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ORIGINAL ARTICLE – MELANOMA

Is a History of Optimal Staging by Sentinel Lymph Node Biopsy in the Era Prior to Adjuvant Therapy Associated with Improved Outcome Once Melanoma Patients have Progressed to Advanced Disease?

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ABSTRACT

Introduction. Sentinel lymph node biopsy (SLNB) is important for staging in patients with primary cutaneous melanoma. Did having previously undergone SLNB also affect outcomes in patients once they have progressed to metastatic melanoma in the era prior to adjuvant therapy?
Methods. Data were retrieved from the Dutch Melanoma Treatment Registry, a prospectively collected, nationwide database of patients with unresectable stage IIIC or IV (advanced) melanoma between 2012 and 2018. Melanoma-

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specific survival (MSS) was compared between patients with advanced cutaneous melanoma, previously treated with a wide local excision (WLE) or WLE combined with SLNB as initial treatment of their primary tumor. Cox regression analyses were used to analyze the influence of different variables on MSS.

Results. In total, 2581 patients were included, of whom 1412 were treated with a WLE of the primary tumor alone and 1169 in whom this was combined with SLNB. At a median follow-up of 44 months from diagnosis of advanced melanoma, MSS was significantly longer in patients who had previously undergone SLNB {median 23 months (95% confidence interval [CI] 19–29) vs. 18 months (95% CI 15–20) for patients treated with WLE alone; $p = 0.002$}. However, multivariate Cox regression did not identify SLNB as an independent favorable prognostic factor for MSS after diagnosis of advanced melanoma.

Conclusion. Prior to the availability of adjuvant systemic therapy, once patients have unresectable stage IIIC or IV (advanced) melanoma, there was no difference in disease outcome for patients who were or were not previously staged with SLNB.

Melanoma treatment has evolved significantly over the past decades. While systemic therapies have become widely available for advanced disease, surgery is still the cornerstone of treatment in localized disease.[1] Nowadays, wide local excision (WLE) of the primary tumor is usually accompanied by a sentinel lymph node biopsy (SLNB) according to the most recent (inter)national guidelines for pT1b melanomas and above, to accurately stage the regional lymph node basin.[2] SLNB in melanoma was first described by Morton et al. and is of paramount prognostic value.[3,4]

This prognostic value was shown in the MSLT-I trial, which randomized patients with intermediate and thick melanomas to either SLNB or nodal observation. If tumor-positive lymph nodes were identified by SLNB, a completion lymph node dissection (CLND) was performed. Although no survival benefit was seen in the SLNB group, SLNB provided valuable prognostic information: both disease-free survival and melanoma-specific survival (MSS) were significantly better in patients with a negative SLNB (83.2% and 90.2%, respectively) compared with patients with a positive SLNB (53.4% and 72.3%, respectively).[5] These results led to the MSLT-II and DeCOG-SLT studies, which randomized patients to either CLND or observation, after a positive SLNB.[6,7] Both studies failed to show a survival benefit and CLND is no longer routinely recommended by guidelines in microscopic (SLNB positive) stage III melanoma.[2]

Additionally, with the arrival of new and effective systemic therapies for advanced melanoma, the treatment landscape has shifted from more extensive surgery to extending indications for systemic therapy. Targeted therapy and immune checkpoint inhibition (ICI) have improved prognosis for patients with advanced/metastatic melanoma. A major factor predictive for response is tumor load, irrespective of which treatment was studied.[8–14] This has caused a shift towards adjuvant and neoadjuvant treatments, also demonstrating benefits in terms of relapse-free survival, albeit not yet in overall survival (OS).[15–18] Hence, early identification of recurrence and distant metastases seems valuable.

In this study, we hypothesized that the early identification of lymph node metastasis by SLNB leads to increased awareness of possible metastases during the follow-up period, which could lead to better outcomes for patients once metastasized. Therefore, the aim of this study was to investigate whether outcome in patients once they have progressed to unresectable stage III/IV melanoma is influenced by previous SLNB.

PATIENTS AND METHODS

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR). In this nationwide prospective database, all Dutch patients undergoing treatment for unresectable stage IIIC and IV metastatic melanoma (hereafter ‘advanced melanoma’) are included. The goal of the registry is to monitor the safety and outcomes of the novel systemic treatments introduced for melanoma patients over the past decade.[19] Nationwide coverage is assured due to the registration being a prerequisite for reimbursement. In compliance with Dutch regulations, the DMTR was approved by the Medical Ethical Committee and was not considered subject to the Medical Research Involving Human Subjects Act. Patients were offered an opt-out option.

Patients

Patients were included between the start of the registry (July 2012) and December 2018. This time span was chosen to ensure sufficient follow-up at data extraction in December 2020 and to avoid including patients who received adjuvant systemic treatment for SLNB-positive melanoma, which was approved in The Netherlands in December 2018. In the DMTR, data on the treatment of advanced melanoma and information on treatment of the primary tumor are registered. Patients treated with a WLE of the primary tumor or WLE accompanied with SLNB were eligible for inclusion in this study. Patients

undergoing adjuvant systemic therapy were excluded. Other exclusion criteria consisted of uveal or mucosal melanoma, melanoma of unknown primary, and macroscopic stage III or IV melanoma at primary diagnosis.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 25 (IBM Corporation, Armonk, NY, USA). Two cohorts of patients were analyzed: patients who did undergo SLNB and patients who did not. Patient, tumor, and treatment characteristics were analyzed using descriptive statistics. Characteristics of the two cohorts were compared using the Chi-square test for categorical variables and the *t* test or Mann–Whitney *U* test for continuous variables. Kaplan–Meier estimates were used to calculate follow-up, recurrence-free survival (RFS), MSS, and OS. RFS was defined and calculated as the time from primary tumor to first registered unresectable recurrence (locoregional or distant) or death, as registered in the DMTR. MSS and OS analyses were performed with two different baselines: the date of the primary tumor and the start of registration (diagnosis of unresectable stage III/IV disease) since all patients in our study develop advance disease in due course. Patients not experiencing an event were censored at the time of last follow-up. Log-rank tests were used to compare survival between the two cohorts. Cox regression analysis was used to analyze the influence of different variables on survival. Variables with a p value of < 0.1 in the univariate analyses were used in the multivariate Cox regression models.

RESULTS

Baseline Characteristics

In total, 2581 patients included in the DMTR database in December 2018 met the inclusion criteria of this study, of whom 1412 were treated with a WLE of the primary tumor alone, and in 1169 patients this was combined with SLNB. Baseline characteristics at the time of primary tumor diagnosis are described in Table 1. Ethnicity data are not collected in the registry. More patients in the SLNB group had primary tumors with unfavorable characteristics, such as high Breslow thickness and ulceration, and fewer patients with a primary melanoma located in the head and neck region underwent SLNB. Of the SLNBs performed, 45% were positive. In the SLNB group, significantly more patients (38%) presented with advanced disease in 2016 or thereafter, compared with those patients (31%) who did not undergo SLNB.

Table 2 shows patient characteristics and the treatment patients received when presenting with advanced disease. Patients in the SLNB group were younger, had a better performance status, less frequently had a tumor harboring a *BRAF* mutation, and were diagnosed more recently (in 2016 and thereafter) with advanced disease than patients in the no-SLNB group. The majority of patients in the SLNB group were treated with anti-PD-1 as first-line systemic therapy (24.6%), as opposed to patients treated with a WLE of the primary tumor alone, who were more likely to be treated with BRAF inhibitors (BRAFi, 32.5%).

As shown in Table 1, prior to the year 2000 SLNB was rarely performed. With passing time, the proportion of patients undergoing SLNB increased; between 2010 and 2014 a similar number of patients were treated with or without SLNB. Therefore, additional analyses were performed in the subgroup of patients with a primary tumor in 2010 or thereafter (this patient population will be referred to as 'primary tumor $\geq$ 2010). Electronic supplementary Table S1 shows the baseline and treatment characteristics of these patients. Similar differences between the SLNB and no-SLNB groups were seen in this cohort of patients.

Recurrence-Free Survival

At data cut-off, median follow-up was 141 months from diagnosis of primary melanoma and 44 months from diagnosis of advanced melanoma. The interval between the primary tumor and first diagnosis of advanced disease (and thus inclusion in the DMTR registry), was longer in patients treated with WLE alone, showing a median of 51.1 months (95% confidence interval [CI] 47.7–54.5), versus 32.5 months (95% CI 30.0–34.9) in patients undergoing WLE and SLNB ($p < 0.001$) (Fig. 1a). When performing the same analyses in the cohort of patients with a primary tumor in 2010 or thereafter, patients in the SLNB group had a slightly shorter time to first diagnosis of advanced melanoma (Fig. 1b), but this difference was not as distinct as in Fig. 1a, with a median of 26.5 months (95% CI 24.6–28.4) versus 24.2 months (95% CI 22.8–25.5) [p = 0.015].

Melanoma-Specific Survival

MSS from the primary tumor was in favor of patients who did not undergo SLNB: 120.0 months (95% CI 108.9–131.2) versus 89.2 (95% CI 80.3–98.3; $p < 0.001$) (Fig. 2a). However, MSS from diagnosis of advanced melanoma was longer in patients who were previously treated with SLNB [23.3 months (95% CI 18.7–28.1) vs. 17.5 months (95% CI 15.3–19.7)] (Fig. 2b). In patients with a primary tumor in 2010 or thereafter, a trend was seen towards a more favorable MSS from primary melanoma in patients who did undergo SLNB (Fig. 2c). In this cohort, MSS from first diagnosis of advanced melanoma

TABLE 1 Baseline characteristics, primary melanoma

Characteristic	All [$n = 2581$]	No SLNB [$n = 1412$]	SLNB [$n = 1169$]	p Value
Sex				**0.043**
Female	1113 (43.1)	634 (44.9)	479 (41.0)	
Male	1467 (56.9)	777 (55.1)	690 (59.0)	
Age (primary), years				0.806
Median (IQR)	58.0 (46.0–68.0)	57.0 (45.3–68.0)	58.0 (47.0–67.0)	
Breslow				**< 0.001**
Median (IQR)	2.2 (1.3–3.8)	1.7 (1.0–3.5)	2.8 (1.8–4.0)	
T stage				**< 0.001**
T1	392 (15.2)	359 (25.4)	33 (2.8)	
T2	744 (28.8)	399 (28.3)	345 (29.5)	
T3	798 (30.9)	300 (21.2)	498 (42.6)	
T4	513 (19.9)	237 (16.8)	276 (23.6)	
Unknown	134 (5.2)	117 (8.3)	17 (1.5)	
Location primary				**< 0.001**
Head and neck	382 (14.8)	292 (20.7)	90 (7.7)	
Trunk	1186 (46.0)	614 (43.5)	572 (48.9)	
Extremity	925 (35.8)	479 (33.9)	446 (38.2)	
Acral	88 (3.4)	27 (1.9)	61 (5.2)	
Type				**< 0.001**
Superficial spreading	1359 (52.7)	732 (51.8)	627 (53.6)	
Nodular	651 (25.2)	291 (20.6)	360 (30.8)	
Acrolentiginous	64 (2.5)	26 (1.8)	38 (3.3)	
Lentigo maligna	48 (1.9)	41 (2.9)	7 (0.6)	
Desmoplastic	25 (1.0)	18 (1.3)	7 (0,6)	
Other	117 (4.5)	78 (5.5)	39 (3.3)	
Unknown	317 (12.3)	226 (16.0)	91 (7.8)	
Ulceration				**< 0.001**
No	1380 (53.5)	782 (55.4)	598 (51.2)	
Yes	836 (32.4)	354 (25.1)	482 (41.2)	
Unknown	365 (14.1)	276 (19.5)	89 (7.6)	
Satellites				**< 0.001**
No	2033 (78.8)	1076 (76.2)	957 (81.9)	
(Micro)satellite	173 (6.7)	79 (5.6)	94 (8.0)	
Unknown	375 (14.5)	257 (18.2)	118 (10.1)	
SLNB result				N.A.
Negative			628 (53.7)	
Positive			537 (45.9)	
Unknown			4 (0.3)	
Year of primary tumor				**< 0.001**
<2000	175 (6.8)	160 (11.3)	15 (1.3)	
2000–2009	759 (29.4)	484 (34.3)	275 (23.5)	
2010–2014	1330 (51.6)	638 (45.2)	692 (59.2)	
≥2015	316 (12.2)	130 (9.2)	186 (15.9)	

Bold values indicate significant at $p < 0.05$

Data are expressed as n (%) unless otherwise specified

SLNB sentinel lymph node biopsy, *IQR* interquartile range

TABLE 2 Baseline and treatment characteristics, advanced melanoma

Characteristic	All [$n = 2581$]	No SLNB [$n = 1412$]	SLNB [$n = 1169$]	p Value
Age at DMTR inclusion, years				**< 0.001**
Median (IQR)	63.0 (53.0–72.0)	64.0 (54.0–73.0)	62.0 (51.0–70.0)	
Year of advanced melanoma				**< 0.001**
2010–2013	664 (25.7)	384 (27.2)	280 (24.0)	
2014–2015	1040 (40.3)	597 (42.3)	443 (37.9)	
≥2016	875 (33.9)	430 (30.5)	445 (38.1)	
BRAF mutation				**0.017**
Present	1464 (56.7)	817 (57.9)	647 (55.3)	
Absent	923 (35.8)	470 (33.3)	453 (38.8)	
Unknown	194 (7.5)	125 (8.9)	69 (5.9)	
WHO performance status				**< 0.001**
0	1094 (42.4)	534 (37.8)	560 (47.9)	
1	767 (29.7)	458 (32.4)	309 (26.4)	
2	228 (8.8)	137 (9.7)	91 (7.8)	
3	75 (2.9)	47 (3.3)	28 (2.4)	
4	15 (0.6	10 (0.7)	5 (0.4)	
Unknown	401 (15.5)	226 (16.0)	176 (15.1)	
LDH level				0.378
Normal	1493 (57.8)	798 (56.5)	695 (59.5)	
Elevated (>250 U/L)	911 (35.3)	508 (36.0)	403 (34.5)	
Unknown	177 (6.9)	106 (7.5)	71 (6.1)	
Brain metastases				0.559
Present	704 (27.3)	381 (27.0)	323 (27.6)	
Absent	1660 (64.3)	912 (64.6)	748 (64.0)	
Unknown	217 (8.4)	119 (8.5)	98 (8.4)	
First-line treatment				
Systemic therapy				**< 0.001**
Chemotherapy	112 (5.7)	60 (5.8)	52 (5.6)	
BRAFi	550 (28.0)	336 (32.5)	214 (23.1)	
Ipilimumab	335 (17.1)	162 (15.7)	173 (18.7)	
BRAFi + MEKi	312 (15.9)	156 (15.1)	156 (16.8)	
Anti-PD-1	431 (22.0)	203 (19.6)	228 (24.6)	
Ipi/Nivo	75 (3.8)	36 (3.5)	39 (4.2)	
Other	139 (7.1)	81 (7.8)	58 (6.3)	
Unknown	1 (0.1)	0	1 (0.1)	
T-VEC	6 (0.3)	1 (0.1)	5 (0.5)	
Surgery				0.303
No	2053 (82.1)	1107 (81.4)	946 (83.0)	
Yes	447 (17.9)	253 (18.6)	194 (17.0)	
Radiotherapy				0.429
No	1737 (69.5)	954 (70.1)	783 (68.7)	
Yes	763 (30.5)	406 (29.9)	357 (31.3)	
Second-line treatment				
Systemic therapy				0.245
Chemotherapy	38 (3.7)	19 (3.5)	19 (3.9)	
BRAFi	136 (13.2)	73 (13.4)	63 (13.0)	
Ipilimumab	299 (29.1)	158 (29.1)	141 (29.1)	
BRAFi + MEKi	138 (13.4)	81 (14.9)	57 (11.8)	
Anti-PD-1	280 (27.2)	144 (26.5)	136 (28.0)	

TABLE 2 continued

Characteristic	All [$n = 2581$]	No SLNB [$n = 1412$]	SLNB [$n = 1169$]	p Value
Ipi/Nivo	57 (5.5)	22 (4.1)	35 (7.2)	
Other	78 (7.6)	44 (8.1)	34 (7.0)	
Unknown	0	0	0	
T-VEC	2 (0.2)	2 (0.4)	0	
Surgery				0.305
No	1012 (90.9)	535 (91.8)	477 (90.0)	
Yes	101 (9.1)	48 (8.2)	53 (10.0)	
Radiotherapy				**0.030**
No	817 (73.4)	412 (70.7)	405 (76.4)	
Yes	296 (26.6)	171 (29.3)	125 (23.6)	

Bold values indicate significant at $p < 0.05$

Data are expressed as n (%) unless otherwise specified

SLNB sentinel lymph node biopsy, *DMTR* Dutch Melanoma Treatment Registry, *IQR* interquartile range, *LDH* lactate dehydrogenase, *BRAFi* BRAF inhibitor, *MEKi* MEK inhibitor, *Ipi* ipilimumab, *Nivo* nivolumab, *T-VEC* talimogene laherparepvec

was similar to the entire study population (Fig. 2d). OS results were comparable with MSS, as shown in electronic supplementary Fig. 1.

Univariate and Multivariate Analyses

Univariate analyses were performed to identify other factors influencing MSS, with both the diagnosis of the primary tumor and the diagnosis of advanced melanoma as baseline. Electronic supplementary Tables S2a and S2b show the results of the univariate analyses in all patients and in patients with primary tumors in 2010 and thereafter, respectively. Factors associated with the primary tumor, such as Breslow thickness, location, ulceration, and type are influencing MSS starting at diagnosis of the primary tumor; however, these factors are not associated with MSS starting at diagnosis of advanced disease. Apart from SLNB, several other factors are associated with MSS calculated from both baselines, including sex, age, and year of diagnosis of both the primary tumor and advanced disease. Additionally, several patient and treatment characteristics at the time of diagnosis of advanced disease were associated with MSS calculated from both baselines: WHO performance status, lactate dehydrogenase (LDH) level, presence of brain metastases, and type of first-line systemic therapy.

In contrast to the previously shown analyses, SLNB was not associated with MSS from either diagnosis of primary tumor or advanced disease in a multivariate model, in either all patients or patients with a primary tumor in 2010 and thereafter. In the multivariate model including all patients, age, ulceration of primary tumor, year of diagnosis of advanced melanoma, WHO performance status, LDH level, and presence of brain metastases were prognostic factors associated with both MSS starting at diagnosis of both the primary tumor and advanced disease (Table 3). Female sex and a primary melanoma on the extremities were favorable prognostic factors associated with MSS calculated from diagnosis of the primary tumor. In patients with a primary melanoma in 2010 or thereafter, factors impacting MSS from both baselines were age, year of diagnosis of advanced melanoma, WHO performance status, LDH level, and presence of brain metastases (Table 4). Favorable prognostic factors correlating with MSS from the primary tumor were ulceration and year of primary tumor. Presence of a *BRAF* mutation was associated with better MSS from advanced disease.

DISCUSSION

For decades, there has been an ongoing debate on the presence or absence of a therapeutic effect of SLNB for melanoma. In our study, a history of undergoing SLNB as initial staging of the primary melanoma was not associated with an improved outcome once patients were diagnosed with unresectable stage IIIC or IV (advanced) melanoma and were treated with systemic therapy. From 2016 onwards, there has been widespread availability of effective systemic therapies for advanced melanoma patients with both BRAF and MEK and immune checkpoint inhibitors.

Our study provides an overview of the implementation of SLNB in common clinical practice in The Netherlands: prior to 2010, the minority of patients diagnosed with

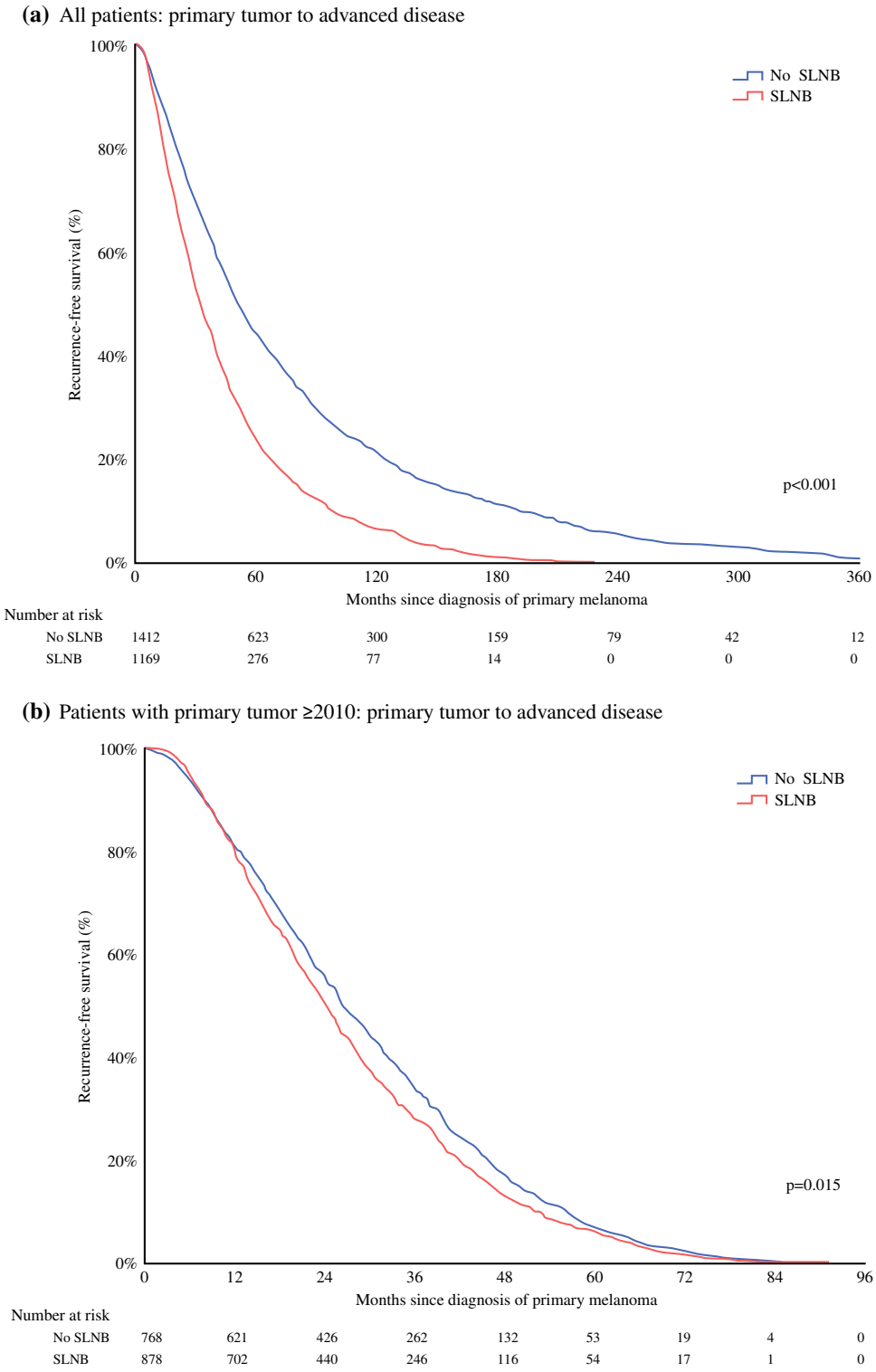


FIG. 1 Recurrence-free survival

primary melanoma were treated with a WLE and SLNB. However, in the last decade, this has shifted towards the majority of patients undergoing SLNB at diagnosis of primary melanoma.[20] Nonetheless, not all patients are undergoing SLNB, despite recommendation in clinical guidelines. Reasons to omit SLNB include patient preference, location of the primary tumor (head and neck), elderly and frail patients, or various other reasons. Additionally, in The Netherlands, primary melanoma excisions are often performed by general practitioners or dermatologists, but surgeons perform SLNB. Therefore, patients need to be referred to a surgeon for re-excision and SLNB

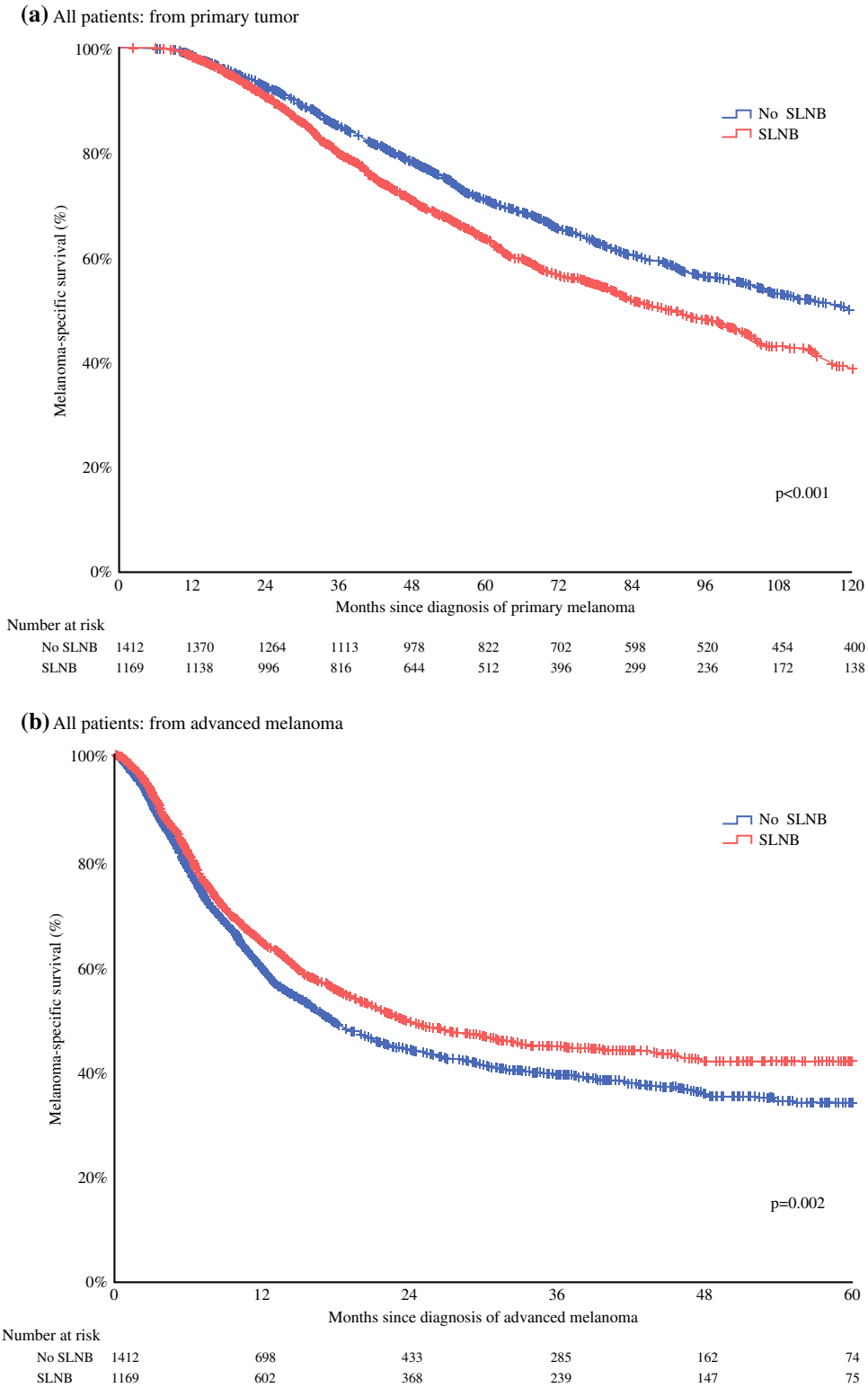
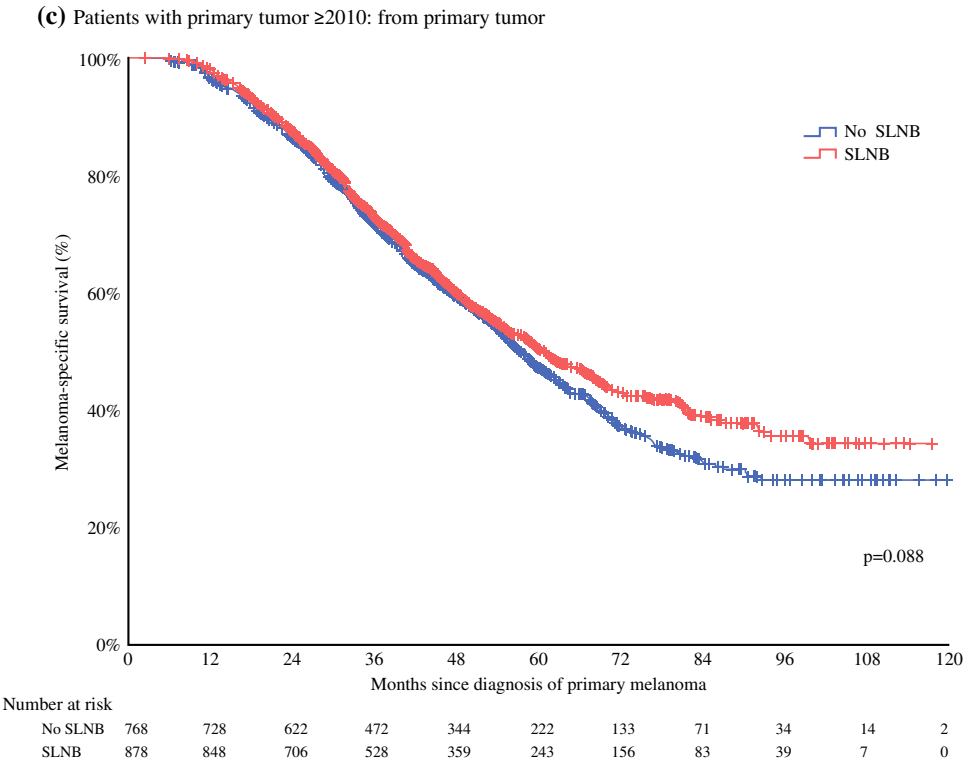


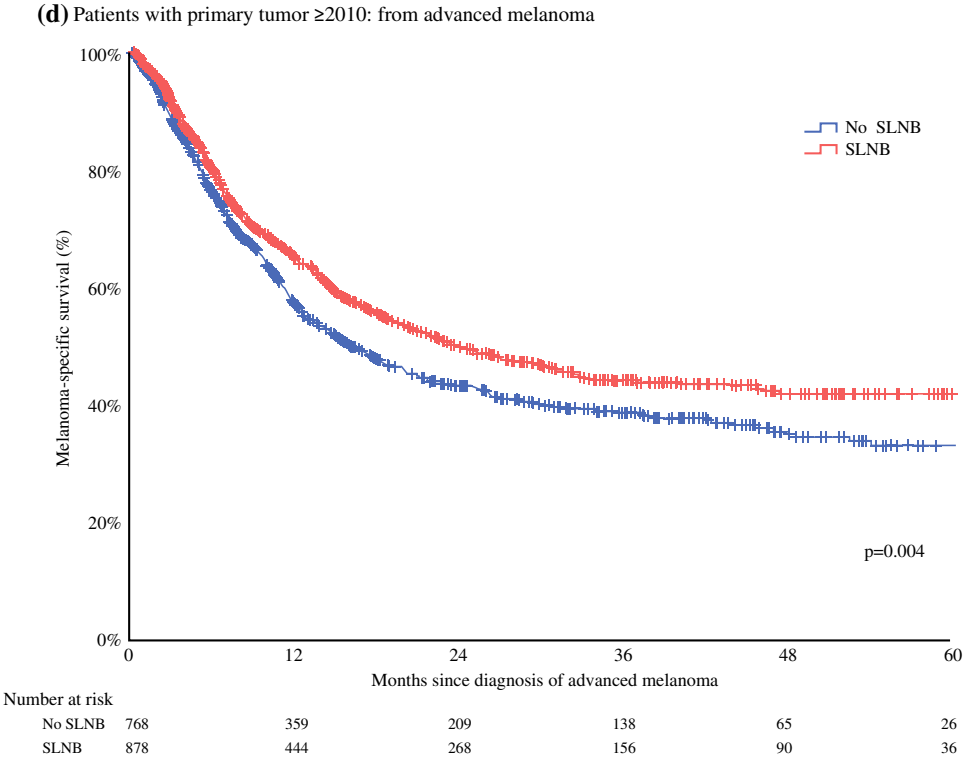
FIG. 2 Melanoma-specific survival

after diagnosis, which results in omission in some patients who undergo re-excision alone by a dermatologist. Unfortunately, the DMTR does not provide data on the reasons to omit SLNB in the treatment of registered patients.

As shown in Fig. 1a, RFS from primary tumor to advanced disease was worse in patients who did undergo SLNB, compared with patients who did not. The most likely explanations are the unfavorable prognostic features of the primary tumor (Table 1) in the SLNB group or a

FIG. 2 continued





higher awareness of recurrence resulting in more intensive surveillance in those patients who have undergone SLNB. However, these differences in RFS diminished in the subgroup of patients with a primary melanoma in 2010 and thereafter, even though patients in this subgroup undergoing SLNB also had unfavorable characteristics of their primary tumors (electronic supplementary Table S1a). It is likely the difference between RFS in the subgroup of

TABLE 3 Multivariate analyses

Variable	MSS primary			MSS advanced disease		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Sex						
Female	0.91	0.80–1.03	0.119	0.88	0.78–0.99	**0.027**
Male	Ref			Ref		
Age, primary	1.01	1.01–1.02	< **0.001**	1.01	1.00–1.01	**0.001**
Location, primary			0.060			0.589
Trunk	Ref			Ref		
Extremity	0.84	0.73–0.96	**0.010**	0.94	0.83–1.07	0.381
Acral	1.20	0.71–1.71	0.673	1.07	0.77–1.49	0.682
Head and neck	0.94	0.78–1.14	0.527	0.91	0.77–1.08	0.278
Breslow	1.00	1.00–1.00	0.232			
Type			0.574			
Superficial spreading	Ref					
Nodular	1.12	0.97–1.30	0.114			
Acrolentiginous	0.87	0.52–1.43	0.574			
Lentigo maligna	0.76	0.44–1.32	0.328			
Desmoplastic	1.05	0.51–2.14	0.898			
Other	0.92	0.69–1.24	0.605			
Unknown	1.05	0.86–1.29	0.639			
Ulceration			**0.004**			**0.029**
No	Ref			Ref		
Yes	1.25	1.09–1.44	**0.001**	1.18	1.03–1.34	**0.016**
Unknown	0.98	0.80–1.21	0.872	1.16	0.97–1.38	0.097
Satellites			0.253			
No	Ref					
(Micro)satellite	0.93	0.71–1.20	0.575			
Unknown	0.85	0.70–1.04	0.112			
SLNB performed						
No	Ref			Ref		
Yes	0.97	0.85–1.10	0.616	0.90	0.80–1.02	0.100
Year of primary tumor			< **0.001**			0.168
<2000	Ref			Ref		
2000–2009	11.65	7.73–17.56	< **0.001**	1.08	0.84–1.38	0.538
2010–2014	70.51	45.07–110.31	< **0.001**	1.21	0.94–1.57	0.136
≥2015	243.33	145.32–407.43	< **0.001**	1.04	0.75–1.45	0.799
Year of advanced melanoma			< **0.001**			< **0.001**
2010–2013	Ref			Ref		
2014–2015	0.50	0.43–0.57	< **0.001**	0.75	0.65–0.85	< **0.001**
≥2016	0.27	0.22–0.31	< **0.001**	0.55	0.47–0.65	< **0.001**
BRAF mutation			0.404			
Absent	Ref					
Present	0.97	0.86–1.11	0.698			
Unknown	0.51	0.19–1.38	0.185			
WHO performance status			< **0.001**			< **0.001**
0	Ref			Ref		
1	1.61	1.39–1.86	< **0.001**	1.66	1.45–1.91	< **0.001**
2	2.06	1.68–2.52	< **0.001**	2.56	2.11–3.11	< **0.001**
3	2.45	1.80–3.35	< **0.001**	4.16	3.10–5.59	< **0.001**
4	2.51	1.36–4.64	**0.003**	4.16	2.31–7.49	< **0.001**

TABLE 3 continued

Variable	MSS primary			MSS advanced disease		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Unknown	1.69	1.40–2.03	< **0.001**	1.58	1.33–1.89	< **0.001**
LDH level			< **0.001**			< **0.001**
Normal	Ref			Ref		
Elevated (>250 U/L)	1.77	1.57–2.01	< **0.001**	1.97	1.75–2.22	< **0.001**
Unknown	0.93	0.67–1.30	0.678	0.99	0.75–1.32	0.970
Brain metastases			< **0.001**			< **0.001**
Absent	Ref			Ref		
Present	1.60	1.41–1.82	< **0.001**	1.77	1.56–2.00	< **0.001**
Unknown	1.34	0.77–2.33	0.304	1.93	1.14–3.29	**0.015**

Bold values indicate significant at $p < 0.05$

HR hazard ratio, *CI* confidence interval, *SLNB* sentinel lymph node biopsy, *LDH* lactate dehydrogenase

patients with a primary tumor in 2010 and thereafter and all patients could be explained by the difference in year of diagnosis of the primary tumor. As described previously, the use of SLNB has increased over the years and therefore patients in the SLNB group of the entire cohort were diagnosed with primary melanoma more recently than patients in the no-SLNB group (Table 1). In the subgroup of patients with a primary melanoma in 2010 and thereafter, the year of diagnosis was more evenly spread between patients previously treated with SLNB or not. A less recent diagnosis may indicate a less aggressive biology (more indolent type) of the melanoma. This is supported by the multivariate analyses, which show a strong correlation between the year of diagnosis of the primary tumor and the MSS calculated from this baseline (Table 3).

The MSS calculated from the diagnosis of advanced melanoma is in favor of the SLNB group, both in all patients and in the subgroup of patients with a primary tumor in 2010 or thereafter (Fig. 2b, d). However, SLNB was not associated with MSS in the multivariate analyses of either subgroup (Tables 3, 4). The multivariate model showed other prognostic factors that could explain the differences seen in the initial analysis. For example, a more recent diagnosis of advanced melanoma showed a favorable prognostic characteristic. As shown in previous studies, improving systemic therapies over the past years has improved the prognosis of advanced melanoma patients every year.[21] Combining this information with data from Table 1, showing that more patients in the SLNB group were diagnosed with advanced disease more recently, could partially explain the differences between univariate and multivariate analyses. Additionally, a higher WHO performance status, an elevated LDH level, and the presence of brain metastases were associated with worse MSS in all subgroups. These confounding factors are thought to explain the difference seen in univariate analyses between patients with or without SLNB. We hypothesized that SLNB patients are diagnosed with advanced melanoma earlier and with a lower tumor burden than patients who have never undergone SLNB, despite patients undergoing SLNB having worse prognostic factors to start with.

Finally, this study only included patients who had undergone a WLE with or without SLNB (either positive or negative) as part of their initial staging and at some point developed unresectable stage IIIC or IV (advanced) melanoma. It did not include all patients who underwent SLNB and never developed unresectable stage IIIC or IV (advanced) melanoma, which is an important limitation of this study. Thus, we cannot definitively state that SLNB is not associated with a survival benefit, although it does suggest that SLNB has no therapeutic impact. Additionally, since all patients in this study developed advanced disease, no conclusions can be drawn on whether SNLB would have prevented recurrences in the first place; therefore, this question cannot be answered with the available data.

Previous studies have shown the value of SLNB in melanoma patients, starting with Morton et al.[5] On the contrary, other studies have suggested that the additional value of SLNB, compared with clinicopathological features of the primary tumor alone, was limited.[22–25] The study by El Sharouni et al. has contradicted these suggestions by demonstrating the additional prognostic information provided by SLNB.[4] In contrast with these previous studies, our study focused on the value of the previously performed SLNB in patients once they have already progressed to advanced/metastatic melanoma.

This study is population-based, which is simultaneously a strength and a weakness. The data from the DMTR assure nationwide coverage and prospective case report form (CRF) data collection by trained data managers, and therefore gives a comprehensive view of the real treatment

TABLE 4 Multivariate analyses, patients with a primary tumor in 2010 and thereafter

Variable	MSS primary			MSS advanced disease		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age, primary	1.01	1.01–1.02	< **0.001**	1.01	1.00–1.01	**0.024**
Breslow	1.00	1.00–1.00	0.411			
Ulceration			**0.006**			0.364
No	Ref			Ref		
Yes	1.29	1.10–1.51	**0.001**	1.12	0.95–1.32	0.166
Unknown	1.11	0.84–1.46	0.460	1.10	0.84–1.44	0.506
Sentinel node performed						
No	Ref					
Yes	0.96	0.83–1.11	0.584	0.89	0.76–1.04	0.130
Year of primary tumor						
2010–2014	Ref					
≥2015	3.17	2.50–4.03	< **0.001**	0.80	0.63–1.02	0.075
Year of advanced melanoma			< **0.001**			< **0.001**
2010–2013	Ref			Ref		
2014–2015	0.52	0.43–0.63	< **0.001**	0.71	0.58–0.86	**0.001**
≥2016	0.29	0.23–0.36	< **0.001**	0.53	0.43–0.66	< **0.001**
BRAF mutation						< **0.001**
Absent				Ref		
Present				0.75	0.64–0.87	< **0.001**
Unknown				0.16	0.02–1.17	0.071
WHO performance status			<**0.001**			< **0.001**
0	Ref			Ref		
1	1.50	1.25–1.80	< **0.001**	1.52	1.26–1.83	< **0.001**
2	1.86	1.44–2.39	< **0.001**	2.46	1.91–3.18	< **0.001**
3	2.35	1.62–3.43	< **0.001**	5.15	3.48–7.62	< **0.001**
4	2.14	1.00–4.20	**0.027**	3.12	1.58–6.17	**0.001**
Unknown	1.55	1.24–1.94	< **0.001**	1.79	1.42–2.26	< **0.001**
LDH level			< **0.001**			< **0.001**
Normal	Ref			Ref		
Elevated (>250 U/L)	1.93	1.66–2.25	< **0.001**	2.01	1.72–2.35	< **0.001**
Unknown	1.01	0.70–1.45	0.964	0.88	0.55–1.39	0.579
Brain metastases			< **0.001**			< **0.001**
Absent	Ref			Ref		
Present	1.52	1.29–1.78	< **0.001**	1.78	1.52–2.10	< **0.001**
Unknown	1.17	0.52–2.64	0.698	1.14	0.47–2.77	0.768

Bold values indicate significant at $p < 0.05$

HR hazard ratio, *CI* confidence interval, *LDH* lactate dehydrogenase

landscape. However, data are limited to the information collected by the CRF, and there is no possibility to retrieve any additional unregistered clinical data (e.g. differences in indication or choice to perform SLNB between different treatment centers, or other characteristics that may influence MSS). It provides an overview of melanoma treatment over the past decades, but in this study confounding by indication is a threat.

CONCLUSION

Prior to the availability of adjuvant systemic therapy, once patients were diagnosed with unresectable stage IIIC or IV (advanced) melanoma, there was no difference in disease outcome for patients who were or were not originally staged with SLNB. We do recommend SLNB in this day and age for the optimal staging of stage I/II melanoma to allow for appropriate selection for adjuvant systemic therapy (trials).

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