General Discussion and Future Perspectives

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General Discussion

Breslow thickness is the most powerful prognostic feature for primary cutaneous melanoma's, closely followed by ulceration[1]. Presence of nodal metastases is another major discriminator in the American Joint Committee on Cancer (AJCC) staging system, dividing patients between stage I or II (no nodal involvement) and stage III (regional nodal involvement or in transit metastases). Finally, stage IV is defined by the presence of distant nodal involvement and/or visceral metastases[1].

Nodal Staging

There is abundant evidence that nodal metastases in melanoma patients equal poor survival[1, 2]. In clinically node negative patients, sentinel node biopsy (SNB) has proven to be a highly discriminative nodal staging tool to further differentiate between patients with a good prognosis (sentinel node (SN) negative) and patients with a less favorable prognosis (SN positive)[3, 4]. As there is no proven therapeutic effect for survival by performing a SNB, it is important to critically reassess the potentially negative aspects of this minimally invasive, albeit invasive nonetheless, surgical staging procedure.

While universally recommended as a staging procedure, not all eligible melanoma patients undergo SNB. This is unlike the practice in other malignancies such as breast cancer. There are several explanations for this discrepancy between guideline recommendations and clinical practice, namely the absence of solid evidence regarding therapeutic effect on survival[5], discrepancies in local health care reimbursements[6, 7], and socio-economic status[8].

In the following paragraphs the indication for SNB is discussed, as well as potential minimally invasive alternatives.

First, recommendations on the indication for SNB will be re-evaluated here. SNB is generally advised for intermediate and thick melanomas: i.e. >1.00mm – 4.00mm or >4.00mm with or without ulceration[9, 10]. In melanomas <1.00mm the risk of a positive SN is minimal, thus standard SNB is not recommended[9]. Although melanoma survival for thin melanomas (Breslow thickness <1mm, pT1) is excellent, it does not equal 100%. This is due to a minority of patients who will develop metastases over time and ultimately die due to melanoma[1, 11]. As the majority of currently diagnosed new cutaneous melanomas consists of thin melanomas (Breslow thickness <1mm, pT1) without clinically evident lymph node metastases[1, 12, 13], additional risk factors have been investigated in order to select those patients who have a high risk of developing nodal metastases, in order to consider SNB for this subgroup as well. As described in detail in **Chapter 2**, several primary tumor features have served as high risk feature, being ulceration (AJCC 6th and 7th edition) high Clark level (IV or V, AJCC 6th edition), or mitotic rate of ≥1 mitosis/mm^2 (AJCC 7th edition)[1, 14]. Since the implementation of the 7th edition AJCC staging system virtually

all melanoma guidelines adopted the recommendation to consider SNB for high risk thin (pT1b) melanomas[9, 15, 16]. **Chapter 2** reports on the effects of these changes in SNB recommendation in the Dutch pT1 melanoma population. No increase in SN positivity rate occurred in this group of patients, remaining <10%. It is questionable whether a surgical staging procedure is the optimal way to go to confirm that 90% of pT1b patients are node negative.

Thick melanomas (pT4) pose a different challenge. Since Breslow thickness and ulceration are the main prognostic features in primary melanoma, and ulceration occurs more often in thicker melanomas, patients with a pT4 melanoma have an a priori worse prognosis than intermediate thickness melanomas, regardless of their nodal status. They form the grey zone between stage II and stage III as was illustrated by Balch et al. in the 7th edition of the AJCC staging system[1]. Thus it is questioned whether nodal staging with SNB adds any substantial information on prognosis in pT4 patients. Nevertheless, several studies have shown that SNB is an accurate discriminator for prognosis in this group as well[3, 17, 18].

Next to reassessment of the indication for SNB, minimally invasive alternatives deserve further attention. **Chapter 3, 4**, and **5** provide varying methods of combined ultrasound (US) and FNAC for non-operative examination of the SN. In **Chapter 3** a new US morphology criterion is presented; the echo free island (EFI). While an infrequent finding in US assessment of the SN, it is associated with presence of peripheral perfusion (PP), another US criterion. Five-year melanoma specific survival was worse for patients with EFI: 80% versus 92% when absent. EFI is found to be a discriminatory US morphology sign which can be useful for early identification of SN metastases in melanoma patients. **Chapter 4** describes the long-term survival results of combined US and FNAC prior to SNB in 1,000 patients. Survival analyses demonstrated that patients with positive US-FNAC had poor survival. 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 continued US surveillance or SNB for higher risk primary tumors. Completely US-FNAC negative patients might only require follow-up and no SN staging, with continued US surveillance as addendum for high risk T3/4 and/or ulcerated primaries. In **Chapter 5** an overview of the literature on ultrasound assessment of the SN is presented, as well as a pilot and study protocol for Gamma probe and ULtrasound guided Fine needle aspiration cytology of the sentinel node Trial (GULF trial). The literature on pre-operative assessment of regional lymph nodes with US in clinically N0 melanoma patients is disparate. Targeted US-FNAC or other new techniques have the potential to replace SNB in the future, however, the reported findings need to be replicated in prospective clinical trials. A pilot

with gamma probe guided US-FNAC shows accurate SN identification in up to 90% of patients. The presented GULF trial study protocol may provide potential improvement to the reported US-FNAC techniques, and ultimately may become a possible replacement of the SNB. While none of the abovementioned procedures have reached the accuracy of the surgical SNB yet, further tailoring of these techniques may change that situation and lead to minimally invasive assessment of SN status. Simultaneously, other minimally invasive techniques have been developed and are currently being tested in clinical trial setting; for instance sonoelastography[19, 20] and multispectral optoacoustic tomography[21], addressed in **Chapter 5**. Based on the currently available evidence, nodal staging in clinically node negative patients is worthwhile for patients with a Breslow thickness of >1mm, considering that below this Breslow thickness the risk of a positive SN is less than 10%. Since all SN positive patients may potentially benefit from adjuvant immunotherapy, performing SNB in thick melanomas (>4mm) can be justified as well.

Thirdly, the approach of nodal staging in daily clinical practice requires re-evaluation. The decision on whether there is an indication for SNB should be made by a well informed and experienced doctor, preferably a melanoma surgeon or - dermatologist. The next question is when to perform SNB. Ideally this is done as soon as possible, in order to provide information on prognosis to the patient in a short period of time after the initial melanoma diagnosis. The current Dutch melanoma guideline even poses a strict time limit for SNB to be performed within 6 weeks, suggesting a potential detrimental effect if not complied with, without evidence to support this cut-off[22].

Considering the fact that there is a global increase in melanomas, and general practitioners and dermatologists increasingly tend to perform high urgency referrals, increased pressure on wait lists can be expected. Potential effects of SNB timing, and subsequently completion lymph node dissection (CLND) timing in case of positive SNs were investigated in **Part II** of this thesis. No difference in recurrence free survival or melanoma specific survival was found for SN positive patients (**Chapter 6**), or SN negative patients (**Chapter 7**), nor a difference in SN positivity rates (**Chapter 7**). Timing of CLND was also not relevant for survival in the cohort investigated in **Chapter 8**. While these are all retrospective studies, they provide evidence that a small variation in timing of SNB or CLND is not detrimental for survival, which can be used in shared decision making. One potential explanation for these findings could be that the time interval investigated is too narrow for any time dependent effect to become apparent. For instance if a time interval of > 1 year was compared with instant SNB or CLND, there might have been a difference in survival. This was the subject of MSLT I and DeCOG respectively. Neither of these studies showed a significant difference in survival for immediate SNB (and CLND in case of positive SN) versus nodal observation (MSLT I) or immediate CLND versus nodal observation (DeCOG)[3, 23]. Another explanation may be that lymphatic metastases occur already at a very early point in melanoma development and

progression; and that lymphatic metastases may be present for years prior to melanoma diagnosis, but are growing very slowly due to suppression by the immune system[24]. In this case, variation in time interval between primary melanoma excision and SNB and/or CLND of a few weeks may be irrelevant compared to the previous years of melanoma development.

The prognostic value of SN tumor burden poses a paradox here, as maximum SN tumor diameter is clearly associated to survival[25, 26]. Potentially our immune system is capable to contain growth of very small micrometastases (i.e. <0.1mm), but once a certain threshold size has been reached, the proliferative and invasive nature of the lymphatic metastases may overrule the suppressing capabilities of the immune system[24], leading to further growth and perhaps to simultaneous accelerated growth of micrometastases at distant sites as well. Kakavand et al. have found that patients with tumoral PD-L1 expression in the sentinel node had a median larger maximum SN tumor burden, which may be an explanation for acquired anti-tumor immunity evasion by the tumor[27]. The threshold at which anti-tumor immunity fails may be size dependent, time dependent, age and gender dependent, and probably dependent on many other patient and tumor characteristics; but what is mainly important is that in our daily clinical practice nodal (staging) surgery does not need to be performed in a fortnight after diagnosis.

Lymphadenectomy for microscopic stage III– necessary?

As mentioned in **Chapter 1** the MSLT 1 did not show an overall survival benefit for SNB (plus CLND in case of a positive SN) compared to patients who underwent WLE alone[3].

Following the results of MSLT 1, the MSLT 2 investigates whether omission of a CLND in SNB positive patients causes any difference in survival outcomes[28]. While final results from the MSLT 2 are still awaited, recently Leiter et al. published the first results of the DECOG trial, in which SN positive patients either underwent CLND or nodal observation with repeated ultrasound imaging[23]. This study showed no survival benefit for CLND at 3 year follow-up. While the study was underpowered due to lower than expected accrual rate, and patients with low SN tumor burden were overrepresented, the fact that there was absolutely no survival difference at 3 years suggests that a survival benefit from CLND is unlikely to be expected. Final results from the MSLT 2 will have to be awaited, as this study has included a larger number of patients with longer follow-up, and thus will be able to provide more information on the possible therapeutic value of CLND.

Meanwhile, daily clinical practice already differs substantially from guideline recommendations. Despite that CLND is still ubiquitously recommended for SN positive patients pending the final study results on its therapeutic value[9, 15, 16, 28], not all patients actually undergo CLND. Bilimoria et al reported that only 50% of the SN positive melanoma patients in the United States of America had a CLND[29], which is in line with results from the worldwide survey performed by Pasquali et al[30]. It is not known whether the

decision to not undergo CLND is generally patient driven or physician driven, but these studies clearly demonstrate that there can be a significant disparity between guideline recommendations and actual daily clinical practice.

Extent of surgery for macroscopic stage III (lymphadenectomy)

Finally, surgery for clinically nodal positive patients is again a different story altogether. The role of lymph node dissection is threefold in these patients: to achieve regional control; to provide more detailed prognostic information based on the number of involved lymph nodes and presence of extracapsular extension, and to achieve curation in a certain proportion of patients. It is universally recommended as standard procedure[9, 15, 16]. An aggressive surgical approach may seem appropriate to achieve maximal regional control and potentially therapeutic benefit, but risk of potentially significant surgical morbidity is increased due to the presence of enlarged or even giant bulky or matted nodes, which may increase surgery time and risk of hemorrhage and infections[31, 32]. In a prospective morbidity analysis of the MSLT I no significant differences in short term morbidity were found between CLND and delayed LND, although there was a higher percentage of wound separation, seroma/hematoma, and hemorrhage in the delayed group[33]. Another consequence of radical lymph node dissection is the frequent development of chronic lymph edema; this occurred significantly more often in delayed LNDs than in CLND (20% vs. 12%)[33]. Less extensive surgery may limit these negative effects. This is relevant especially in patients with positive groin lymph nodes, which have a higher complication rate than patients with axillary or head and neck lymph node involvement[31, 33]. There is no uniform approach to patients with groin lymph node metastases; either a combined superficial and deep lymph node dissection is performed removing all inguinal, iliac and obturator nodes; or a superficial inguinal lymph node dissection is performed removing only inguinal lymph nodes. Since only 30% of removed pelvic (iliac and obturator) nodes are positive after a combined groin dissection, this approach may be too radical, as there is no uniform evidence that standard removal of pelvic nodes improves survival[34-39]. **Chapter 9** provides a two-step approach for patients with palpable groin lymph node metastases in order to safely minimize the number of negative pelvic lymph node dissections. Considering the low OS rates for patients with pelvic nodal involvement[34], patients with a high risk of pelvic nodal involvement may ultimately be spared an additional pelvic groin dissection as well. Instead they can be offered systemic targeted therapy or immunotherapy, since this has shown to improve survival in irresectable stage III and stage IV melanomas[2].

Systemic Therapy and Future Perspectives

Adjuvant treatment of high risk stage II/III disease with anticancer vaccines were not effective or even harmful[40], and interferon alfa has shown to only have a marginal effect

on relapse free survival, but not on overall survival in the entire group[41-43]. Trials with pegylated interferon alfa did show a survival benefit, but only for microscopic stage III disease in ulcerated primaries[44-46].

Recently, immunotherapy has led to a breakthrough in the adjuvant treatment of stage III melanoma. Ipilimumab, a selective CTLA4 checkpoint inhibitor, can inhibit immune tolerance and thus might cause regression of tumor cells, as was reflected in improved stage IV survival[47]. In the adjuvant ipilimumab trial by the EORTC (EORTC 18071) a significant survival benefit was demonstrated (hazard ratio 0.76, 95% confidence interval 0.64-0.89, $p<0.001$)[48]. Grade III to IV immune related adverse events occurred in 41.6% in the ipilimumab group, and five patients (1.1%) died due to immune related adverse events. These results will have to be validated in order to adequately value the costs of these side effects versus the gains in terms of recurrence free and melanoma specific survival, but so far, results are promising. This trial has opened the gateway for other studies investigating checkpoint blockade treatment in the adjuvant setting for melanoma and other types of cancer. The results of the EORTC 1325, which investigates pembrolizumab (PD-1 checkpoint inhibitor) are currently awaited, as full accrual was reached in October 2016. Molecular targeted therapy is currently studied as adjuvant treatment as well, for instance in the COMBI-AD trial, which compares simultaneous use of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) versus placebo for high risk BRAF V600 positive melanoma patients. It has reached full accrual in December 2014 and is awaiting analyses.

In the near future, minimally invasive alternatives to the SNB such as US or MSOT[21] guided FNAC will be implemented in standard care, and ultimately will replace surgical SNB as we know it. Nevertheless, nodal staging has become increasingly important in the light of adjuvant systemic therapy with checkpoint inhibitors or combined targeted therapy. Thus an initial increase in the number of performed SNBs can be expected in the coming years. The same may be true for CLND; depending on entry criteria for upcoming adjuvant trials. A next step would be to randomize between SNB only and adjuvant therapy versus SNB plus CLND and adjuvant therapy; considering the fact that only 20% of SN positive patients have additional positive non-SNs. The role of melanoma surgery thus may become more limited in stage III disease. At the other hand patients with previously irresectable stage III or IV disease may become suitable candidates for surgery after successful treatment with either checkpoint inhibitors or BRAF- and/or MEK-inhibitors, as is currently being investigated in a phase-II setting in the REDUCTOR trial[49].

Melanoma has claimed many lives and will sadly continue to do so, but finally time seems to be on our side. When once aggressive radical surgery was the only available option to slow disease progression and achieve local control, over the years better insight into melanoma biology has taught us which factors can determine the prognosis

of each melanoma patient. Treatment options can be tailored based on this. Minimal invasive staging procedures continue to be developed, and reconsideration of the extent of nodal surgery is in place in the light of limited therapeutic effect and promising adjuvant therapies.

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