



Practice variation in Sentinel Lymph Node Biopsy for melanoma patients in different geographical regions in the Netherlands



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ABSTRACT

Background: Due to the lack of solid evidence for treatment benefit of Sentinel Lymph Node Biopsy (SLNB) as part of loco-regional surgical treatment of non-distant metastatic melanoma, there might be variation in surgical treatment strategies in the Netherlands. The objective of the current study was to assess differences in the performance of SLNB, in geographical regions in the Netherlands, of non-distant metastatic melanoma patients (American Joint Committee on Cancer (AJCC) stage I-III).

Materials and methods: A total of 28 550 melanoma patients, diagnosed between 2005 and 2013, were included in this population based retrospective study. Data were retrieved from the Netherlands Cancer Registry (NCR). Treatment strategies in 8 regions of the Netherlands were compared according to stage, excluding patients with distant metastasis (AJCC stage IV).

Results: Throughout the Netherlands, there was substantial practice variation across the regions. The performance of SLNB in patients with clinically unsuspected lymph nodes and Breslow thickness >1.0 mm was significantly different between the regions. In a post hoc analysis, we observed that patients aged over 60 years, female patients and patients with a melanoma located in head and neck have lower odds to receive a SLNB.

Conclusion: There is considerable loco-regional practice variation which cannot completely be explained by the patient and tumor characteristics, in the surgical treatment of non-distant metastatic melanoma patients in the Netherlands. Although national guidelines recommend considering SLNB in all patients with a melanoma thicker than 1 mm, only half of the patients received a SLNB. Future research should assess whether this practice variation leads to unwanted variations in clinical outcome.

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Abbreviations: SLNB, Sentinel Lymph Node Biopsy; MSLT, Multicentre Selective Lymphadenectomy Trial; CLND, Complete Lymph Node Dissection; AJCC, American Joint Committee on Cancer; NCR, Netherlands Cancer Registry; NOS, Not Otherwise Specified; TNM, Tumor Node Metastasis; TLND, Therapeutic Lymph Node Dissection; IQR, Interquartile range.

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1. Introduction

The incidence of melanoma in the Netherlands has increased at a high rate over the last decades. In 2001, 2852 patients were newly diagnosed with invasive melanoma; this has increased to 6787 in 2016 [1].

Although the rising trend in incidence is stabilizing or declining in Australia, New Zealand, North America, Israel and Norway, the incidence rates of melanoma in western European countries are expected to increase [2–4].

Guidelines in the Netherlands recommend a narrow local excision

followed by a wide local excision with proper resection margins of 1 or 2 cm, depending on the thickness of the melanoma [5–7]. In melanoma thicker than 1 mm or with unfavourable characteristics such as ulceration or mitoses, Sentinel Lymph Node Biopsy (SLNB) is advised based upon level II evidence. SLNB is a minimal invasive method to detect the presence of occult nodal metastasis. It has been shown to be the most powerful prognostic factor for survival in clinically node negative patients [8,9]. While following these guidelines is important to achieve the optimal staging for the majority of the patients, the surgical treatment of non-distant metastatic melanoma is still surrounded with clinical uncertainty.

The final results of the Multicentre Selective Lymphadenectomy Trial I (MSLT-I) showed no 10-year melanoma specific survival benefit of wide excision and SLNB with immediate Complete Lymph Node Dissection (CLND), compared to wide excision and nodal observation with delayed CLND. However, biopsy-based management did prolong disease-free survival rates for patients with intermediate-thickness melanomas [10]. These results are also criticized by others [11].

The Multicentre Selective Lymphadenectomy Trial II (MSLT-II) showed that immediate completion lymph-node dissection did not increase melanoma specific survival in melanoma patients with sentinel-node metastases, but did increase the rate of regional disease control [12].

Also, there is evidence that treatment preferences of the medical specialist influence the decision to perform a SLNB [13].

Given the recent developments, new adjuvant treatment options for non metastatic melanoma patients might improve the recurrence-free survival, staging these patients properly will become more and more important [14,15]. This proper staging can lead to a more specific patient and tumor treatment in well informed melanoma patients [16].

The aim of the present study is to investigate and describe regional differences in loco-regional surgical treatment strategies of non-distant metastatic melanoma patients, American Joint Committee on Cancer AJCC stage I-III in the Netherlands.

2. Materials and methods

In this population-based retrospective study, data from the Netherlands Cancer Registry (NCR) were used. The NCR registers data of all patients diagnosed with cancer and covers all hospitals in the Netherlands, which is geographically divided in 9 regions (Fig. 1). The following data were extracted from the database: sex, year of birth, age at diagnosis, incidence year, localisation, morphology, Breslow thickness, number of lymph nodes assessed, number of positive lymph nodes, local resection, SLNB, CLND, radiotherapy, follow up time, survival status (death or alive) and regions. As registration rules for SLNB were different in one region, treatment strategies in this region could not be compared, this region was excluded from the analyses.



Fig. 1. Geographical regions in the Netherlands and the number of patients included per region.

All new diagnosed patients with primary invasive non-distant metastatic melanoma, excluding patients with distant metastasis (AJCC stage IV), patients with morphology of the melanoma: nodular melanoma, superficial spreading melanoma and malignant melanoma Not Otherwise Specified (NOS) were selected. Data were collected at primary presentation only. A total of 28 550 non-distant metastatic melanoma patients diagnosed between 2005 and 2013 were included. Missing data on Breslow thickness (6.9%) were considered missing completely at random; these patients were excluded and the analyses were further stratified on Breslow thickness and lymph node status. Tumor Node Metastasis stage (TNM) classification at time of diagnosis was used. Patients were categorised in three groups: 1: Breslow thickness ≤ 1.0 mm without nodal metastasis (N0), 2: Breslow thickness > 1.0 mm with non-palpable lymph nodes or unknown lymph node status (cN0 or cNx) and 3: patients with clinically suspicious lymphadenopathy (cN+) with any melanoma Breslow thickness.

3. Statistics

Statistical analyses were performed using STATA/SE version 12.0. For comparison of the patient characteristics and differences in treatment strategies in the regions, Chi squared tests were used. All analyses were stratified for stage.

Loco-regional surgical treatment for non-metastatic melanoma (local resection, SLNB, CLND and TLND) in the 8 regions in the Netherlands, according to stage, was compared using Chi squared tests. A sensitivity analysis was performed excluding patients with cNx. A difference was considered statistically significant if the p-value was ≤ 0.05 .

In post hoc analysis, a multivariable logistic regression analysis was performed to explore which variables were associated with the performance of a SLNB. The explanatory variables were sex, age, location, morphology, Breslow thickness, incidence year and region. In this post hoc analysis the variable age was divided in smaller categories of five year to more accurately assess a possible cut-off value for the association of age with SLNB performance. To explore possible underlying mechanisms for variation in SLNB performance among the regions, differences in patient and melanoma characteristics within the intermediate thickness melanomas were assessed for linear trend.

4. Results

4.1. Sociodemographic and clinical characteristics

Of the 28 550 melanoma patients included in this study, 15 763 (55.2%) were female (Table 1). The largest age-category was > 65 years ($n = 9\ 239$, 32.4%). Median age was 57 years (Interquartile range (IQR) 45 years–68 years). The number of newly diagnosed patients increased during the studied time period, from 2962 patients in 2005 to 3994 patients in 2013. The trunk was the most commonly affected body site ($n = 11\ 429$), (40.0%). The histological type was superficial spreading melanoma in 74.3% of the patients ($n = 21\ 210$). Most of the patients ($n = 16\ 152$, 56.6%) were diagnosed with thin melanomas, Breslow thickness ≤ 1.0 mm. Median Breslow thickness was 0.9 mm (IQR 0.54mm–1.75 mm). Over the regions, the number of included patients varied from 1734 (6.1%) in region 1 to 5413 (19.0%) in region 5 (Table 1, Fig. 1).

4.2. Differences in loco-regional surgical treatment strategies across the regions

4.2.1. Thin melanomas

In patients with Breslow thickness ≤ 1.0 mm, N0, all patients

Table 1

Characteristics of all patients diagnosed with melanoma in the population-based Netherlands Cancer Registry 2005–2013.

| Characteristic | Number | Percentage |
|-----------------------|---|-------------|
| Sex | Male | 12 787 44.8 |
| | Female | 15 763 55.2 |
| Age | <45 | 7023 24.6 |
| | 45–54 | 5881 20.6 |
| | 55–64 | 6407 22.4 |
| | 65+ | 9239 32.4 |
| Incidence years | 2005 | 2962 10.4 |
| | 2006 | 2485 8.7 |
| | 2007 | 2660 9.3 |
| | 2008 | 2876 10.1 |
| | 2009 | 3035 10.6 |
| | 2010 | 3270 11.5 |
| | 2011 | 3554 12.5 |
| | 2012 | 3714 13.0 |
| | 2013 | 3994 14.0 |
| Localisation melanoma | Head & Neck | 3025 10.6 |
| | Trunk | 11 429 40.0 |
| | Upper Extremities | 6223 21.8 |
| | Lower Extremities | 7799 27.3 |
| | Other | 74 0.3 |
| Morphology | Nodular | 3769 13.2 |
| | Superficial | 21210 74.3 |
| | Malignant NOS ^a | 3571 12.5 |
| Stage | Breslow thickness ≤ 1.0 , N0 | 16152 56.6 |
| | Breslow thickness > 1.0 , cN0 or cNx ^b | 12070 42.3 |
| | Breslow thickness > 1.0 , cN+ ^c | 328 1.2 |
| Regions | 1 | 1734 6.1 |
| | 2 | 3224 11.3 |
| | 3 | 4722 16.5 |
| | 4 | 2655 9.3 |
| | 5 | 5413 19.0 |
| | 6 | 2506 8.8 |
| | 7 | 3788 13.3 |
| | 8 | 4508 15.8 |

a = Not Otherwise Specified, N0 = no lymph node metastasis, b = clinical N-stage (no lymph nodes (cN0) or unknown (cNx)), c = clinical suspicious lymphadenopathy.

($n = 16\ 152$) in all regions underwent local excision. The proportion of patients receiving SLNB in this patient group differed statistically significant ($p < 0.001$) between the regions, varying from 0.8% in region 5–8.6% in region 1 (Table 2). The percentage of patients with a positive SLNB differed from 2.3% in region 1 versus 16.3% in region 6 but this difference was not statistically significant ($p = 0.22$) (Table 2). SLNB proportions were in the same range after excluding patients with cNx.

4.2.2. Intermediate and thick melanoma

All patients with a Breslow thickness > 1.0 mm, cN0 or cNx ($n = 12\ 070$) underwent local resection. The performance of SLNB was significantly different across the regions ($p < 0.001$), ranging from 22.5% in region 5–56.5% in region 6. Of these patients, 21%–25.8% had a positive SLNB; this proportion was not significantly different across the regions ($p = 0.21$). The proportion of patients receiving CLND after a positive SLNB was significantly different across the regions ($p < 0.001$), varying from 51.2% in region 1–75.6% in region 6 (Table 2).

The post hoc analysis (Table 3) in patients with Breslow thickness > 1.0 mm, cN0 or cNx showed that patients aged > 60 years received significantly fewer SLNB's than younger patients. Also female patients had a significantly lower odds of receiving a SLNB (OR 0.85, 95%CI 0.78–0.94; $p = 0.001$). Patients with a melanoma located in the head and neck area had about a 3 fold lower likelihood of receiving SLNB compared to patients with a melanoma on the trunk or extremities.

Patients with a melanoma with Breslow thickness between 2

Table 2
Treatment of the melanoma patients and proportion of patients with a positive SLNB, according to regions in the Netherlands and stage.

| Treatment | Regions N (%) | | | | | | | | p-value ^a |
|--|---------------|------------|------------|------------|------------|------------|------------|------------|----------------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
| Breslow thickness ≤ 1.0, N0 | | | | | | | | | |
| Local resection | 995 (100) | 1920 (100) | 2642 (100) | 1598 (100) | 2973 (100) | 1397 (100) | 2029 (100) | 2598 (100) | N.A. ^b |
| SLNB ^c | 86 (8.6) | 42 (2.2) | 128 (4.8) | 50 (3.1) | 23 (0.8) | 43 (3.1) | 54 (2.7) | 90 (3.5) | <0.001* |
| SLNB positive | 2 (2.3) | 3 (7.1) | 13 (10.2) | 4 (8.0) | 2 (8.7) | 7 (16.3) | 3 (5.6) | 6 (6.7) | 0.22 |
| Breslow thickness > 1.0, cN0 or cNxd | | | | | | | | | |
| Local resection | 716 (100) | 1270 (100) | 2029 (100) | 1022 (100) | 2384 (100) | 1070 (100) | 1714 (100) | 1865 (100) | N.A. |
| SLNB | 326 (45.5) | 601 (47.3) | 936 (46.1) | 482 (47.2) | 536 (22.5) | 604 (56.5) | 634 (37.0) | 674 (36.1) | <0.001* |
| SLNB (selection cN0) ^g | 288 (49.8) | 501 (48.8) | 731 (45.5) | 368 (46.5) | 308 (25.5) | 380 (56.2) | 498 (42.4) | 466 (36.0) | <0.001* |
| SLNB positive | 84 (25.8) | 134 (22.3) | 234 (25.0) | 101 (21.0) | 136 (25.4) | 127 (21.0) | 154 (24.3) | 142 (21.1) | 0.21 |
| CLND ^e after SLNB+ | 43 (51.2) | 93 (69.4) | 138 (59.0) | 70 (69.3) | 100 (73.5) | 96 (75.6) | 98 (63.6) | 106 (74.7) | <0.001* |
| Breslow thickness > 1.0, cN⁺f | | | | | | | | | |
| Local resection | 22 (95.7) | 34 (100) | 51 (100) | 35 (100) | 56 (100) | 38 (97.4) | 44 (97.8) | 43 (95.6) | 0.44 |
| TLND ^h | 21 (91.3) | 20 (58.8) | 41 (80.4) | 25 (71.4) | 41 (73.2) | 29 (74.4) | 27 (60.0) | 35 (77.8) | 0.067 |

a = p-value for differences between all the regions, b = Not Applicable, c = Sentinel Lymph Node Biopsy, d = clinical nodal stage, e = Completion Lymph Node Dissection, f = clinical suspicious lymphadenopathy, * = significant value, g = sensitivity analysis excluding cNx, h = Therapeutic Lymph Node Dissection.

and 4 mm had a higher odds of receiving a SLNB (OR 1.54, 95% CI 1.37–1.72; $p < 0.001$ for 2.1–3.0 mm and OR 1.55, 95% CI 1.32–1.82; $p < 0.001$ for 3.1–4.0 mm). During the studied time period the proportion of patients who received SLNB increased, with an odds ratio in 2006 of 1.34 (CI 1.09–1.65; $p = 0.006$ proportion: 16%) to an odds ratio of 3.75 (CI 3.10–4.55; $p < 0.001$, proportion: 23%) for patients diagnosed in 2013 when compared with patients whose incidence year was 2005 (proportion: 12%). Patients living in the regions 5, 7 and 8 have a significantly lower odds for performance of SLNB in comparison with patients living in region 1 (respectively OR 0.38, 95% CI 0.31–0.46; $p < 0.001$, OR 0.69, 95% CI 0.56–0.84; $p < 0.001$, OR 0.73, 95% CI 0.59–0.89; $p = 0.002$).

There were significant differences in patient and tumor characteristics, in line with the proportion SLNB; however the differences do not fully explain the geographical variation in SLNB. (Table 4).

4.2.3. Clinically suspicious lymphadenopathy

Only a few patients ($n = 5$) with macro metastasis in the lymph node (cN+, M0) did not receive local resection. There was a non-significant variation across the regions in performance of TLND in these patients, with 60.0% in region 7–91.3% in region 1 ($p = 0.067$) (Table 2).

5. Discussion

This large observational study shows large differences in sentinel lymph node biopsy in stage I and stage II melanoma patients among regions in the Netherlands. In only half of the patients with a melanoma >1.0 mm (and clinically unsuspected lymph nodes) SLNB was performed. In case of a positive SLNB, a consecutive CLND was performed in half to three quarters of the patients. During the studied time period, the Dutch melanoma guideline did not recommend to perform a SLNB for melanoma patients with a thin melanoma of less than 1 mm [7]. However in the revised guidelines (revised on 01-03-2016 version 2.1) [7] SLNB is recommended in patients with ulcerations or mitosis $\geq 1/\text{mm}^2$, this would explain the small chance to receive SLNB. Current study confirms that, in general, this guideline is followed for these patients; however they still have a small chance (between 0.8% and 8.6%, dependent on the region) to receive SLNB. The SLNB positivity rate in these patients was between 2.3% and 16.3%. Possibly these are the patients for whom a SLNB is recommended in the revised guideline. In a large retrospective study where 32 527 cases of T1 melanoma were included, the overall SLN positivity rate was 7.8%. Performing a SLNB was correlated with T-stage, thickness, level,

ulceration, age, and geographic region. Patients with SLNB + had a significant diminished cancer-specific survival [17].

For patients with thicker melanomas of 1.0 mm or more, the Dutch guideline recommends to consider performance of SLNB. However, we observed that only a quarter to half of the patients with a Breslow thickness >1.0 mm and clinically unsuspected lymph nodes indeed received SLNB during the observed period (Table 2). This finding is in line with the results of a previous observational study that reported a low performance of SLNB (45.2%) for patients with a melanoma of 1 mm or thicker between 2004 and 2011 in the north eastern part of the Netherlands [18]. Also in a large study in the United States where 16,598 patients were included, in only half of the patients use of a SLNB was reported [19]. In the latter study SLNB was not only associated with clinicopathologic factors but also with health system factors.

Approximately one out of four patients with Breslow thickness >1.0 mm, cN0 or cNx in our study had metastasis in the regional lymph nodes (SLNB+). These tumor foci are apparently too small to detect clinically and may also be missed by radiological examination due to low sensitivity of high resolution ultrasound [20,21]. Thus, SLNB provides pathologic status information that would otherwise be missed in approximately half of the patients, according to the present study. This accurate staging will become more important in the future if new (neo)adjuvant treatment options for non distant metastatic melanoma patients may become available. In the current study, several patient and melanoma characteristics were associated with receiving a SLNB. Older patients over the age of 60 years received significantly fewer SLNB than younger patients. This was also found in another study where patients over the age of 55 years were less likely to receive SLNB than younger patients [18]. An explanation for this could be that older patients more often have comorbidities which may lead to the decision to refrain from a SLNB [22,23]. Older patients also have more aggressive primary melanoma features as a higher ulceration rate and mitotic index (among others) and age is associated with a higher mortality; in contrast they have a lower SLNB + rate [24,25] Physicians may therefore be more reluctant to perform SLNB for these patients and potentially feel less urge to perform a diagnostic procedure for a patient that does not have a long life ahead. However we are dealing here with a minimal invasive staging procedure with minimal morbidity and the possibility, in case of a positive sentinel lymph node, of a better regional disease control and a better quality of life [26–28]. Nevertheless, the results of the MSLT-II study have not shown a melanoma-specific survival gain, so for patients with a positive SLNB, shared decision making with high quality information is

Table 3
Association of patient and melanoma characteristics on the SLNB-rate (multivariable analysis).^a

| Patients with a melanoma Breslow thickness >1.0, cN0 or cNx ^b | Adjusted OR (95%CI) | p-value |
|--|---------------------|---------|
| Age (years) | | |
| ≤20 | Reference | |
| 21–25 | 0.96 (0.52–1.78) | 0.89 |
| 26–30 | 0.95 (0.54–1.70) | 0.87 |
| 31–35 | 0.89 (0.51–1.54) | 0.67 |
| 36–40 | 0.84 (0.49–1.43) | 0.52 |
| 41–45 | 0.84 (0.50–1.42) | 0.52 |
| 46–50 | 0.91 (0.54–1.53) | 0.72 |
| 51–55 | 0.64 (0.38–1.08) | 0.10 |
| 56–60 | 0.67 (0.40–1.12) | 0.26 |
| 61–65 | 0.55 (0.33–0.93) | 0.03* |
| 66–70 | 0.48 (0.28–0.80) | 0.005* |
| 71–75 | 0.39 (0.23–0.66) | <0.001* |
| 76–80 | 0.24 (0.14–0.41) | <0.001* |
| 81–85 | 0.08 (0.04–0.14) | <0.001* |
| 86–90 | 0.03 (0.01–0.06) | <0.001* |
| >91 | 0.006 (0.0008–0.05) | <0.001* |
| Sex | | |
| Male | Reference | |
| Female | 0.85 (0.78–0.94) | <0.001* |
| Localisation | | |
| Head and Neck | Reference | |
| Trunk | 3.48 (2.92–4.14) | <0.001* |
| Upper Extremities | 3.95 (3.28–4.77) | <0.001* |
| Lower Extremities | 4.19 (3.49–5.04) | <0.001* |
| Morphology | | |
| Nodular | Reference | |
| Superficial | 0.92 (0.83–1.03) | 0.14 |
| Breslow thickness | | |
| 1.0–2.0 | Reference | |
| 2.1–3.0 | 1.54 (1.37–1.72) | <0.001* |
| 3.1–4.0 | 1.55 (1.32–1.82) | <0.001* |
| 4.1–5.0 | 1.04 (0.84–1.28) | 0.74 |
| 5.1–6.0 | 1.00 (0.76–1.32) | 0.99 |
| 6.1–7.0 | 1.18 (0.83–1.70) | 0.35 |
| 7.1–8.0 | 0.89 (0.57–1.40) | 0.62 |
| 8.1–9.0 | 0.68 (0.39–1.18) | 0.17 |
| 9.1–10.0 | 0.54(0.25–1.13) | 0.10 |
| >10.1 | 0.44 (0.30–0.65) | <0.001* |
| Incidence Year | | |
| 2005 | Reference | |
| 2006 | 1.34(1.09–1.65) | 0.006* |
| 2007 | 1.54(1.26–1.90) | <0.001* |
| 2008 | 1.83(1.49–2.24) | <0.001* |
| 2009 | 2.15(1.76–2.63) | <0.001* |
| 2010 | 2.16(1.78–2.63) | <0.001* |
| 2011 | 3.01(2.48–3.66) | <0.001* |
| 2012 | 3.19(2.63–3.88) | <0.001* |
| 2013 | 3.75(3.10–4.55) | <0.001* |
| Region | | |
| 1 | Reference | |
| 2 | 1.14(0.92–1.41) | 0.24 |
| 3 | 1.11(0.92–1.36) | 0.28 |
| 4 | 1.24(0.99–1.54) | 0.06 |
| 5 | 0.38(0.31–0.46) | <0.001* |
| 6 | 1.70(1.36–2.14) | <0.001* |
| 7 | 0.69(0.56–0.84) | <0.001* |
| 8 | 0.73(0.59–0.89) | 0.002* |

* = Values p < 0.05.

^a Localisation 'other' and morphology 'NOS' excluded for this analyses.

^b Clinical nodal stage.

important to make an informed choice on whether to undergo lymph node dissection or observation [12,16].

According to the literature, in patients with a melanoma in the head and neck area, SLNB is less often performed as it is technically a more challenging procedure to perform in this area [29]. The results of our study indeed confirm that performance of SLNB in patients with a melanoma located outside the head and neck area was associated with significantly higher odds to receive SLNB. In

this study we also observed that female patients have significantly lower odds to receive SLNB compared with male patients, for which no explanation was found. These findings of a lower odds to receive SLNB for female patients, older patients and patients with a melanoma located in the head and neck area, was also previously observed in a study where 4571 clinically node negative melanoma patients with a Breslow thickness > 4 mm were identified [30]. Furthermore in the Dutch study earlier mentioned, an association with performance of SLNB with a lower SES and diagnosis made in a university hospital was observed [18]. In current study only the clinicopathologic features of the patients in the regions were compared. Future research should focus on the specific reason why these patients have a lower chance to receive a SLNB.

During the studied time period the proportion of patients who received SLNB increased which could indicate that there is a slow growing awareness of the importance of SLNB and increased adherence to the advice in the guideline.

The rate of performance of CLND in SLNB positive patients with Breslow thickness >1.0 mm cN0 or cNx varied from 51.2% to 75.6% in the regions. This confirms the results of another observational study which found that only 328 of the 495 (66%) patients who had positive lymph nodes underwent CLND. In that study there were two factors associated with omitting CLND: older age and melanoma of the lower extremities [31]. Treatment related morbidity due to inguinal CLND is high compared to axillary dissection; wound complications often occur on the short term and on the long term lymphedema is a common complication [32–35]. In the current study, the TLND rate for patients with a clinically suspect sentinel lymph node was higher than for patients with clinically unsuspected lymph nodes and ranged between 58.8% and 91.3%.

5.1. Limitations and strengths

Although the intention was to analyse data from all regions in the Netherlands, the registration rules from 1 out of 9 regions were too different to be used in this study. Nevertheless, the treatment strategies of the remaining 8 regions were compared. Data was used from 28 550 patients diagnosed between 2005 and 2013 in a real life population without patient selection. Specific attention was given to the coding of the variable SLNB and outliers in the regions and over time, leading to the exclusion of one region and earlier incidence years. Some accidental coding errors might however have occurred. Data before 2010 may be less reliable due to registration rules, however time trends did show a similar trend in all regions indicating that there were no large differences over time and between the regions.

In the post-hoc analysis the factors associated with the performance of SLNB were examined. However we were restricted by the variables that were available in the database and were therefore not able to analyse this in detail.

We were not able to evaluate the adherence to the guidelines of resection margins as this was not registered in the database. We acknowledge that other patient and melanoma specific factors may also play a role in selecting patients for SLNB which should be subject of future studies.

6. Conclusion

There is considerable regional practice variation in the surgical loco-regional treatment of non-distant metastatic melanoma patients in the Netherlands. This variation is present for both SLNB and CLND performance. Only half of the patients actually received a SLNB, and consequently many patients are not adequately staged. This practice variation can possibly be explained by the patient and tumor characteristics and the coherent comorbidity. Although

Table 4
Differences in patient and melanoma characteristics.

| Region | | 5 | 8 | 7 | 1 | 3 | 4 | 2 | 6 | p value |
|--------------|-------------|-----------------|-----------------|-----------------|---------------|-----------------|---------------|---------------|---------------|---------|
| SLNB | Yes | 536 (22.5) | 674 (36.1) | 634 (37.0) | 326 (45.5) | 936 (46.1) | 482 (47.2) | 601 (47.3) | 604 (56.5) | <0.001 |
| Sex | Male | 1.015 (50.9) | 744 (52.0) | 760 (48.9) | 340 (53.3) | 865 (47.5) | 456 (51.4) | 451 (46.1) | 394 (48.2) | 0.008 |
| | Female | 981 (49.2) | 688 (48.0) | 794 (51.1) | 298 (46.7) | 957 (52.5) | 431 (48.6) | 527 (53.9) | 423 (51.8) | |
| Age | ≤60 | 923 (46.2) | 736 (51.4) | 783 (50.4) | 312 (48.9) | 888 (48.7) | 445 (50.2) | 554 (56.7) | 411 (50.3) | 0.002 |
| | >60 | 1.073 (53.8) | 696 (48.6) | 771 (49.6) | 326 (51.1) | 934 (51.3) | 442 (49.8) | 424 (43.4) | 406 (49.7) | |
| Localisation | Head & Neck | 289 (14.5) | 186 (13.0) | 181 (11.7) | 73 (11.4) | 237 (13.0) | 114 (12.9) | 103 (10.5) | 103 (12.6) | 0.07 |
| | Other | 1.707 (85.5) | 1.373 (88.4) | 1.373 (88.4) | 565 (88.6) | 1.585 (87.0) | 773 (87.2) | 875 (89.5) | 714 (87.4) | |
| Breslow | Median | 2.0 | 1.855 | 1.95 | 2.0 | 2.0 | 1.7 | 1.8 | 1.9 | 0.03 |

compliance with the SLNB staging guidelines is increasing over time, future research should assess factors associated with the omission of SLNB in detail, to improve a better minimal invasive melanoma staging and to assess whether this practice variation leads to unwanted variations in clinical outcome.

Conflicts of interest

None.

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