Summary

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This thesis aims to give insight in the current approach to nodal staging of melanoma patients in the light of continuing lack of evidence of a therapeutic effect from the sentinel node biopsy (SNB). This includes reassessment of guideline recommendations on SNB regarding thin melanomas, a subgroup at low risk of nodal involvement; and discussion of potential minimally invasive alternatives for the SNB, including a prospective trial protocol (**part I**). Current practice regarding the timing of elective nodal staging surgery is evaluated in the light of a stressed referral system and lack of evidence for a highly urgent approach (**part II**); and finally a two-step approach to therapeutic groin dissections is presented in order to minimize the number of patients who will undergo extensive groin lymph node dissection without having pelvic nodal metastases (**part III**).

Part I – Nodal Staging

In **Chapter 2** the effects of implementation of the Dutch Melanoma Guideline 2.0 on nodal staging of thin melanomas were investigated, with in particular the new recommendation to consider SNB for high risk thin melanomas, namely pT1B melanomas. For this study all newly diagnosed thin (pT1) melanomas between 2003 and 2014 were selected from the Netherlands Cancer Registry, in total this concerned near 30,000 patients. Main findings were that next to a general increase in pT1 melanomas, introduction of the mitotic rate criterion for pT1b substaging and the recommendation to perform SNB for pT1b melanoma has led to a proportional increase in pT1b melanomas, and an increase in performed SNBs. Sentinel node (SN) positivity rate has not increased and survival remained stable for pT1b melanomas, indicating that mitotic rate alone as criterion for pT1b has not improved selection of high risk pT1 patients for optional further (nodal) staging. Based on the results of this study, recommendations on SNB for pT1b melanomas might be reconsidered.

Chapter 3 reports on an ultrasound morphology criterion of the SN, which may add to the increased sensitivity and specificity of preoperative ultrasound assessment of clinically nodal negative melanoma patients. In this study 1,000 melanoma patients who underwent ultrasound of the SN area prior to a planned SNB at the Charité Universitätsmedizin Berlin, Berlin, Germany were examined to investigate a new ultrasound morphology criterion predictive of SN tumor involvement: "Echo free island" (EFI). Of the 953 patients in which EFI information was available, EFI was present in 40 patients (4%). EFI sensitivity and specificity were 10.8% and 97.6%, positive and negative predictive value were 50% and 80.2%. Presence of EFI was significantly correlated to presence of peripheral perfusion, another ultrasound criterion. Five-year melanoma specific survival (MSS) was worse for patients with EFI: 80% versus 92% when absent. EFI is found to be a

discriminatory ultrasound morphology sign which can be useful for early identification of sentinel node metastases in melanoma patients. It is an early sign of involvement and thus associated with a decreased survival.

Chapter 4 addresses the long-term results of a potentially minimally invasive alternative for the SNB. This approach consisting of ultrasound (US) assessment using the Berlin morphology criteria and use of fine needle aspiration cytology (FNAC) in case of suspicious or malignant US findings was investigated in 1,000 melanoma patients scheduled for SNB at the Charité Universitätsmedizin Berlin, Berlin, Germany. Survival analyses demonstrated that patients with positive US-FNAC had poor survival. After adjustment for SN status and other known prognostic features, patients with positive US-FNAC had worse survival than patients with normal US. Patients with suspicious US and negative FNAC and patients with normal US had comparable survival. A step-wise approach to melanoma patients is supported by these results: in case of a positive FNAC and/or clearly malignant US finding patients can be spared a SNB and be offered a lymphadenectomy instead. In case of suspicious US and negative FNAC, patients could be offered continue US surveillance or SNB for higher risk primary tumors. Completely US-FNAC negative patients might only require follow-up and no SN staging, with continue US surveillance as addendum for high risk T3/4 and/or ulcerated primaries.

In **Chapter 5** an overview of the literature regarding nodal staging of clinically node negative melanoma patients is given, as well as a presentation of a pilot and consequent study protocol for a minimally invasive alternative to the SNB. The literature on pre-operative assessment of regional lymph nodes with US in clinically N0 melanoma patients is disparate. Targeted US of the SN area in combination with FNAC or other new techniques has potential to become a minimally invasive alternative for the SNB, however, findings need to be replicated in prospective clinical trials first. A pilot with gamma probe guided US-FNAC shows that accurate SN identification in up to 90% of patients is feasible. The presented study protocol of the Gamma probe and ULtrasound guided Fine needle aspiration cytology of the sentinel node Trial (GULF trial) may provide potential improvement to the reported US-FNAC techniques and ultimately even a possible replacement of the SNB.

Part II – Timing of SNB and CLND

In **Chapter 6** a retrospective series of 1,015 SN positive patients from 9 European Organization for Research and Treatment of Cancer Melanoma Group Centers is investigated. Timing of a SNB after melanoma diagnosis is not associated with 5-year disease free survival (DFS) and MSS outcomes. Patients who underwent SNB after a longer time interval had a slightly larger SN tumor burden, and although this may have implications for prognosis this study did not detect any difference in survival. These findings indicate

that it is safe and equally informative to perform SNB after a prolonged interval of >9 weeks. This information can be used to counsel patients.

Chapter 7 describes the largest SNB population to date to report on the effects of SNB timing on SN positivity rate and survival. A total of 3,546 patients from 4 European Organization for Research and Treatment of Cancer Melanoma Group Centers undergoing SNB from 1997 – 2013 were selected. No differences in survival were found for different time interval cut-offs. As expected, a short change in time interval (up to 1 month) has no obvious impact on SN positivity rate and prognosis. Whether intervals longer than 3 months may have an effect cannot be determined by this study. This reassuring information supports the removal of strict time intervals for wide local excision (WLE) and SNB from melanoma guidelines and can be used in daily clinical practice to counsel patients and reduce the number of high urgency referrals.

Chapter 8 shows that in a selection of 784 SN positive melanoma patients from the cohort described in **Chapter 6** with updated follow-up, non-SN positivity and survival were not associated with completion lymphadenectomy (CLND) timing. Which indicates that it is safe to wait for at least 3 months after diagnosis, as there is no need to perform CLND as soon as possible. This information can be used to counsel patients and referring physicians and can potentially relieve pressure on the wait list.

Part III – Extent of Lymph Node Dissections in the Groin Area

Chapter 9 provides an accurate two-step approach to predict presence of pelvic nodal metastases in patients undergoing therapeutic superficial groin dissection. A total of 209 therapeutic combined groin dissection (CGD) patients from four tertiary centers in The Netherlands (1992–2013) were selected based on complete preoperative imaging and pathology reports. Combined use of preoperative imaging and a preliminary prediction model based on histopathology results of the inguinal (superficial) part of CGD could accurately predict negative deep pelvic nodes in up to 84 % of patients, thereby potentially identifying a group of low-risk patients in whom the extent of surgery might safely be minimized. The risk factors and the prediction model will be further investigated in a prospective, multicenter registry trial for CGDs.