Implementation of the 7th Edition AJCC Staging System: Effects on Staging and Survival for pT1 Melanoma. *A Dutch Population Based Study*

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Int J Cancer. 2017 Apr 15;140(8):1802-1808. doi: 10.1002/ijc.30607

Abstract

Background In the 7th edition of the AJCC staging system the mitotic rate criterion replaced Clark level to increase correct classification of high risk thin melanoma patients (pT1B). Additionally, sentinel node biopsy (SNB) was recommended for nodal staging for pT1B melanomas. Aim: to evaluate the effects on pT1 substaging and clinical implications in the national pT1 melanoma population.

Methods All pT1 melanomas diagnosed in the Netherlands from 2003 – 2014 were selected from the Netherlands Cancer Registry (IKNL). Patients were stratified by cohort: according to AJCC edition: 1) 2003–2009 (6th) and 2), 2010–2014 (7th). Relative survival was calculated to estimate melanoma specific survival.

Results A total of 29.546 pT1 melanoma patients were included. The pT1b proportion increased from 10.1% in cohort 1, to 21.5% in cohort 2. The proportion of performed SNBs per cohort increased: for pT1b melanomas alone from 4.5% to 13.0%. SNB positivity rate decreased from 10.5% to 8.8% for the entire pT1 population, and for pT1b melanomas from 11.3% to 8.6%. At 5 year, the relative survival rate was similar for pT1a and pT1b in both cohorts, namely pT1a 100% vs pT1b 97% (cohort 1), and pT1a 100% vs. pT1b 98% (cohort 2).

Conclusion The 7th edition of the AJCC staging system has caused an increased number of patients to undergo SNB, without an increase in SNB positivity rate. Survival between pT1 subgroups remains similar. The mitotic rate criterion for pT1b classification and the recommendation to perform SNB for pT1b melanomas should be reconsidered.

Introduction

The incidence of newly diagnosed cutaneous melanomas continues to increase globally and in the Netherlands[1, 2]. The majority of all new melanoma patients have a thin melanoma (pT1, Breslow thickness ≤1.00mm), which has a good prognosis (10-year survival is 92%-95%)[3-5]. A minority of these patients however will develop regional and distant metastases, and ultimately die due to melanoma.

One of the most important prognostic factors for primary melanomas is the Breslow thickness, which has become the main allocator for the different primary tumor (pT) categories[3, 6, 7]. In the 6th edition of the American Joint Committee on Cancer (AJCC) Staging System the presence of ulceration was major criterion for pT1b classification besides a high Clark level (4/5), and recommendations for Sentinel Node Biopsy (SNB) were based on classification as pT1b melanoma[8, 9].

In the 7th edition of the AJCC Staging System, high Clark level was replaced by mitotic rate; i.e. the microscopic presence of 1 or more mitotic cells per 1mm2. This was found to be a stronger prognostic factor than high Clark level[3, 10]. The extent of its power in thin melanomas is however debated; the cut-off point of 1 or more mitosis per mm2 may be too low to be used as discriminating prognostic feature, and the large variety in histopathological examination protocols (number of examined slides, number of searched high power fields, size of high power fields) make it highly operator dependent[11]. Importantly, the decision to perform further nodal staging with a SNB in pT1 melanomas is based on this criterion in the Dutch melanoma guidelines[4]. As SNB is a minimally invasive surgical staging procedure, but an invasive procedure nonetheless[12, 13]. Changes in melanoma classification due to the update from 6th to 7th edition may have a large effect on the absolute number of patients that will be offered a SNB. This will also affect the absolute number of patients at risk for morbidity, due to the fact that the incidence of pT1 melanomas is high compared to pT2-4 melanomas.

Besides the question if a SNB is warranted in thin melanomas, it is not known if the mitotic rate criterion stratifies thin melanomas more accurately as high risk patients in the Dutch population. A corresponding higher risk of a positive SNB would be expected.

Aim of this study is to evaluate the effects of implementation of the 7th edition of the AJCC staging system and subsequent change to the national guidelines on pT1 substaging and clinical implications in the national pT1 melanoma population.

Patients and Methods

Patients

Population-based data was retrieved for all pT1 melanoma patients diagnosed from 2003 – 2014 from the Netherlands Cancer Registry (NCR), which is embedded within the Netherlands Comprehensive Cancer Organisation[2]. The NCR is annually linked to the Municipal Personal Records database to retrieve information on vital status and date of death. The follow-up data were completed until January 1st 2015.

The following patient and melanoma features were collected: gender, age at diagnosis, year of diagnosis, Breslow thickness, pT classification, stage, SNB performed yes/no, SNB result, whether completion lymph node dissection was performed (CLND), CLND result, number of removed lymph nodes, number of removed positive lymph nodes, follow-up from date of diagnosis in months, and status at last follow-up (dead or alive).

Patients were divided into two cohorts based on year of diagnosis and use of the AJCC Staging System 6th edition, cohort 1 (2003-2009) or 7th edition, cohort 2 (2010-2014). Due to the registration methods used during cohort 1 data on SNB where not accurate for this cohort. In case of a positive SN, CLND data sometimes overruled the SN data. This way, it was not possible to distinguish between patients with a lymph node dissection (LND) following a positive SN or with clinically involved lymph nodes warranting therapeutic LND. The registration methods for SNB were adapted prior to 2010 with the option to register SN data separately from LND data: SNB data for cohort 2 thus were accurate.

A quality control on accuracy of tumor staging has been performed for the entire database in 2016 prior to selection of data.

Statistics

Primary patient and tumor features were analyzed using X^2-tests or Mann- Whitney U test, as appropriate. The proportion of pT1a and pT1b was determined per cohort and per year of diagnosis. Incidence-rates were standardized for age according to the world standard population (WSR, World Standardized Rate) and are presented per 100,000 person-years. The proportion of performed SNBs was determined per cohort and per pT1 category, as well as the proportion of positive SNs. Follow-up was calculated from date of diagnosis until last follow-up or death. Survival times were calculated from the melanoma diagnosis to death (any cause) and considered censored for patients alive at last follow-up. Cause of death was not known.

Survival time was defined as time from diagnosis to death, or January 1, 2015 for those patients who were still alive. Relative survival was used as proxy of disease specific survival and was calculated correcting for age- and gender-specific background mortality[14]. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses

were performed using SPSS Version 21.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows Version 21.0 (IBM Corp., Armonk, NY, USA), and SAS version 9.4 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA).

Results

Patients

A total of 29.546 pT1 melanoma patients was registered for the time period 2003 – 2014. Of these patients, 23,879 (80.8%) were classified as pT1a, 4,779 (16.2%) as pT1b, and 888 (3.0%) were not further classified due to missing data on either Clark level or mitotic rate of the presence of ulceration at the time of registration. See **Table 1** for patient and melanoma features. Breslow thickness was comparable between cohort 1 and 2 (median 0.60 and 0.58), although statistically significant ($p<0.001$), probably due to the large number of patients in the study population. In Cohort 2 more patients were of the male sex and median age was higher (**Table 1**). Median follow-up for cohort 1 was 92 months [IQR 72 – 115 months]; median follow-up for cohort 2 was 28 months [IQR 14 – 43 months]. The incidence of thin melanomas increased over the investigated time period, starting at 1503 new pT1 melanomas in 2003 (pT1a 2.6 /100,000 person-years and pT1b 0.3 100,000 person-years (WSR)), up to 3430 new pT1 melanomas in 2014 (pT1a 4.9 /100,000 person-years and pT1b 1.5 /100,000 person-years (WSR)) (**Figure S1**).

pT1b Classification

The pT1b proportion differed significantly between both entire cohorts: 10.1% in cohort 1 vs. 21.5% in cohort 2 ($p<0.0001$). There was a clear increase in the pT1b proportion from 2011 onwards (**Figure 1**).

Sentinel Node Biopsies

The proportion of pT1 patients undergoing SNB doubled over time; 2.0% in cohort 1 vs. 4.8% in cohort 2 ($p<0.0001$) (**Figure 2).** The proportion of pT1b patients undergoing SNB increased almost threefold in cohort 2 (**Figure 2**). The proportion of patients with a positive SN was comparable in both cohorts (10.6% vs 9.0% without patients with unknown results, $p=0.445$) (**Table 2**). Of all positive SN patients, 46% (n=44) underwent a CLND (20 (69%) in cohort 1, 24 (36%) in cohort 2). The proportion and number of positive non-SNs was unknown, as this was registered combined with the number of positive SNs in the NCR.

Previous AJCC staging systems and others report a cut-off at 0.75 mm Breslow. To analyze this point, we have used this distribution in both cohorts with the current pT1a and pT1b: ≤ 0.75 mm and 0.76 – 1.00 mm without/with mitoses (**Table 2**).

Table 1. Patient and tumor characteristics of all patients diagnosed with tumor stage I melanoma in the Netherlands, 2003-2014.

	Cohort I 2003 - 2009	Cohort II 2010 - 2014	
	N (%) / median [IQR]	N (%) / median [IQR]	p
Gender			
male	5,324 (38.8)	6,964 (44.0)	<0.0001
female	8,401 (61.2)	8,857 (56.0)	
Age	53 [41 - 64]	58 [46 - 68]	<0.0001
Breslow	0.60 [0.40-0.78]	0.60 [0.40 - 0.80]	<0.0001
pT category			
pT1 nos	744 (5.4)	144 (0.9)	
pT1a	11,600 (84.5)	12,279 (77.6)	<0.0001
pT1b	1,381 (10.1)	3.398 (21.5)	
All pT1	13,725 (100)	15,821 (100)	
SNB			
Yes	276 (2.0)	759 (4.8)	<0.0001
No	13,449 (98.0)	15,062 (95.2)	
SN result			
Negative	245 (88.8)	677 (89.2)	
Positive	29 (10.5)	67 (8.8)	0.279
Not found	2 (0.7)	15 (2.0)	
LND			
Yes	48 (0.3)	55 (0.3)	0.976
No	13.677 (99.7)	15.766 (99.7)	
LND result			
Negative	41 (85.4)	47 (85.5)	
Positive	7 (14.6)	7 (12.7)	0.626
Unknown	0 (-)	1 (1.8)	

Patient and tumor characteristics of all patients diagnosed with tumor stage I melanoma in the Netherlands, 2003-2014. Features were analyzed using X^2-tests or Mann- Whitney U test, as appropriate. Abbreviations: SD, standard deviation; IQR, interquartile range; nos, not otherwise specified; SNB, sentinel node biopsy; SN, sentinel node; LND, lymph node dissection.

Survival

At 5 year, the relative survival rate was similar for pT1a and pT1b in both cohorts, namely pT1a 100% (standard error (SE) 0.2%) vs 100% (SE 0.5%), and pT1b 97% (SE 0.8%) vs. 98% (SE 1.2%) (**Figure 3**). The small group of unspecified pT1 patients had survival rates comparable with pT1a (data not shown). Five-year relative survival rate for pT1a patients with/without SNB was both 100% (cohort 1) and 96% vs. 100% (cohort 2), 5-year relative survival for pT1b patients with/without SNB was both 97% (cohort 1) and 97% vs. 98% (cohort 2).

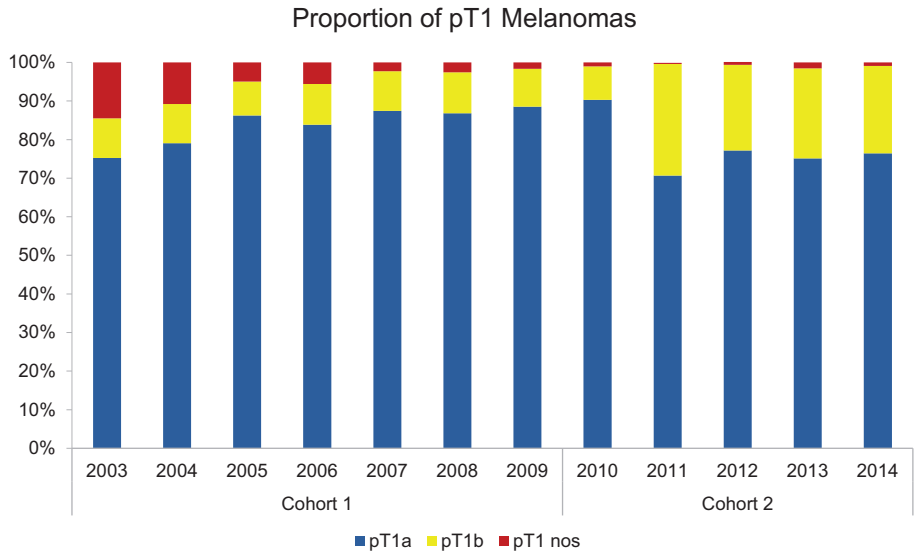


Figure 1. Proportion of pT1a (blue), pT1b (yellow) and pT1 nos (red) patients in percentages of the total annual number of patients. NOS; not otherwise specified.

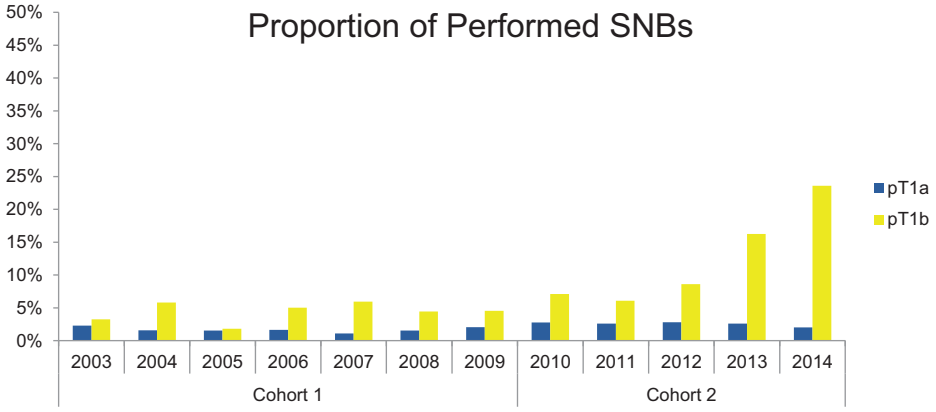
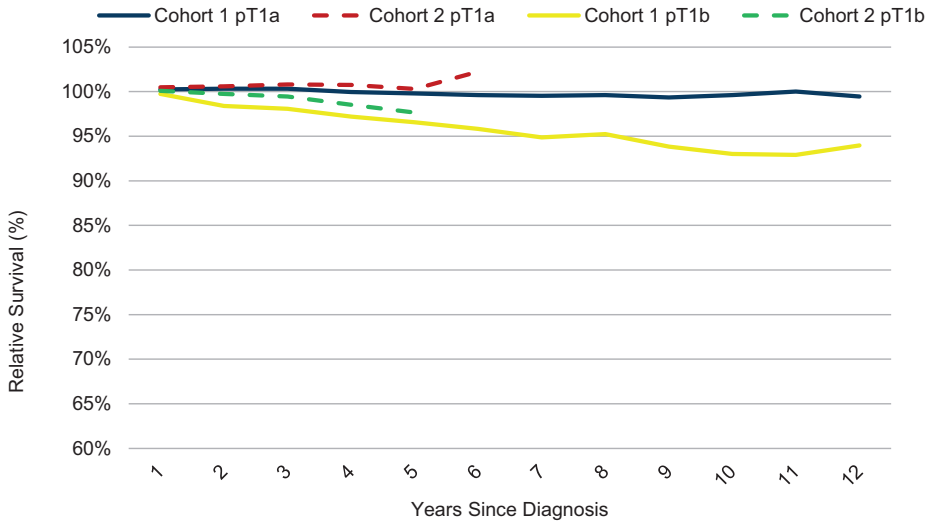


Figure 2. Proportion of performed sentinel node biopsies (SNBs) for pT1a (blue), pT1b (yellow), in percentages per year.

Five-year relative survival rate per SN status was 100% (SE 1.3%) vs. 88% (SE 6.5%) for SN negative vs. SN positive patients in cohort 1. In cohort 2 only 4-year relative survival rate could be calculated due to a low number of cases: this was 99% (SE 1.4%) for SN negative patients vs 85% (SE 8.2%) for SN positive patients. Relative survival for Breslow ≤0.75mm and >0.75mm was calculated for pT1a and pT1b, stratified per cohort (**Figure 4**).



No. at Risk*

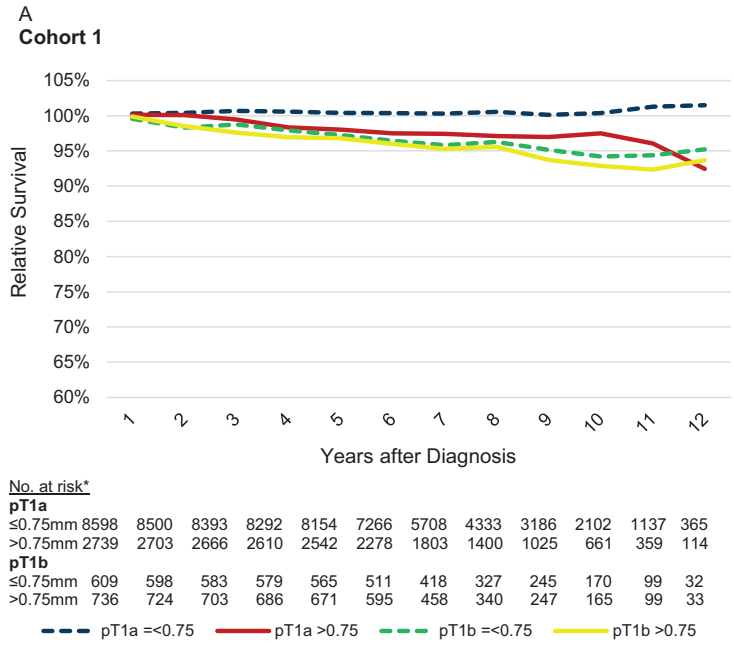
Cohort 1												
pT1a	11576	11437	11289	11125	10911	9742	7679	5882	4343	2881	1581	511
pT1b	1378	1354	1317	1295	1263	1127	892	677	499	342	203	67
Cohort 2												
pT1a	11127	8463	5869	3506	1228	23						
pT1b	2008	1209	642	354	116							

Figure 3. Relative Survival per pT1 category and Cohort. Relative survival for cohort 1 pT1a (blue), pT1b (yellow) and cohort 2 pT1a (red), pT1b (green). *: Effective number at risk.

Discussion

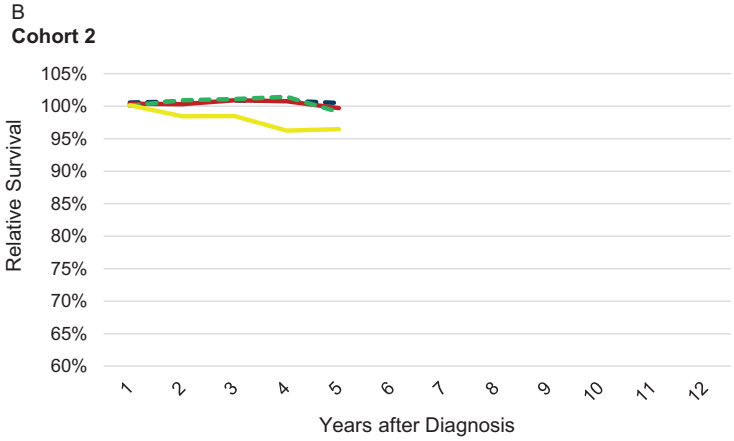
An increasing incidence of melanoma has been seen in the Netherlands already during many recent years[1, 15]. In the current report, we continue to see this increasing incidence of melanoma and see an increasing incidence of thin melanomas over the investigated time period (**Figure S1**) too**.** The proportion of pT1b patients increased considerably from 2011. One year later, (in 2012) the new version of the Dutch Melanoma Guideline was finalized, including the recommendation to consider SNB for pT1b melanoma and higher (previously for T2 melanoma and higher)[4]. The Dutch Cancer Registry started using the 7th edition of the AJCC staging system since 2010, but not all hospitals updated their staging system or clinical practice immediately, causing a temporary delay in the new classification of pT1b primaries according to the 7th AJCC edition.

The increased proportion of performed SNBs for pT1 patients (from 2% to 4.8%) was mainly caused by a steep increase in SNBs performed for pT1b patients in cohort 2. This could be expected considering the recommendation to offer SNB (but not mandatory to perform) for pT1b patients in the updated Dutch Melanoma Guideline in 2012.



No. at risk*

pT1a												
≤0.75mm	8598	8500	8393	8292	8154	7266	5708	4333	3186	2102	1137	365
>0.75mm	2739	2703	2666	2610	2542	2278	1803	1400	1025	661	359	114
pT1b												
≤0.75mm	609	598	583	579	565	511	418	327	245	170	99	32
>0.75mm	736	724	703	686	671	595	458	340	247	165	99	33



No. at Risk*

pT1a					
≤0.75mm	8664	6565	4528	2703	949
>0.75mm	2192	1712	1217	735	257
pT1b					
≤0.75mm	981	589	306	162	52
>0.75mm	938	567	304	175	60

Figure 4. Relative Survival per Breslow Category and Cohort. Relative survival for Breslow ≤0.75mm and >0.75mm per pT1 category, for cohort 1 (A) and cohort 2 (B). *: Effective number at risk.

When taking into account that after 2012 all pT1b patients should be offered a SNB according to the updated guidelines, the proportion of performed SNBs in the second cohort (13.0%) is still relatively low compared to the proportion of performed SNBs for intermediate thickness melanomas (pT1b – T3b): this was approximately 40% between 2003-2011[5]. Again for intermediate thickness melanomas the guidelines recommend to offer a SNB, but it is not mandatory to perform a SNB. A significant increase in the actual number of patients being exposed to SNB surgery can be observed (from 62 to 443 pT1b patients). As pT1 melanomas form the majority of all newly diagnosed melanomas, this has clear clinical implications: a more stressed referral system, increased wait lists, and increased costs. Let alone the increased number of patients being exposed to potential, albeit low, chance of morbidity related to the SNB, and CLND in case of a positive SN.

The actual number of patients with a negative SNB increased from 245 to 677. If all the potential pT1b patients would undergo a SNB, the number of additional SNB procedures would increase with 2,955 nationwide (fourfold increase for all pT1 melanomas). This would have massive budget implications to the national health care system, but more importantly the potential absolute number of patients at risk for unnecessary morbidity (approximately 300 individuals).

An interesting finding was that CLND was performed less often in cohort 2, which did not result in a decreased survival. This is in line with the results of the MSLT-1 and DeCOG trials, showing no survival difference for patients with immediate or delayed CLND[16, 17].

Previous AJCC staging systems and others report a cut-off at 0.75 mm Breslow in order to offer patients a SNB[18, 19]. In cohort 2, SNB positivity rate for pT1a ≤0.75mm and 0.76 – 1.00mm was 5.7% vs. 10.0% (p=0.357), and for pT1b 7.4% vs. 9.4% (p=0.572) (**Table 2**). Although not significant in this series, SN positivity rate was higher for melanomas with a Breslow thickness of >0.75mm in both pT1a and pT1b patients. SN positivity rate appears to be mainly driven by Breslow thickness and not by mitotic rate as it is currently defined.

Relative survival was excellent for the Dutch population. An increase in survival difference between pT1 substages was not observed, indicating that the stratification of high risk patients did not improve.

Summarizing, our data show an increase in the proportion of pT1b melanomas and a parallel increase in the proportion of performed SNBs in pT1b melanomas, but no increase in the proportion of positive SNs or a clear worse prognosis for all pT1b melanomas in the second cohort (7th edition AJCC). This implies that there has been stage migration between pT1a and pT1b, more specifically, patients formerly classified as pT1a now being classified as pT1b solely on presence of at least 1 singly mitosis/mm2. In a Surveillance, Epidemiology, and End Results (SEER) cancer registry study, the proportion of pT1b melanomas increased from 16.1% to 22.4%, but the proportion of performed SNBs for pT1b melanomas decreased (from 40.9% to 33.3%), and no significant increase

Table 2. Proportion of Performed and Positive SNBs per Breslow Category and per Cohort.

Cohort, group	Breslow (mm)	SNB performed			SN status		
		No	Yes	p	Negative	Positive	p
		N (%)	N (%)		N (%)	N (%)	
I pT1a	<0.75	8375 (99.4)	47 (0.6)		43 (95.6)	2 (4.4)	
	≥0.75	2803 (95.4)	135 (4.6)	<0.0001	119 (88.1)	16 (11.9)	0.249
	Total	11,178 (98.4)	182 (1.6)		162 (90.0)	18 (10.0)	
I pT1b	<0.75	561 (99.1)	5 (0.9)		5 (100)	0	
	≥0.75	731 (93.6)	50 (6.4)	<0.0001	43 (86.0)	7 (14.0)	1.00
	Total	1,292 (95.9)	55 (4.1)		48 (87.3)	7 (12.7)	
I All	<0.75	9,464 (99.4)	55 (0.6)		51 (96.2)	2 (3.8)	
	≥0.75	3,702 (94.9)	201 (5.1)	<0.0001	175 (87.1)	26 (12.9)	0.081
	Total	13,166 (98.1)	256 (1.9)		226 (89.0)	28 (11.0)	
II pT1a	<0.75	9,346 (99.0)	91 (1.0)		82 (94.3)	5 (5.7)	
	≥0.75	2,335 (92.4)	193 (7.6)	<0.0001	171 (90.0)	19 (10.0)	0.357
	Total	11,681 (97.6)	284 (2.4)		253 (91.3)	24 (8.7)	
II pT1b	<0.75	1,704 (93.2)	124 (6.8)		113 (92.6)	9 (7.4)	
	≥0.75	1,153 (79.8)	291 (20.2)	<0.0001	259 (90.6)	27 (9.4)	0.572
	Total	2,857 (87.3)	415 (12.7)		372 (91.2)	36 (8.8)	
II All	<0.75	11,162 (98.1)	215 (1.9)		195 (93.3)	14 (6.7)	
	≥0.75	3,516 (87.9)	486 (12.1)	<0.0001	431 (90.2)	47 (9.8)	0.184
	Total	14,678 (95.4)	701 (4.6)		626 (91.1)	61 (8.9)	

Proportion of performed SNBs and SN results per cohort and per pT1 category, subdivided by Breslow thickness <0.75mm or ≥0.75mm. Patients with unknown pT1 category and/or unknown Breslow thickness were censored for analysis. P-values were calculated with X^2-test or Fisher's exact test as appropriate. Abbreviations: SNB, sentinel node biopsy; SN, sentinel node.

in the proportion SN positive pT1b patients (7.1 vs 8.5%) was found[20]. Since they only compared the year 2010 (7th edition) with 2004-2009 (6th edition) any changes due to the implementation of the 7th edition after 2010 are not included in their analyses, which is a drawback of that study.

On top of the increase of diagnosed pT1b melanomas due to the mitotic rate criterion, the recommendation to perform nodal staging with a SNB in these patients may have driven some pathologists to perform an active search for mitoses (possibly even make and examine additional slides) in order to be able to diagnose a melanoma as pT1b, leading to overdiagnosis. This will further trouble the identification of true high risk patients. Also this will diminish the potential benefits of nodal staging for pT1b melanoma patients, which may not weigh up against the costs of SNB surgery.

Several studies have reported on the prognostic value of mitotic rate in thin melanomas[21-24], which formed the basis of including this in the 7th edition of the AJCC staging system[3, 10]. Kirkland et al. question the mitotic rate criterion of the 7th AJCC staging edi-

tion considering the fact that it is associated with the decision to offer a SNB[11]. They conclude in their review that despite its statistically significant value as prognostic variable, the chosen cut-off of 1 mitosis/mm2 does not have a clear clinically relevant impact on survival rates (nor on SN positivity rates), and thus does not warrant the decision to perform SNB in these patients in a routine fashion. This is supported by Wat et al. who found no association between mitotic rate and SN status in pT1 melanomas[25], and by Speijers et al. who also could not confirm a relationship between mitotic rate and SN status, nor for mitotic rate and survival[26].

Due to the fact that the data used are derived from a national registry system, available data is restricted to the registration performed at the time of diagnosis. Unfortunately not all data on SNBs performed in cohort 1 are available, as explained in the methods section. Potentially there may have been more patients who underwent a SNB which is registered as an LND only.

The actual details for pT1 substaging were not available for the current study (i.e. mitotic rate, Clark level and ulceration), but all T staging was based on these criterions according to the AJCC staging system valid at the time of diagnosis.

In cohort 2 the male gender was overrepresented, and median age was higher. This may have biased results, but these features were adjusted for in survival analyses to minimize potential bias.

The cause of death is unknown for all patients, since the registry data are anonymized after initial registry. However, we used a method to calculate relative survival adjusting for tumor and patient specific features, which forms an adequate alternative for disease specific survival.

Despite these drawbacks, data are present from all melanomas diagnosed between 2003 and 2014 on a national level, including not only primary tumor data but also SN and LND data, and mature follow-up data. This provides valuable insight in incidence and prognosis of pT1 melanomas from the entire Dutch population.

Conclusions

pT1 incidence has increased in the Netherlands over the past decade. Introduction of the mitotic rate criterion for pT1b substaging and the recommendation to perform SNB for pT1b melanoma has led to a proportional increase in pT1b melanomas, and an increase in performed SNBs. SN positivity rate has not increased and survival remained stable for pT1b melanomas, indicating that mitotic rate alone as criterion for pT1b has not improved selection of high risk pT1 patients for optional further (nodal) staging.

Based on the results of this study, and considering the fact that survival of Cohort 2 was not different at 5 year follow-up, recommendation on SNB for pT1b melanomas may be reconsidered as well.

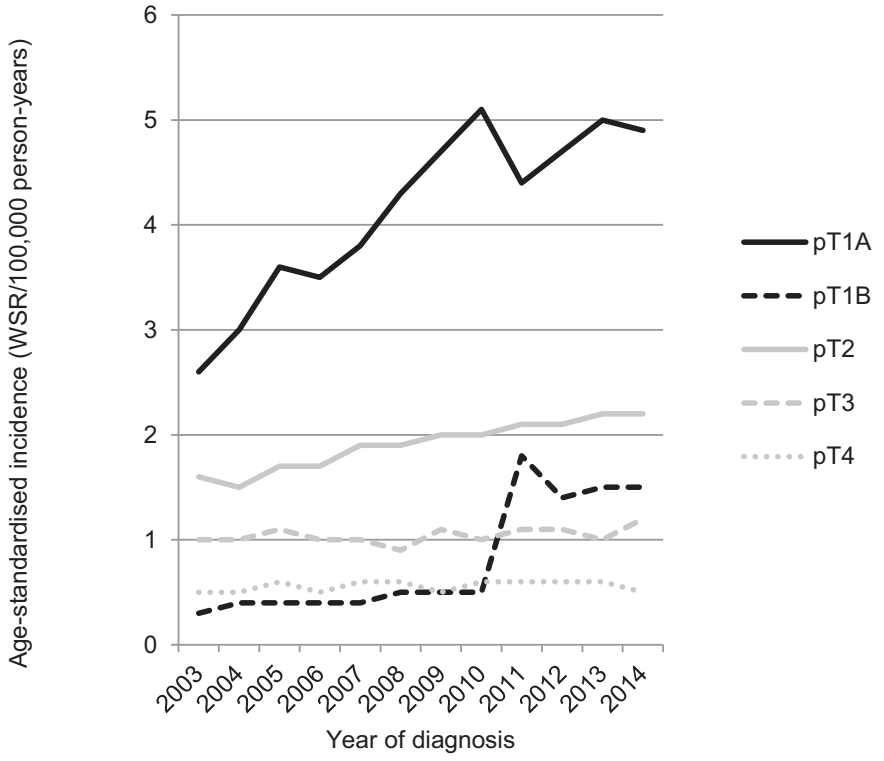


Figure S1. Melanoma Incidence per T Stage

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