out to be negative; there was absolutely no survival benefit for patients undergoing elective lymph node dissection compared to patients who received nodal observation only, albeit that some studies suggested benefits for subgroups[19-24]. Meanwhile, the morbidity of an elective lymph node dissection was substantial, consisting of prolonged wound infections, seroma and development of chronic lymph edema. As only around 20% of all patients undergoing elective lymph node dissection have positive nodes, a more elegant way was sought to identify these patients with poor prognosis. This led to the introduction of the lymphatic mapping

technique for sentinel node biopsy by Morton et al[25]. In short, this technique consists of preoperative lymphoscintigraphy with Tc99-colloid, dermal injection of patent blue around the melanoma scar, and perioperative use of a handheld gamma-probe Geiger teller to localize the sentinel node(s)[25, 26]. The concept of the sentinel node was based on the hypothesis that melanoma cells spread from the primary tumor site to the sentinel node prior to reaching adjacent lymph nodes in the same regional lymph node basin. In case of lymphatic metastasis the sentinel node will be affected first, acting as a barrier. If the sentinel node is negative, adjacent lymph nodes are unlikely to be affected[25, 27-29].

### *SNB and CLND*

Since then, it has proven its staging value unequivocally[11, 30, 31], but its therapeutic value is still under debate. To date no prospective trial has demonstrated evidence of a clear survival benefit due to sentinel node biopsy. The largest international multicenter clinical randomized trial investigating wide local excision and sentinel node biopsy versus wide local excision and nodal observation, the MSLT1, did not show a difference in melanoma specific (MSS) survival, primary endpoint of the trial for all included patients[30]. These results support the alternative hypothesis that melanoma spreads simultaneously to lymph nodes and distant sites, rendering the sentinel node as an indicator of metastatic spread instead of a barrier.

Ideally, nodal status is to be determined in a non-invasive manner, especially when regarding the lack of evidence proving a therapeutic effect. Ultrasound of clinically non-suspicious lymph node regions is a procedure which has been investigated extensively, and while proven to be effective in reducing the number of SNBs for breast cancer[32], results for melanoma remain variable at best[16, 33, 34]. Voit et al. showed that in highly dedicated hands a fair sensitivity and specificity could be reached[35, 36], but these results remain to be reproduced in a multicenter setting.

Since the therapeutic value of SNB remains to be proven, any additional value of completion lymphadenectomy is likely to be limited. While results of the MSLT 2 trial[37] randomizing between CLND and nodal observation only after a positive SN are to be awaited, the DeCOG trial by Leiter et al. with a similar trial design, did not show any distant metastasis free survival difference at 3-years follow-up[38]. Full accrual was not reached due to a lower than expected inclusion rate, and the majority of patients had a small SN tumor burden, but the fact that there was absolutely no difference in survival renders the hypothesis that CLND is therapeutic more unlikely.

Then why perform a SNB and CLND at all? To date, the SNB remains the most powerful nodal staging tool for melanoma, which is highly valuable in informing patients and their treating physicians on prognosis[11, 30].

After decades of conducting randomized clinical trials, effective immunotherapies such as ipilimumab (CTLA4 inhibitor)[39-41] and nivolumab/pembrolizumab (anti-PD1)[42-44]

finally have become a game changer for advanced melanoma (i.e. irresectable stage III and stage IV patients). Their efficacy in prolonging recurrence free survival and potentially even melanoma specific survival is shown) [39-41, 43-45]. This is of great value to stage III patients too; as these therapies have the potential to be effective in adjuvant setting as well[46]. Past adjuvant trials mainly were negative; for instance the EORTC 18991 trial with (peg-) interferon-alpha versus placebo, which only showed a potential reduced hazard ratio for ulcerated primaries[47] and the Sunbelt Melanoma Trial with high-dose interferon alpha-2b with no survival differences[48]. Primary results from the EORTC 18071 (adjuvant ipilimumab versus placebo) trial[49] are promising, showing 11% overall survival benefit for patients treated with ipilimumab at a dose of 10mg/kg, and also a reduced hazard ratio for recurrence free survival, in particular for microscopic stage III (i.e. SN positive patients)[50]. This has put adjuvant melanoma treatment into a whole new perspective. Since trials like these require adequate nodal staging with SNB and CLND in case of a positive SN as a major inclusion criterion [49, 51], SNB and CLND remain worthwhile for now.

***Therapeutic LND***

Clinically evident lymph node metastases require a whole different approach, as regional control and quality of life become equally important to staging. Regional control is often best reached with radical surgery, but the extent of surgery is not always well defined. Lymph node dissections in the groin area are of particular interest with regards to this aspect; as these are typically divided into superficial (inguinal + femoral lymph nodes) and combined superficial and deep (deep inguinal, iliac, obturator lymph nodes) dissections[52]. There is clear evidence that pelvic lymph node metastases (iliac or obturator level) are associated with poor survival[53-56]. As a groin dissection is a morbid procedure, associated with wound infections and development of chronic lymph edema[57-59], proper patient selection is necessary. Historic cohorts show contradicting results on the potential association between extent of surgery and survival [53, 60-62]. One of the possible options to minimize the number of patients whom undergo a combined groin dissection and have negative pelvic nodes is to follow a two-step approach. Identification of patients with a low suspicion of pelvic lymphadenopathy based on preoperative CT- or PET-CT imaging, may prevent these patients from undergoing iliac lymphadenectomy if the pathology results of a superficial groin dissection are in line with these findings. While this approach does not diminish the number of patients at risk for morbidity to zero, this may reduce the number of negative pelvic dissections.

Ultimately, as is the case for patients undergoing CLND, therapeutic lymph node dissections may be reserved as a final resource in case of failed adjuvant therapy. In short, now is the time to reassess the need for an aggressive surgical approach, and perhaps to start to convince ourselves that "less is more".

## Outline of This Thesis

### *Part I – Nodal Staging*

Part I of this thesis investigates whether nodal staging of the clinically node negative melanoma patient can be performed using less invasive alternatives, and whether the indication for nodal staging in thin melanomas is justified. In **Chapter 2** the national thin (pT1) melanoma population is examined according to substaging: both the 6th AJCC staging edition and the 7th edition to see whether "high risk" thin melanomas are identified and stratified more accurately. Secondly the effects of the implementation of the 2nd version of the Dutch Melanoma Guideline are visualized including the recommendation to consider a sentinel node biopsy (and thus nodal staging) for pT1b melanomas. In **Chapter 3** ultrasound morphology criteria of the sentinel node, more specific the "echo free island", are discussed, developed to improve accuracy of ultrasound and fine needle aspiration cytology (FNCAC) techniques in clinically node negative melanomas. The "echo free island" may serve as an early sign of micrometastasis in the sentinel node, which should raise suspicion in the ultrasonographist. In **Chapter 4** the long-term results of ultrasound and FNAC of the sentinel node are presented. The Berlin ultrasound morphology criteria, primarily designed to assess the sentinel node for presence of micrometastases, warranting FNAC for confirmation, might be of prognostic value. **Chapter 5** gives an overview of the current evidence on ultrasound of the sentinel node in melanoma, presents the results of a pilot study and presents the study protocol of the GULF trial; Gamma probe and ultrasound guided FNAC of the sentinel node, designed as a potential minimally invasive alternative for the surgical sentinel node biopsy.

Alteration of the staging techniques is one way to minimalize morbidity; another is to reassess the indication for nodal staging.

### *Part II – Timing of Surgery*

Part II focuses on the timing of nodal staging. Time is of the essence in current oncology practice, but the maximum referral times and wait-list times posed by national melanoma guidelines are not based on solid evidence. In a highly stressed referral system, a delicate balance between urgent referrals and minimization of long wait-lists is needed, as otherwise the value of a true high urgency referral is lost, which potentially negatively affects prognosis of patients who do need treatment as soon as possible. In **Chapter 6** the timing of sentinel node biopsy is investigated in sentinel node positive patients, as they are most likely to benefit from early removal of positive lymph nodes. **Chapter 7** includes both sentinel node positive and negative patients, as timing of sentinel node biopsy may affect the sentinel node positivity rate as well as survival outcome. In **Chapter 8** the timing of completion lymphadenectomy is investigated, as removal of any ad-

ditional positive lymph nodes may potentially be the last therapeutic procedure. Should it be performed within a certain amount of time? Is there a window of opportunity?

***Part III – Extent of Groin Dissections***

The final part of this thesis focuses on the extent of surgery, in particular the extent of groin lymph node dissection. There is clear evidence that presence of pelvic lymph node metastases (iliac or obturator level) is associated with poor survival. By correctly identifying these patients prior to iliac lymphadenectomy, which is a morbid procedure, patients without pelvic lymph node metastases can be spared the pelvic part of a groin dissection. **Chapter 9** presents a possible two-step approach for melanoma patients with palpable groin metastases and no suspicious preoperative imaging (CT or PET/CT) who are scheduled for superficial groin dissection (inguinal lymph nodes only) or combined superficial and deep groin dissection (inguinal and iliac lymph nodes).

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# Part I – Nodal Staging