CHAPTER 9

General conclusion and future perspectives
As described in this thesis, the sentinel lymph node biopsy (SLNB) is a strong prognostic factor for disease-free survival (DFS) and disease-specific survival (DSS) in patients with cutaneous melanoma (CM). The SLNB seems to be a safe and reliable procedure with a low postoperative complication rate of 7%. In the early years the false-negative (FN) rate was 17% and dropped to 2% nowadays (unpublished data). Obviously, completion lymph node dissection (CLND) has a higher complication rate than the SLNB staging procedure. Patients who underwent axillary CLND, after tumor-positive sentinel lymph node (SLN) in the axilla, reported more quality of life related problems than patients who underwent axillary SLNB alone or inguinal SLNB with or without groin CLND. Remarkably however, recently published data show that early CLND, in case of a tumor-positive SLN, decreases both lymphedema and length of inpatient hospital stay compared to delayed CLND.\(^1\)

The ultimate question whether SLNB in patients with CM improves DSS, will be answered in the near future. A previous study showed that the actuarial rate of nodal metastases was the same in the SLNB group (20.8%) as in the observation (wide excision only) group (20.5%) at 10 years.\(^2\) The results of the fourth interim analysis, presented at the Society of Surgical Oncology’s 63\(^{rd}\) Annual Cancer Symposium 2010 in abstract form, are promising. At 10-years, melanoma-specific survival for all randomized patients with trunk and extremity primaries was 78.1% for SLNB patients vs. 71.0% for patients who had wide excision followed by nodal observation, the so called WEO group (p=0.046; HR=0.73). For 1.2-3.5 primaries, 10-years DFS was 72.5% with SLNB vs. 64.2% with WEO (p=0.005; HR=0.74). Ten-year survival was significantly higher after immediate CLND for tumor-positive SLN than delayed CLND for clinical nodal recurrence (63.2% vs. 36.5%; p=0.001, log rank; HR=0.49).\(^3\)

Another question rises regarding the tumor-status of the SLN. It is obvious that patients with a tumor-negative SLN can be saved from CLND. However, it is yet not clear what to do with tumor-positive patients? The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) tries to find an answer on this question. Meanwhile, the Rotterdam criteria (<0.1mm, 0.1-1.0mm and >1.0mm for the largest diameter of the largest metastasis in the SLN) showed that a CLND might not be indicated when the tumor load in the SLN is < 0.1 mm.\(^4\)

Moreover, progression to palpable nodal disease might not have occurred even if the tumor-positive SLN had not been removed. The term prognostic false-positivity is used to describe this phenomenon.\(^5\) Patients with a possible false-positive SLN are incorrectly up-staged, are given inaccurate prognostic information and can undergo unnecessary CLND and adjuvant therapy. It is of paramount importance that the near future clarifies the proper treatment of tumor-positive SLN patients.

As mentioned earlier, the FN rates in our institute are today 2%. These rates are comparable with others.\(^6\) Fortunately, there is no apparent difference in overall survival between patients with a true-positive SLN and patients with a FN SLN. A possible factor that could
cause a FN SLNB is surgical error. Morton noted that the rate of a FN result dropped by half when surgeons, not facile with the technique, gained experience. At the University Medical Center Groningen the FN rate dropped from 17% to 2% recently in patients with a median follow-up of 30 months (unpublished data). It is therefore possible that the false-negative rates decrease in the future by gaining more experience. Future studies should reveal this.

Pending the final results of the MSLT-I, the SLNB in patients with CM represents a valuable staging procedure and the SLNB is incorporated in the 7th American Joint Committee on Cancer (AJCC) staging system. Stage III is now redefined: N1 and N2 are subdivided in micrometastasis ("a") and macrometastasis ("b"). Micrometastases are diagnosed after SLNB.

The SLNB has no proven survival benefit (yet) compared to wide local excision only. The SLNB is a minimally invasive procedure to stage the regional nodes with low morbidity rates. The procedure should be discussed with and recommended to patients when at least one of the following indications is present: (1) the risk of clinically occult nodal metastases is sufficient to justify the SLNB (approximately > 10%); (2) the prognostic information from the SLNB would be of value to the patient and the treating physicians; (3) the tumor status of the SLN would be useful in guiding decisions regarding CLND and adjuvant therapy; (4) nodal staging information is important for entry into clinical trials in which the patient is interested; and/or (5) the morbidity and risks of the SLNB are acceptable to the physician and the patient.

The SLNB should be discussed with and offered to patients with melanomas equal or greater than 1.0 mm in Breslow thickness and clinically negative regional lymph nodes. The AJCC melanoma staging manual 2009 has re-defined the T1 melanomas (Breslow thickness ≤ 1.0 mm). T1a melanomas have no ulceration and <1/mm² mitoses. T1b melanomas are defined as those whose tumor thickness is ≤ 1.0 mm and that have at least one mitosis per square millimetre or tumor ulceration present. The SLNB should also be recommended selectively for patients with T1b melanomas. Preliminary evidence from several other large studies suggests that T1 melanomas with a mitotic rate of ≥ 1/mm² and a Breslow thickness of ≥ 0.76 mm are associated with an approximately 10% risk of occult metastases in their SLNs. Of course, future research is needed to define the role of SLNB in these cases.

Finally in 2011 there might be some breakthrough in the treatment of melanoma. First the role of the SLNB in patients with melanoma will be ultimately defined and guidelines will become available how to deal with (sub)micrometastasis in the SLN. Beside this, there is an enormous growing insight into the tumor biology of melanoma and the metastatic growth patterns. New insights with respect to systemic treatment look promising. There are advances in immunotherapy with immunoregulatory monoclonal antibodies (e.g.,
anti-CTLA-4 antibody ipilimumab). Pathway-signalling inhibition based on mutation-driven drug development is another way to treat metastatic melanoma disease. One is the BRAF mutation that is found in approximately 60% of melanoma patients. The selective BRAF inhibitor PLX4032 has been demonstrated to have very impressive response rates. Altogether, for the first time there might be an improvement in the management of melanoma patients for all stages of disease.

The current phase III PLX4032 trials are all closed and the final results will be available at the end of 2011 or early 2012. This new target therapy will possible provide more questions than answers. Is there a role for adjuvant surgery after PLX4032 treatment in responding patients? Is there a need to combine this new drug with anti-angiogenic treatment or a combination with a MEK inhibitor which will soon be available? For the time being, surgery will be pivotal in the primary treatment of melanoma, for local, regional, and metastatic disease control.
REFERENCES


