summary and conclusions
Part I: Regional treatment; Isolated limb infusion

Between 6-11% of patients with stage I and II melanoma will develop local recurrences or in-transit metastases. In-transit metastases are the result of lymphatic dissemination of melanoma cells between the site of the primary melanoma and the draining regional lymph nodes. After development of in-transit metastases, prognosis becomes poor, with a 5-year survival rate ranging from 3 to 59%.

If local recurrences or in-transit melanoma metastases become too extensive for local treatments such as surgery, cryotherapy, laser ablation, electro-surgery or local immunotherapy, the therapy of choice is often regional chemotherapy. Isolated limb perfusion (ILP) was the first successful technique, introduced in the late 1950s, that was used for this indication. Because of isolation of the limb in ILP the chemotherapy dosage could be increased up to a 10-fold compared to the dose that would be tolerated systemically. However, ILP, is technically demanding, time consuming and costly. A simplified, minimally invasive alternative to ILP called isolated limb infusion (ILI) was developed more recently at Melanoma Institute Australia (MIA). Since its introduction in 1994 the ILI technique has been progressively modified to increase the therapeutic index. Nowadays an increasing number of melanoma centers around the world has implemented ILI as the preferred technique to administer regional chemotherapy in patients with locally advanced melanoma confined to a limb.

In Chapter 1 the effect of several ILI protocol modifications and increased experience with the technique at MIA is described. In this chapter the results for 94 patients treated by ILI in an ‘early’ treatment period (1992–1999) are compared with the results for 91 patients treated in a ‘late’ period (2000–2007). All patients had advanced limb melanoma and received the combination of the cytotoxic drugs melphalan and actinomycin D. The patient characteristics of both groups were similar, except for a greater tumor load in the ‘late’ group, who had a significantly greater number of lesions (median 4 vs. 5; p = 0.02) and deeper tumor infiltration (p = 0.03). Drug circulation times were longer in the ‘late’ group: 22 vs. 31 minutes (p < 0.001) and higher initial and final limb temperatures were achieved. Overall response rates were 85% in both groups. The ‘late’ group showed a trend towards less toxicity (p = 0.06). This study showed that despite the significantly greater tumor load of patients treated in the ‘late’ period, response rates following ILI for advanced melanoma were similar
to those of the ‘early’ treatment period. This could be attributed to increased experience and protocol modifications, allowing longer drug exposure times and higher limb temperatures to be achieved without increasing toxicity.

In Chapter 2 the adjustment of melphalan dose according to ideal body weight (IBW) as a possible method to decrease limb toxicity without compromising outcome was analyzed. Consecutive patients treated by lower limb ILI for melanoma at MIA between 1998 and 2009 (n = 99) were reviewed. Toxicity and outcomes were tested for correlation with differences between the administered melphalan dose and the calculated adjusted melphalan dose, both in mg and mg/l, and with the differences between actual limb volume and calculated adjusted limb volume. No correlation was found between these three aforementioned parameters for either Wieberdink toxicity grade or outcome. Body mass index (BMI) did not correlate with limb toxicity either. Interestingly, a higher total melphalan dose correlated not only with increased toxicity but also with a lower response rate. It was concluded that in this study adjusting the melphalan dose for IBW did not appear to reduce toxicity following ILI. This study was not designed to detect a negative effect on outcome, so the effect of dose reduction on outcome remains uncertain.

Chapter 3 contains a systematic review of reported ILI experiences worldwide. A literature search was conducted according to the guidelines for systematic reviews in order to select eligible papers reporting limb toxicity and response rates following ILI using melphalan and actinomycin D to treat limb melanoma. A total of 576 patients from seven publications was included. Regional toxicity following ILI was low: no visible effect of the treatment (Wieberdink toxicity grade I) or slight erythema or edema (toxicity grade II) was observed in 79% of the patients, while considerable erythema and/or edema with blistering (toxicity grade III) was experienced by 19%. In 2% of the patients there was a threatened or actual compartment syndrome (toxicity grade IV) and no procedure-related amputation (toxicity grade V) was reported. A complete response was observed in 33% of the patients and a partial response in 40%, resulting in an overall response rate of 73%. Stable disease and progressive disease were the result of the treatment in 14% and 13% of the patients, respectively. In conclusion, this first systematic review of ILI using melphalan and actinomycin D indicated that regional toxicity was generally low, with satisfactory response rates.
When comparing ILI and ILP, it must be borne in mind that ILI is often performed in older patients and in those with higher stages of disease, which has previously been shown to decrease the likelihood of a favorable response.

Response rates following ILI reported by other institutions around the world are generally lower than those reported by MIA. Since small adjustments to the protocol and increased experience can improve outcome (Chapter 1), in Chapter 4 the protocol of the ILI technique for regional high dose chemotherapy for patients with advanced malignancies confined to a limb as it is currently performed at MIA is described. The ILI technique has undergone important modifications since the first published description of the protocol in 1994, and this description of the MIA ILI protocol may provide details that allow other surgeons to improve their results.

Chapter 5 summarizes current knowledge of the ILI procedure. The ILI technique is described, with special attention to the differences and similarities between ILI and ILP. The different drugs that have been and could be used for ILI are also described. Besides its role in the treatment of locally advanced melanoma, ILI can also be used for primary, locally advanced, inoperable extremity sarcoma, refractory chromomycosis, localized cutaneous T-cell lymphoma, squamous cell carcinoma and Merkel cell carcinoma, even refractory warts of the hands. Further, limb toxicity, side effects and results following ILI for melanoma, sarcoma and other non-melanoma skin malignancies are discussed. Finally, the use of ILI as induction therapy, followed by surgical excision of residual disease, is discussed.

Part II: Regional melanoma staging
Sentinel lymph node biopsy (SLNB) is recommended in melanoma guidelines around the globe. In the Netherlands, physicians are advised to offer SLNB as a diagnostic procedure to all patients with clinical stage IB and stage II disease. Despite these recommendations in the guidelines, the reported use of SLNB is limited. In the United States SLNB is used in only 47 - 60% of patients eligible for the procedure. In Chapter 6 the use of SLNB in the Netherlands is described, and an analysis of which patient and tumor characteristics influenced the use of SLNB is presented. Patients living in the northeastern part of the Netherlands who were diagnosed with an invasive cutaneous melanoma with a Breslow thickness ≥1 mm and were treated between 2004
and 2011 were selected from the Netherlands Cancer Registry. A regression analysis was performed to assess the association of patient and tumor characteristics and SLNB use. SLNB was performed in 42% of the 2413 included patients. The frequency of performing SLNB increased between 2004 and 2011 from 24% to 55% (p < 0.001). Patients were less likely to undergo a SLNB if they had a melanoma located in the head-and-neck area (p < 0.001), when they were 55 years or older (p = 0.001), and if they had a low socio-economic status (SES, p = 0.03). The SLNB procedure was more likely to be used when the melanoma was diagnosed in a university hospital (p = 0.045) or when the Breslow thickness was 2.01-4.0 mm (p = 0.03). This study showed that the use of the SLNB has increased significantly between 2004 and 2011. However, in 2011 it was still only performed in 55% of the Dutch patients eligible for the procedure. In patients with head-and-neck melanomas, older patients and patients with low SES, SLNB was less frequently performed. In patients with 2.01-4.0-mm-thick melanomas and those who were diagnosed in a university hospital SLNB was performed more frequently.

Part III: Anatomic site and the risk of melanoma brain metastases

Brain metastases are a common and serious complication of metastatic melanoma, and indicate a poor prognosis. Until recently, treatment options for these patients were very limited. Recently, however, new systemic treatment options have become available that significantly increase survival. Primary cutaneous head and neck melanomas (HNM) are reported to be associated with a higher incidence of brain metastases than primary trunk and limb melanomas (TLM). In Chapter 7, the incidence of brain metastases in patients with primary HNM is reported and risk factors for these metastases are analyzed. From a large, prospectively-collected database, 1,687 HNM patients and 8,793 TLM patients who presented with American Joint Committee on Cancer (AJCC) stage I and II disease were identified. Survival was assessed using the Kaplan-Meier method and a multivariate Cox regression analysis. Independent risk factors were determined by binary logistic regression analysis. The incidence of brain metastases 5 years after diagnosis of HNM was 6.7% compared to 4.7% for the incidence of brain metastases in patients with melanoma elsewhere (p = 0.003). Patients with primary scalp melanomas were most likely to develop brain metastases (12.7%). Independent risk factors for brain metastasis in patients with HNM were Breslow thickness, ulceration, and melanoma located on the scalp. It was concluded
that patients with primary scalp melanomas have a higher incidence of brain metastasis than patients with melanomas at other head and neck sites. More intensive monitoring of patients with scalp melanomas might lead to the earlier diagnosis of brain metastasis, offering the prospect of earlier intervention and possibly improved outcomes.

Conclusion
Locally irresectable recurrent or in-transit melanoma metastases confined to a limb can effectively be treated by ILI. Especially in elderly patients ILI should be considered as the treatment of choice, because of low regional toxicity and satisfactory response rates. The overall response rate after ILI is 73%, while stable disease is achieved in 14% and progressive disease is seen in 13%. ILI can also successfully be used in other malignancies confined to a limb, such as squamous cell carcinomas and Merkel cell carcinomas and advanced, inoperable extremity sarcomas. Over the years, increased experience and protocol modifications have gradually improved treatment outcomes. Dose adjustment according to ideal body weight does not seem to decrease toxicity.

Nodal status as determined by SLNB is required for AJCC melanoma staging. The use of this procedure in the Netherlands is still limited, although the frequency of performing SLNB has significantly increased between 2004 and 2011 from 24% to 55% (P < 0.001). Patients with head-and-neck melanomas, elderly patients and those with low SES are less likely to undergo SLNB.

The brain is a common site for melanoma metastases and these metastases are associated with a poor prognosis. Patients with primary scalp melanomas are at particular risk of developing brain metastases (12.7%). More intensive monitoring of these patients should be considered, since early detection and local and/or systemic treatment may improve their quality of life and survival.