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Original Research

Stage-specific trends in incidence and survival of cutaneous melanoma in the Netherlands (2003–2018): A nationwide population-based study

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KEYWORDS
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Incidence;
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Abstract ***Objective:*** To examine stage-specific trends in the incidence and survival of cutaneous melanoma in the Netherlands between 2003 and 2018, as well as the uptake of the sentinel lymph node biopsy (SLNB) and novel drugs during that period.
Methods: Data were obtained from the nationwide population-based Netherlands Cancer Registry for all patients diagnosed with invasive primary cutaneous melanoma (n = 60,267). We presented age-standardized incidence rates, the proportion of patients with an SLNB, the proportion of patients who received a novel drug (for their primary diagnosis) and one- and five-year relative survival rates.
Results: Between 2003 and 2018, the incidence rate increased from 10.9 to 23.9 for men and from 15.6 to 27.3 for women. This increase reflected the increasing incidence rate of patients

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with stage I and III. The proportion of patients with an SLNB increased from 23% to 64%. A reasonable increase was observed in the proportion of patients with a positive outcome (from 2% to 11%). For patients with stage IV, there was a shift from chemotherapy towards novel drugs as from 2013. The five-year relative survival rate increased from 81% to 92% for men and from 88% to 96% for women. This increase reflected the increasing five-year relative survival rate of patients with stage II, III, and IV.

Conclusion: We observed an increase in incidence for patients with stage I and III and an improvement in survival for patients with stage II, III and IV. These trends can be partly explained by the introduction of the SLNB and the novel drugs.

1. Introduction

Cutaneous melanoma (hereafter: melanoma) is a malignant tumour of the skin that originates from the melanocytes in the epidermis [1]. The incidence of melanoma has been steadily increasing over the last few decades. In 2020, melanoma was the sixth most commonly diagnosed cancer in Europe. A total of 150,627 patients were diagnosed with melanoma, and 26,360 patients died from the disease. The Netherlands is one of the European countries with the highest incidence and mortality rate. In 2020, the Netherlands ranked second in terms of incidence (27.0 per 100,000 person-years) and seventh in terms of mortality (2.3 per 100,000 person-years) [2].

The treatment and survival of melanoma largely depends upon the stage of disease. Surgery is considered the gold standard for patients with localized disease (hereafter: stage I or II) and patients with regional lymph node metastases (hereafter: stage III). One of the most important developments in the surgical management of melanoma is the introduction of the sentinel lymph node biopsy (SLNB) [3]. Information obtained from the SLNB has made it possible to stage patients more accurately, which has resulted in upstaging of patients whose regional lymph node metastases would otherwise have been missed.

Treatment options for patients with unresectable stage III and patients with distant metastases (hereafter: stage IV) have been limited for many years. Chemotherapy was the standard of care, but it never demonstrated to improve survival [4]. Advances in the understanding of melanoma biology has led to the introduction of novel immunotherapies and targeted therapies. The first two novel drugs, ipilimumab (an anti-CTLA-4 antibody) and vemurafenib (a BRAF inhibitor), were approved by the European Medicines Agency in 2011 and 2012, respectively. Since then, several other drugs became available for the treatment of patients with unresectable stage III and patients with stage IV [5].

Although previous studies [6–9] examined trends in the incidence and survival of melanoma in the Netherlands, none of them reported recent or stage-specific trends. Therefore, we examined stage-specific trends in the incidence and survival of melanoma in the Netherlands between 2003 and 2018, i.e. the period in which the 6th, 7th and 8th editions of the tumor–node–metastasis (TNM) classification were valid. In addition, we analyzed the uptake of the SLNB and the novel drugs during that period.

2. Methods

2.1. Data source

Data were obtained from the nationwide population-based Netherlands Cancer Registry (NCR). The NCR is based on notification of all newly diagnosed cancer patients by the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA Foundation) and the national registry of hospital discharge (for non-pathologically confirmed cancers). After notification, specially trained data managers routinely collect data on patient, tumour and treatment characteristics from medical records. Data on the vital status and date of death are annually retrieved from the database of deceased persons of the Central Bureau of Genealogy and the Personal Records Database [10].

2.2. Patient population

From the NCR, we selected all patients diagnosed with invasive primary cutaneous melanoma between 2003 and 2018. Patients with a prior malignancy (exception: basal cell carcinoma) and patients diagnosed at autopsy were excluded.

2.3. Data analysis

Data were extracted on year of diagnosis, age, gender, topography (i.e. site of the primary tumour), morphology (i.e. histology of the tumour), tumour thickness, tumour stage, number of metastatic lymph nodes, number of metastatic organs, surgery, systemic therapy, vital status and date of death. Topography and morphology were coded according to the International

Classification of Diseases for Oncology [11]. The tumour stage was coded according to the Union for International Cancer Control TNM classification valid at the time of diagnosis: 6th edition between 2003 and 2009, 7th edition between 2010 and 2016, and the 8th edition from 2017 onwards [12–14]. The pathological stage took precedence over the clinical stage. Patients who were diagnosed with melanoma of unknown primary (MUP) were staged accordingly.

Patients were stratified by year of diagnosis, stage at diagnosis and/or gender. Baseline patient and tumour characteristics were summarized using descriptive statistics. Age was presented as mean and standard deviation, as well as median and interquartile range. Topography, morphology, tumour thickness, tumour stage, number of metastatic lymph nodes and number of metastatic organs were presented as counts and proportions. Incidence was presented as age-standardized incidence rates (European Standardized Rate [ESR] per 100,000 person-years). To examine trends in incidence, the annual percent change (APC) and 95% confidence intervals (CIs) were calculated using the Joinpoint Trend Analysis Software of the National Cancer Institute [15]. The uptake of the SLNB was analyzed by dividing the number of patients with an SLNB by the number of eligible patients (i.e. patients with pT1b or higher without clinically detected lymph node metastases). We additionally presented whether the outcome of the SLNB was positive, negative or unknown. The uptake of the novel drugs was analyzed by calculating the proportion of patients who received chemotherapy, immunotherapy or targeted therapy for their primary diagnosis. This was presented as from the introduction of the novel drugs in the Netherlands (in 2012) for patients with stage III and IV. Survival was presented as one- and five-year relative survival rates. Relative survival was calculated by dividing the survival of the melanoma population by the survival of the melanoma-free population. All analyses were conducted using STATA statistical analysis software, version 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

3. Results

3.1. Trends in baseline patient and tumour characteristics

A total of 60,267 patients were diagnosed with invasive primary cutaneous melanoma in the Netherlands between 2003 and 2018. Table 1 presents the trends in baseline patient and tumour characteristics. The median age at diagnosis increased from 50 years in 2003 to 59 years in 2018. During the same period, the proportion of men increased from 40% to 48%. Minor changes were observed in the categorical distribution of topography, morphology and tumour thickness. Despite these changes, patients remained most frequently diagnosed with melanoma on the trunk, superficial spreading melanoma and a tumour thickness of less than or equal to one millimeter (mm).

Of all patients, 27,040 patients (45%) were men, and 33,227 patients (55%) were women. Supplemental Table 1 presents the baseline patient and tumour characteristics by gender. In general, baseline characteristics were reasonably comparable between men and women, with the exception of age and morphology. Men were somewhat older and most frequently diagnosed with melanoma on the trunk. Women were most frequently diagnosed with melanoma on the lower extremities.

3.2. Trends in incidence

Fig. 1 shows the trends in incidence. Between 2003 and 2018, the overall incidence rate (i.e. the incidence rate irrespective of the stage at diagnosis) increased substantially for both genders: from 10.9 to 23.9 for men (APC 2003–2012: 6.5% [95% CI: 5.4%–7.6%]; APC 2012–2018: 3.2% [95% CI: 1.2%–5.2%]) and from 15.6 to 27.3 (APC 2003–2018: 4.0% [95% CI: 3.6%–4.5%]) for women. This increase reflected the increasing incidence rate of patients with stage I and III as the incidence rate of patients with other stages (II, IV and MUP) remained reasonably stable.

3.3. Uptake of the sentinel lymph node biopsy

Fig. 2 presents the uptake of the SLNB. The proportion of patients with an SLNB increased from 23% to 64% between 2003 and 2018. The steepest increase was observed as from 2013. Of the patients with an SLNB, the proportion of patients with a positive outcome increased from 2% to 11% during the same period. As the proportion of patients whose outcome was unknown decreased substantially (from 79% to 7%), there was also a substantial increase in the proportion of patients with a negative outcome (from 19% to 82%). Only minor differences were observed in the uptake of the SLNB between men and women (see Supplemental Fig. 1).

3.4. Uptake of the novel drugs

Fig. 3 shows the uptake of the novel drugs. As from 2012, only a minority of patients with stage III received a novel drug for their primary diagnosis. The annual proportion of patients who received targeted therapy was less than 4%. For patients who received immunotherapy, the annual proportion was less than 6%, except for 2018. Between 2017 and 2018, the proportion increased substantially: from 5% to 16%. For patients with stage IV, there was a shift from chemotherapy towards immunotherapy and targeted therapy as from 2013. Since then, the proportion of patients who received immunotherapy or targeted therapy for their primary diagnosis increased substantially: from 1% to 46% and from 1% to 27%

Table 1
Trends in baseline patient and tumour characteristics.

The years of diagnosis	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
	n = 2,327	n = 2,492	n = 2,720	n = 2,740	n = 2,909	n = 3,185	n = 3,364	n = 3,626	n = 3,985	n = 4,081	n = 4,344	n = 4,482	n = 4,666	n = 5,216	n = 4,938	n = 5,192
Age, *years*																
Mean (SD)	51 (17)	52 (16)	52 (16)	53 (16)	53 (16)	54 (16)	54 (16)	55 (16)	55 (16)	56 (16)	56 (15)	57 (16)	57 (15)	58 (15)	59 (15)	59 (15)
Median (IQR)	50 (39–63)	51 (40–63)	51 (40–63)	52 (40–65)	52 (41–64)	53 (42–65)	53 (42–65)	55 (44–66)	54 (44–66)	56 (45–67)	56 (46–67)	57 (46–68)	57 (46–68)	58 (47–69)	59 (48–70)	59 (49–71)
Gender, *n (%)*																
Male	924 (40%)	1,065 (43%)	1,157 (43%)	1,163 (42%)	1,237 (43%)	1,389 (44%)	1,411 (42%)	1,644 (45%)	1,783 (45%)	1,891 (46%)	1,977 (46%)	2,061 (46%)	2,148 (46%)	2,403 (46%)	2,319 (47%)	2,468 (48%)
Female	1,403 (60%)	1,427 (57%)	1,563 (57%)	1,577 (58%)	1,672 (57%)	1,796 (56%)	1,953 (58%)	1,982 (55%)	2,202 (55%)	2,190 (54%)	2,367 (54%)	2,421 (54%)	2,518 (54%)	2,813 (54%)	2,619 (53%)	2,724 (52%)
Topography, *n (%)*																
Head and neck	284 (12%)	297 (12%)	327 (12%)	305 (11%)	318 (11%)	344 (11%)	388 (12%)	441 (12%)	461 (12%)	465 (11%)	482 (11%)	522 (12%)	538 (12%)	580 (11%)	601 (12%)	623 (12%)
Trunk	795 (34%)	885 (36%)	1,002 (37%)	1,001 (37%)	1,095 (38%)	1,193 (37%)	1,289 (38%)	1,388 (38%)	1,499 (38%)	1,622 (40%)	1,711 (39%)	1,769 (39%)	1,806 (39%)	1,986 (38%)	1,909 (39%)	2,035 (39%)
Upper extremity	425 (18%)	492 (20%)	509 (19%)	525 (19%)	539 (19%)	659 (21%)	692 (21%)	733 (20%)	794 (20%)	795 (19%)	932 (21%)	903 (20%)	977 (21%)	1,133 (22%)	1,056 (21%)	1,090 (21%)
Lower extremity	727 (31%)	728 (29%)	772 (28%)	805 (29%)	827 (28%)	869 (27%)	866 (26%)	917 (25%)	1,086 (27%)	1,063 (26%)	1,099 (25%)	1,144 (26%)	1,188 (25%)	1,345 (26%)	1,208 (24%)	1,299 (25%)
Unknown	96 (4%)	90 (4%)	110 (4%)	104 (4%)	130 (4%)	120 (4%)	129 (4%)	147 (4%)	145 (4%)	136 (3%)	120 (3%)	144 (3%)	157 (3%)	172 (3%)	164 (3%)	145 (3%)
Morphology, *n (%)*																
Superficial spreading	1,348 (58%)	1,470 (59%)	1,705 (63%)	1,740 (64%)	1,852 (64%)	2,050 (64%)	2,190 (65%)	2,473 (68%)	2,746 (69%)	2,801 (69%)	3,122 (72%)	3,247 (72%)	3,415 (73%)	3,982 (76%)	3,712 (75%)	3,947 (76%)
Nodular	344 (15%)	318 (13%)	349 (13%)	341 (12%)	314 (11%)	400 (13%)	433 (13%)	401 (11%)	445 (11%)	480 (12%)	483 (11%)	417 (9%)	453 (10%)	441 (8%)	441 (9%)	435 (8%)
Lentigo maligna	54 (2%)	71 (3%)	55 (2%)	78 (3%)	68 (2%)	91 (3%)	93 (3%)	126 (3%)	131 (3%)	176 (4%)	166 (4%)	196 (4%)	186 (4%)	180 (3%)	194 (4%)	218 (4%)
Acral lentiginous	17 (1%)	29 (1%)	22 (1%)	21 (1%)	19 (1%)	19 (1%)	19 (1%)	17 (0%)	30 (1%)	42 (1%)	49 (1%)	37 (1%)	42 (1%)	36 (1%)	40 (1%)	34 (1%)
Other	85 (4%)	97 (4%)	108 (4%)	95 (3%)	88 (3%)	78 (2%)	98 (3%)	96 (3%)	80 (2%)	71 (2%)	96 (2%)	97 (2%)	76 (2%)	64 (1%)	77 (2%)	73 (1%)
Unknown	479 (21%)	507 (20%)	481 (18%)	465 (17%)	568 (20%)	547 (17%)	531 (16%)	513 (14%)	553 (14%)	511 (13%)	428 (10%)	488 (11%)	494 (11%)	513 (10%)	474 (10%)	485 (9%)
Tumour thickness, *mm, n (%)*																
≤1.00	1,084 (47%)	1,215 (49%)	1,359 (50%)	1,327 (48%)	1,427 (49%)	1,696 (53%)	1,769 (53%)	1,990 (55%)	2,226 (56%)	2,295 (56%)	2,503 (58%)	2,555 (57%)	2,648 (57%)	3,095 (59%)	2,839 (57%)	2,991 (58%)
1.01–2.00	514 (22%)	520 (21%)	562 (21%)	610 (22%)	676 (23%)	657 (21%)	703 (21%)	729 (20%)	785 (20%)	821 (20%)	889 (20%)	929 (21%)	954 (20%)	1,040 (20%)	915 (19%)	990 (19%)
2.01–4.00	346 (15%)	360 (14%)	391 (14%)	370 (14%)	357 (12%)	360 (11%)	430 (13%)	420 (12%)	450 (11%)	471 (12%)	439 (10%)	542 (12%)	530 (11%)	530 (10%)	517 (10%)	533 (10%)
>4.00	208 (9%)	227 (9%)	215 (8%)	241 (9%)	239 (8%)	253 (8%)	237 (7%)	245 (7%)	280 (7%)	266 (7%)	310 (7%)	242 (5%)	310 (7%)	311 (6%)	357 (7%)	332 (6%)
Unknown	175 (8%)	170 (7%)	193 (7%)	192 (7%)	210 (7%)	219 (7%)	225 (7%)	242 (7%)	244 (6%)	228 (6%)	203 (5%)	214 (5%)	224 (5%)	240 (5%)	310 (6%)	346 (7%)
Tumour stage, *n (%)*																
I	1,490 (64%)	1,628 (65%)	1,819 (67%)	1,802 (66%)	1,969 (68%)	2,212 (69%)	2,308 (69%)	2,552 (70%)	2,816 (71%)	2,938 (72%)	3,179 (73%)	3,285 (73%)	3,378 (72%)	3,904 (75%)	3,532 (72%)	3,747 (72%)
II	475 (20%)	512 (21%)	504 (19%)	532 (19%)	504 (17%)	530 (17%)	579 (17%)	579 (16%)	627 (16%)	626 (15%)	644 (15%)	654 (15%)	705 (15%)	712 (14%)	694 (14%)	704 (14%)
III	206 (9%)	203 (8%)	225 (8%)	220 (8%)	258 (9%)	233 (7%)	275 (8%)	284 (8%)	327 (8%)	317 (8%)	338 (8%)	350 (8%)	376 (8%)	386 (7%)	427 (9%)	411 (8%)
IV	97 (4%)	84 (3%)	99 (4%)	105 (4%)	106 (4%)	116 (4%)	124 (4%)	133 (4%)	135 (3%)	122 (3%)	118 (3%)	142 (3%)	157 (3%)	169 (3%)	155 (3%)	151 (3%)
MUP	59 (3%)	63 (3%)	70 (3%)	79 (3%)	72 (2%)	94 (3%)	77 (2%)	77 (2%)	80 (2%)	76 (2%)	65 (1%)	51 (1%)	50 (1%)	42 (1%)	47 (1%)	63 (1%)
Unknown	0 (0%)	2 (0%)	3 (0%)	2 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	83 (2%)	116 (2%)
Number of metastatic lymph nodes, *n (%)*																
No examination	1,781 (77%)	1,989 (80%)	2,227 (82%)	2,195 (80%)	2,294 (79%)	2,544 (80%)	2,594 (77%)	2,855 (79%)	3,076 (77%)	3,129 (77%)	3,167 (73%)	3,162 (71%)	3,089 (66%)	3,466 (66%)	3,270 (66%)	3,415 (66%)
0	369 (16%)	344 (14%)	326 (12%)	381 (14%)	429 (15%)	455 (14%)	548 (16%)	558 (15%)	660 (17%)	692 (17%)	895 (21%)	1,027 (23%)	1,250 (27%)	1,431 (27%)	1,304 (26%)	1,405 (27%)
1	103 (4%)	86 (3%)	96 (4%)	90 (3%)	112 (4%)	108 (3%)	127 (4%)	136 (4%)	166 (4%)	161 (4%)	187 (4%)	183 (4%)	205 (4%)	208 (4%)	241 (5%)	249 (5%)
2	38 (2%)	32 (1%)	30 (1%)	33 (1%)	31 (1%)	40 (1%)	49 (1%)	43 (1%)	48 (1%)	44 (1%)	44 (1%)	61 (1%)	66 (1%)	68 (1%)	62 (1%)	66 (1%)
3	11 (0%)	13 (1%)	9 (0%)	13 (0%)	20 (1%)	16 (1%)	17 (1%)	12 (0%)	9 (0%)	31 (1%)	21 (0%)	20 (0%)	31 (1%)	21 (0%)	19 (0%)	26 (1%)
≥4	14 (1%)	24 (1%)	24 (1%)	25 (1%)	17 (1%)	20 (1%)	26 (1%)	20 (1%)	23 (1%)	20 (0%)	25 (1%)	27 (1%)	24 (1%)	19 (0%)	35 (1%)	27 (1%)
Unknown	11 (0%)	4 (0%)	8 (0%)	3 (0%)	6 (0%)	2 (0%)	3 (0%)	2 (0%)	3 (0%)	4 (0%)	5 (0%)	2 (0%)	1 (0%)	3 (0%)	7 (0%)	4 (0%)
Number of metastatic organs, *n (%)*																
0	2,255 (97%)	2,408 (97%)	2,590 (95%)	2,611 (95%)	2,768 (95%)	3,044 (96%)	3,208 (95%)	3,457 (95%)	3,810 (96%)	3,911 (96%)	4,190 (96%)	4,301 (96%)	4,466 (96%)	5,003 (96%)	4,750 (96%)	5,009 (96%)
<3	58 (2%)	67 (3%)	107 (4%)	94 (3%)	92 (3%)	101 (3%)	102 (3%)	115 (3%)	121 (3%)	120 (3%)	103 (2%)	118 (3%)	132 (3%)	135 (3%)	107 (2%)	107 (2%)
≥3	14 (1%)	17 (1%)	23 (1%)	35 (1%)	49 (2%)	40 (1%)	54 (2%)	54 (1%)	54 (1%)	50 (1%)	51 (1%)	63 (1%)	68 (1%)	78 (1%)	81 (2%)	76 (1%)

IQR, interquartile range; mm, millimeter; MUP, melanoma of unknown primary; *n*, number; SD, standard deviation.

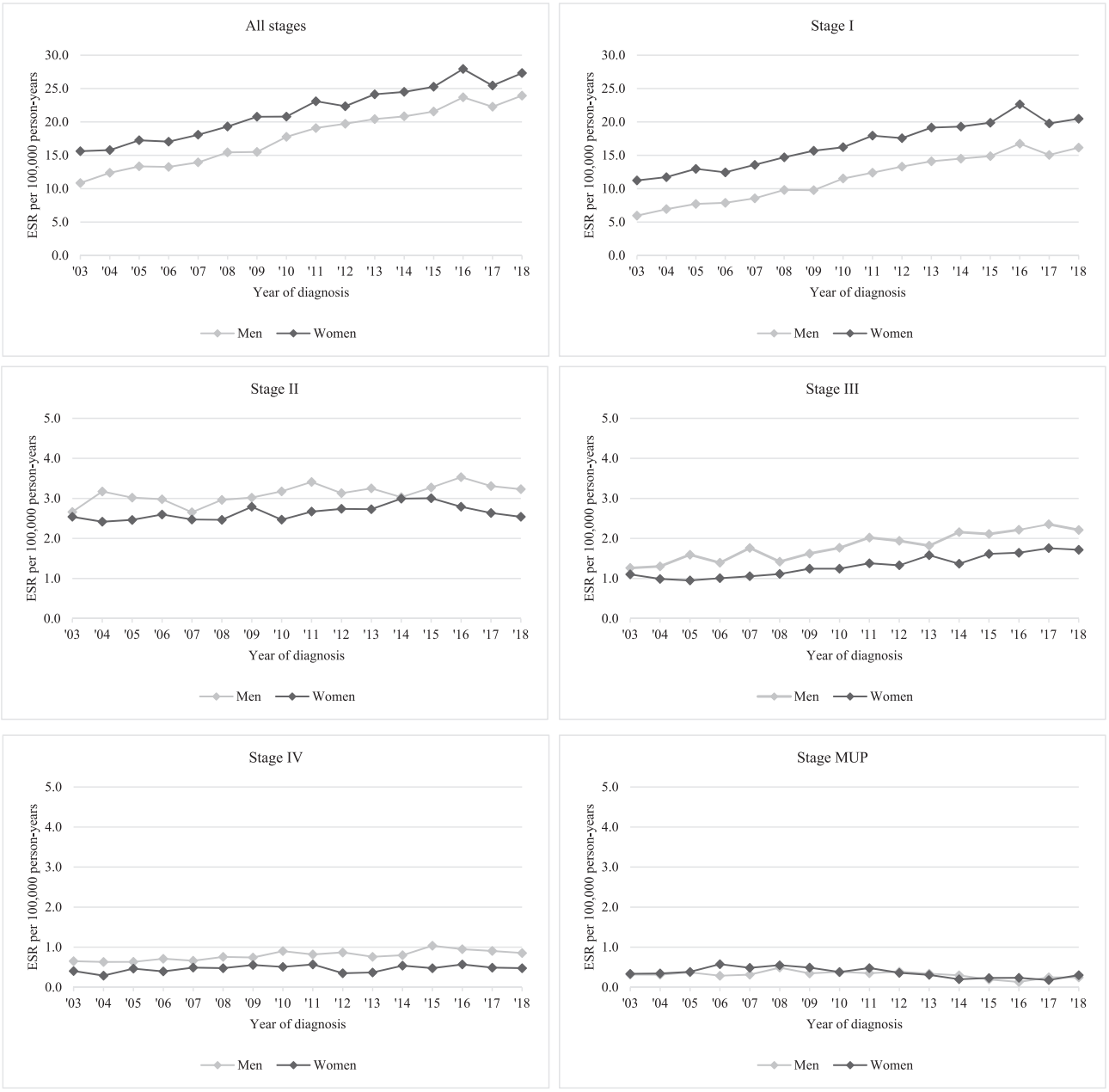

Fig. 1. Trends in incidence stratified by stage at diagnosis and gender[a,b,c]. ESR, European Standardized Rate; MUP, melanoma of unknown primary. [a] Please note the different scales on the y-axis. [b] Incidence rates are presented in numbers in Supplemental Table 2. [c] The annual percent change and 95% confidence intervals are presented in Supplemental Table 3.

between 2013 and 2018, respectively. The proportion of patients who received chemotherapy decreased from 40% to 0% during the same period. There were no remarkable differences in the uptake of the novel drugs between men and women (see Supplemental Fig. 2).

3.5. Trends in survival

Fig. 4 presents the trends in survival. Between 2003 and 2018, the overall one-year relative survival rate (i.e. the relative survival rate irrespective of the stage at diagnosis) remained stable for both genders. The overall five-year relative survival rate increased, however, substantially: from 81% to 92% for men and from 88% to 96% for women. This increase predominantly reflected the increasing five-year relative survival rate of patients with stage II and III: from 66% to 81% (stage II) and from 62% to 69% (stage III) for men and from 72% to 85% (stage II) and from 62% to 74% (stage III) for women. A steep increase in the five-year relative survival rate was also observed for patients with stage IV in recent years. Between 2013 and 2015, the five-year relative survival rate increased from 12% to 24% for men and from 21% to 31% for women. Although our observation period was not sufficient to evaluate the five-year relative survival

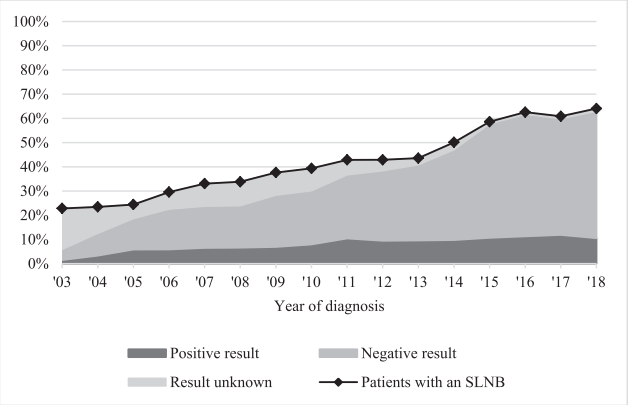

Fig. 2. Uptake of sentinel lymph node biopsy. SLNB, sentinel lymph node biopsy.

rate beyond 2015, it is worth noting that the one-year relative survival rate of patients with stage IV decreased as from 2016. Relative survival rates of patients with stage I and MUP remained reasonably stable.

4. Discussion

In our study, we examined stage-specific trends in the incidence and survival of cutaneous melanoma in the Netherlands between 2003 and 2018, as well as the uptake of the SLNB and the novel drugs during that period. The incidence increased substantially for patients with stage I and III but remained reasonably stable for patients with other stages (II, IV and MUP). For patients with stage I, this may have been driven by several factors, including increased exposure to ultraviolet radiation and earlier diagnosis due to enhanced awareness. For example, it is commonly known that men are more reluctant to go to the doctor than women. Hence, greater attention has been given to men in awareness campaigns in recent years. The results of our study suggest that these efforts may have resulted in earlier diagnosis among men as the incidence of patients with stage I increased more steeply in men than in women.

Both factors also may have driven the increased incidence of patients with stage III. In addition, we believe that the increase is due to upstaging of patients. Because of the SLNB, patients who (without the SLNB) would have been diagnosed with stage II are now diagnosed with stage III. During our study period, the proportion of patients with an SLNB almost tripled: from 23% in 2003 to 64% in 2018. The increase was most pronounced as from 2013. This may be owing to changes in guideline recommendations. According to the fourth revision of the Dutch melanoma guideline (published in 2004), SLNB was only recommended for patients who wanted to be optimally informed about their prognosis [16]. In the fifth revision of the guideline (published in 2012), it became a standard diagnostic procedure for patients diagnosed with a tumour thickness of more than 1.0 mm and/or ulceration [17]. Although we already observed a reasonable increase in the proportion of patients with a positive outcome (from 2% to 11%), there is room for improvement as one-third of the eligible patients still do not undergo an SLNB. Even if this would not result in a higher proportion of patients with a positive outcome, more patients will be accurately staged and can, therefore, receive the most appropriate care.

The upstaging of patients is probably also responsible for the increased survival of patients with stage II and III. As the survival of patients who are upstaged is worse than the survival of patients with stage II but better than the survival of patients who are clinically diagnosed with stage III, survival of both patient groups increases. This may suggest that we did not observe a real increase in survival, but rather a more accurate estimation of the survival. On the other hand, we should not underestimate the impact of the novel drugs. Even though only a small proportion of patients with stage III received a novel drug for their primary diagnosis, they may have received one or more novel drugs after developing disease progression. The same applies to patients with stage II. According to a previous Dutch study [18], approximately 30% of the

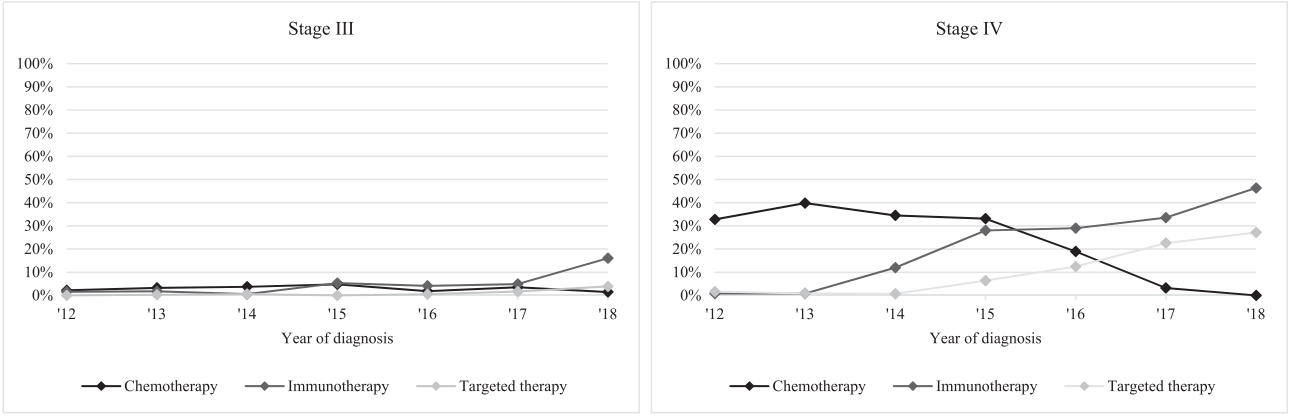

Fig. 3. Uptake of the novel drugs stratified by stage at diagnosis.

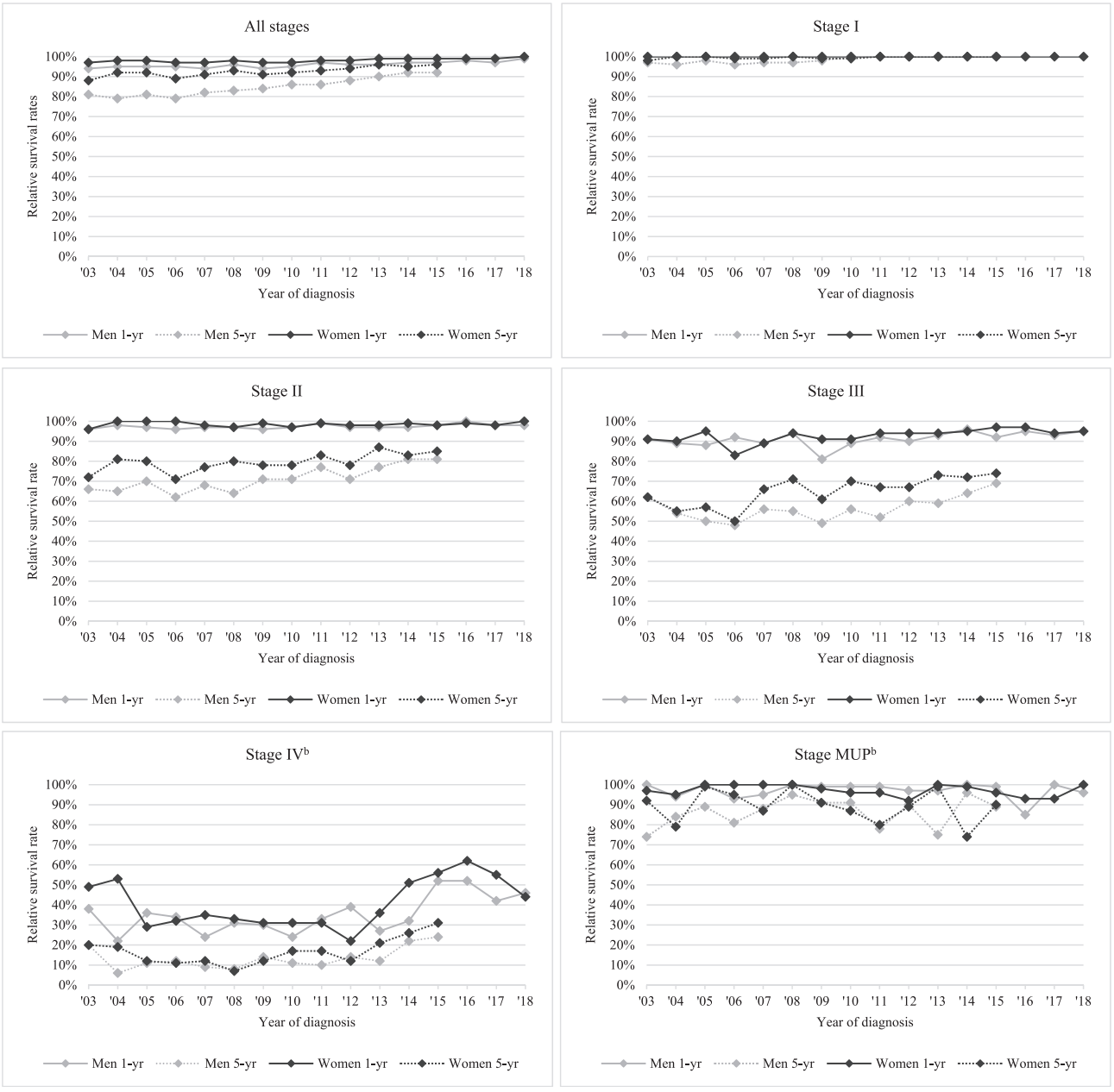

Fig. 4. Trends in survival stratified by the stage at diagnosis and gender[a]. MUP, melanoma of unknown primary; yr, year. [a] Relative survival rates are presented in numbers in Supplemental Table 4. [b] Please note the low patient numbers (see Supplemental Table 1).

patients with stage II and 50% of the patients with stage III will eventually develop disease progression. Two-thirds of these patients will develop distant metastases either as first or subsequent recurrence. Whether our patients received one or more novel drugs after developing disease progression could not be examined with our data.

Compared to patients with stage III, the proportion of patients who received a novel drug for their primary diagnosis was much higher for patients with stage IV. For these patients, there was a shift towards the novel drugs as from 2013. Patients more frequently received immunotherapy than targeted therapy. This is mainly because targeted therapy can only be applied to patients whose melanoma harbors a mutation in the BRAF gene. Approximately 60% of the melanomas harbor this mutation [19]. The novel drugs have had a large impact on the survival of patients with stage IV. Between 2013 and 2015, there was an absolute change in the one- and five-year relative survival rate of 25% and 12% for men and 20% and 10% for women, respectively. It should, however, be noted that the one-year relative survival rate decreased as from 2016. This is, however, most likely due to low patient numbers as we only included patients who were primarily diagnosed with stage IV. A previous Dutch study showed that the one-year survival rate of

all patients with stage IV (irrespective of their stage at diagnosis) increased from 48% in 2013–2014 to 59% in 2015–2017 [20].

Our study has some key strengths, including the national coverage and the extensiveness of the results. Furthermore, to our knowledge, we present the most recent insight into stage-specific trends in the incidence and survival of patients diagnosed with melanoma in a European country. Other studies reported comparable trends but covered earlier time periods and/or did not report stage-specific trends [21–25].

Our study should, however, also be viewed in the light of some limitations. First, our analyses were limited to stage at diagnosis as only the primary diagnosis is recorded for all patients by the NCR. Therefore, we were not able to provide insight into the proportion of patients that received a novel drug after developing disease progression or to draw conclusions on the effect of disease progression and novel drugs on survival. Second, our data did not allow for differentiating between patients with resectable and unresectable stage III. This would have provided more adequate insight into the uptake of the novel drugs as they were only available for patients with unresectable stage III during our study period.

In conclusion, we observed an increase in incidence for patients with stage I and III, and an improvement in survival for patients with stage II, III and IV. These trends can be partly explained by the introduction of the SLNB and the novel drugs. As the indication for these drugs recently expanded to resectable stage III, we expect that survival will continue to improve.

Author contributions

Brenda Leeneman, Conceptualization, Methodology, Validation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration, Kay Schreuder, Conceptualization, Methodology, Validation, Formal analysis, Resources, Data Curation, Writing - Review & Editing, Project administration, Carin A. Uyl - de Groot, Conceptualization, Validation, Writing - Review & Editing, Supervision, Alexander C.J. van Akkooi, Writing - Review & Editing, John B.A.G. Haanen, Writing - Review & Editing, Marlies Wakkee, Writing - Review & Editing, Margreet G. Franken, Conceptualization, Methodology, Validation, Writing - Review & Editing, Supervision, Marieke W.J. Louwman, Conceptualization, Methodology, Validation, Resources, Writing - Review & Editing, Supervision.

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Conflict of interest statement

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The remaining authors declare no conflicts of interest.

Appendix A. Supplementary data

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