Original Article

Longer Survival From Melanoma in Germany

A Registry-Based Time Series Study

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Summary

Background: New treatment options for cutaneous melanomas with a poor prognosis have been available since 2011, including immune therapies and targeted drugs. Randomized controlled trials have demonstrated that these treatments improve survival, but no population-level studies have been available to date.

Methods: All patients in the database of the Center for Cancer Registry Data (Zentrum für Krebsregisterdaten) who had a diagnosis of melanoma (ICD10: C43) in the years 2000 to 2019 were included in the study. The relative five-year survival (5YRS) was calculated for four 5-year periods (2000–04, 2005–09, 2010–14, 2015–19). The data were standardized/stratified according to sex, age group, and UICC stage to correct for differences between regions and over time. Regression models were used to detect statistically significant secular trends.

Results: 301 486 individuals were included in the study. The overall 5YRS rose from 93% (2000–04) to 95% (2015–19). The 5YRS in 2015–19 was similar to or greater than that in 2000–04 for all subgroups. The largest rises in 5YRS were between 2010–14 and 2015–19, and specifically in advanced stages: for UICC stage IV tumors, the 5YRS rose from 31% to 36%. There was a significant rising trend across the four time periods ($p < 0.001$).

Conclusion: The survival of melanoma patients has improved over the past 20 years. From 2010–14 to the most recent period, the largest changes were seen in advanced tumor stages. This favorable development coincided with the introduction of new therapies.

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In 2022, approximately 25,000 individuals were newly diagnosed with cutaneous melanoma in Germany, and there were around 3000 deaths from this form of skin cancer (1). The long-term trends for melanoma incidence show a sharp rise, and this rise is expected to continue in the future (2). Over 90% of melanomas are caused by UV radiation (3). The prognosis of melanoma patients strongly depends on tumor stage and time of diagnosis. While patients in the most favorable stage, UICC stage I, are not affected by additional mortality from their cancer (relative 5-year survival [5YRS] ≥ 100%), the 5YRS drops to below 35% in stage IV (1).

In 2011, the first novel immunotherapies using immune checkpoint inhibitors were approved in Germany for the treatment of advanced melanoma, followed by further treatment improvements such as BRAF and MEK inhibitors as well as combination therapies (4–6). With this, new and promising treatment options became available, in particular for melanomas with a poor prognosis. However, the question remains as to whether the use of these novel treatments has resulted in an improvement in survival at the population level. Given that reliable cancer registry data are now available for large parts of Germany for a 20-year period, this study aims to investigate whether survival following a melanoma diagnosis has improved over time in Germany, and whether any improvements that may have occurred coincide with the introduction of the new treatments.

Methods

The analysis was based on the dataset of the German Center for Cancer Registry Data (*Zentrum für Krebsregisterdaten*). This includes the individual data of all newly diagnosed cancer patients, currently up to 2019. All patients with an initial diagnosis of "invasive malignant melanoma of skin" (ICD-10: C43) between 2000 and 2019 were included. Since (complete) registration did not start in 2000 or earlier in all registries, survival data is available only for a portion of all incident cases, particularly for the initial years. Children and adolescents under 15 years

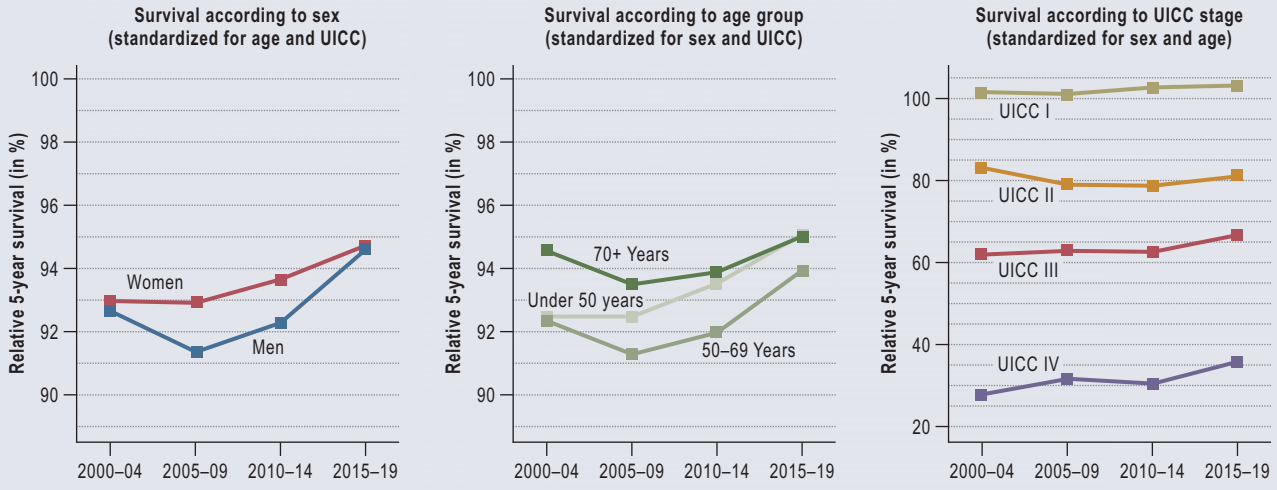
Table

Description of the study population

	Total period 2000–2019 (N = 301 486)	5-Year periods			
		2000–2004 (N = 36 401)	2005–2009 (N = 67 372)	2010–2014 (N = 95 434)	2015–2019 (N = 102 279)
Age group, N (%)					
< 50 Years	77 353 (25.7)	11 717 (32.3)	19 808 (29.4)	25 171 (26.4)	20 657 (20.2)
50–69 Years	116 810 (38.7)	15 383 (42.2)	26 731 (39.7)	35 087 (36.8)	39 609 (38.7)
70+ Years	107 323 (35.6)	9301 (25.5)	20 833 (30.9)	35 176 (36.9)	42 013 (41.1)
Sex, N (%)					
Women	149 567 (49.6)	19 237 (52.8)	34 185 (50.7)	47 198 (49.5)	48 947 (47.9)
Men	151 919 (50.4)	17 164 (47.2)	33 187 (49.3)	48 236 (50.5)	53 332 (52.1)
Recorded UICC stage*, N (%)					
I	110 267 (36.6)	11 617 (31.9)	23 733 (35.2)	35 540 (37.2)	39 377 (38.5)
II	29 606 (9.8)	4663 (12.8)	6028 (8.9)	8604 (9.0)	10 311 (10.1)
III	16 588 (5.5)	1938 (5.3)	3483 (5.2)	5152 (5.4)	6015 (5.9)
IV	8308 (2.8)	1072 (2.9)	1746 (2.6)	2588 (2.7)	2902 (2.8)
Missing	136 717 (45.3)	17 111 (47.0)	32 382 (48.1)	43 550 (45.6)	43 674 (42.7)
Imputed UICC stage*, N (%)					
I	217 042 (72.0)	23 446 (64.4)	48 062 (71.3)	70 426 (73.8)	75 108 (73.4)
II	48 791 (16.2)	8447 (23.2)	11 162 (16.6)	13 935 (14.6)	15 246 (14.9)
III	27 346 (9.1)	3436 (9.4)	6402 (9.5)	8485 (8.9)	9023 (8.8)
IV	8308 (2.8)	1072 (2.9)	1746 (2.6)	2588 (2.7)	2902 (2.8)
German federal state, N (%)					
Baden-Württemberg	21 773 (7.2)	-	437 (0.6)	7205 (7.5)	14 131 (13.8)
Berlin	7624 (2.5)	1645 (4.5)	2000 (3.0)	2629 (2.8)	1350 (1.3)
Brandenburg	7643 (2.5)	1581 (4.3)	1993 (3.0)	2551 (2.7)	1518 (1.5)
Free Hanseatic City of Bremen	2716 (0.9)	482 (1.3)	709 (1.1)	707 (0.7)	818 (0.8)
Free State of Bavaria	53 782 (17.8)	6190 (17)	13 146 (19.5)	16 965 (17.8)	17 481 (17.1)
Free State of Saxony	16 490 (5.5)	3260 (9.0)	3765 (5.6)	4353 (4.6)	5112 (5.0)
Free State of Thuringia	8150 (2.7)	1634 (4.5)	2213 (3.3)	2219 (2.3)	2084 (2.0)
Hamburg	7209 (2.4)	1610 (4.4)	1713 (2.5)	1742 (1.8)	2144 (2.1)
Hesse	25 421 (8.4)	1531 (4.2)	5789 (8.6)	8374 (8.8)	9727 (9.5)
Mecklenburg–Western Pomerania	5814 (1.9)	1004 (2.8)	1438 (2.1)	1747 (1.8)	1625 (1.6)
Lower Saxony	39 157 (13)	6336 (17.4)	9399 (14.0)	11 485 (12.0)	11 937 (11.7)
North Rhine–Westphalia	66 621 (22.1)	3357 (9.2)	15 425 (22.9)	24 302 (25.5)	23 537 (23.0)
Rhineland-Palatinate	12 392 (4.1)	2244 (6.2)	3152 (4.7)	3845 (4.0)	3151 (3.1)
Saarland	4096 (1.4)	773 (2.1)	1007 (1.5)	1111 (1.2)	1205 (1.2)
Saxony-Anhalt	7924 (2.6)	1570 (4.3)	2098 (3.1)	2305 (2.4)	1951 (1.9)
Schleswig-Holstein	14 674 (4.9)	3184 (8.7)	3088 (4.6)	3894 (4.1)	4508 (4.4)
Histological confirmation, N (%)					
Available	294 881 (97.8)	34 477 (94.7)	64 768 (96.1)	93 565 (98.0)	102 071 (99.8)

* UICC stage reclassified based on category of tumor size, lymph node metastasis, distant metastasis, and ulceration according to TNM-8
TNM, tumor, node, metastasis; UICC, *Union internationale contre le cancer*

Figure 1



Trends over time in relative 5-year survival for malignant melanoma of skin in four time periods according to sex, age group, and UICC stage
UICC, *Union internationale contre le cancer*

(N = 319), patients entered in the registry on the basis of a death certificate only (DCO) and for whom there is thus no information on survival (N = 7896), as well as persons for whom there is no information on date of death (N = 19) were excluded. The study population is descriptively defined in terms of demographic (age, sex, federal state of registered residence) and cancer-specific characteristics (tumor stage, histological confirmation). A high proportion of histologically confirmed findings indicates good data quality.

TNM Classification

The classification of cancer stage changed during the time period in question (TNM-5 to TNM-8; TNM classification of the *Union internationale contre le cancer* [UICC]). In order to achieve better comparability of stages over time, the UICC stage for all melanomas was reclassified on the basis of information regarding tumor size (T), lymph node metastasis (N), distant metastasis (M), and ulceration according to the TNM-8 rule. In the absence of information relating to the presence of distant metastasis, this also included assuming non-presence, provided there was no clinical or pathological evidence pointing to distant metastasis (7). However, TNM version 5, which was still used in 45% of records in the 2000–2004 period, has different limits for the classification of tumor size compared to later editions of the TNM system (for example, T1 in TNM-5 includes melanomas measuring up to 0.75 mm in diameter, in later editions, up to 1 mm). Accordingly, UICC stages I and II in TNM-5 include smaller melanomas than in later editions, as a result of which one can expect an artificial worsening of survival from 2000–2004 to 2005–2009.

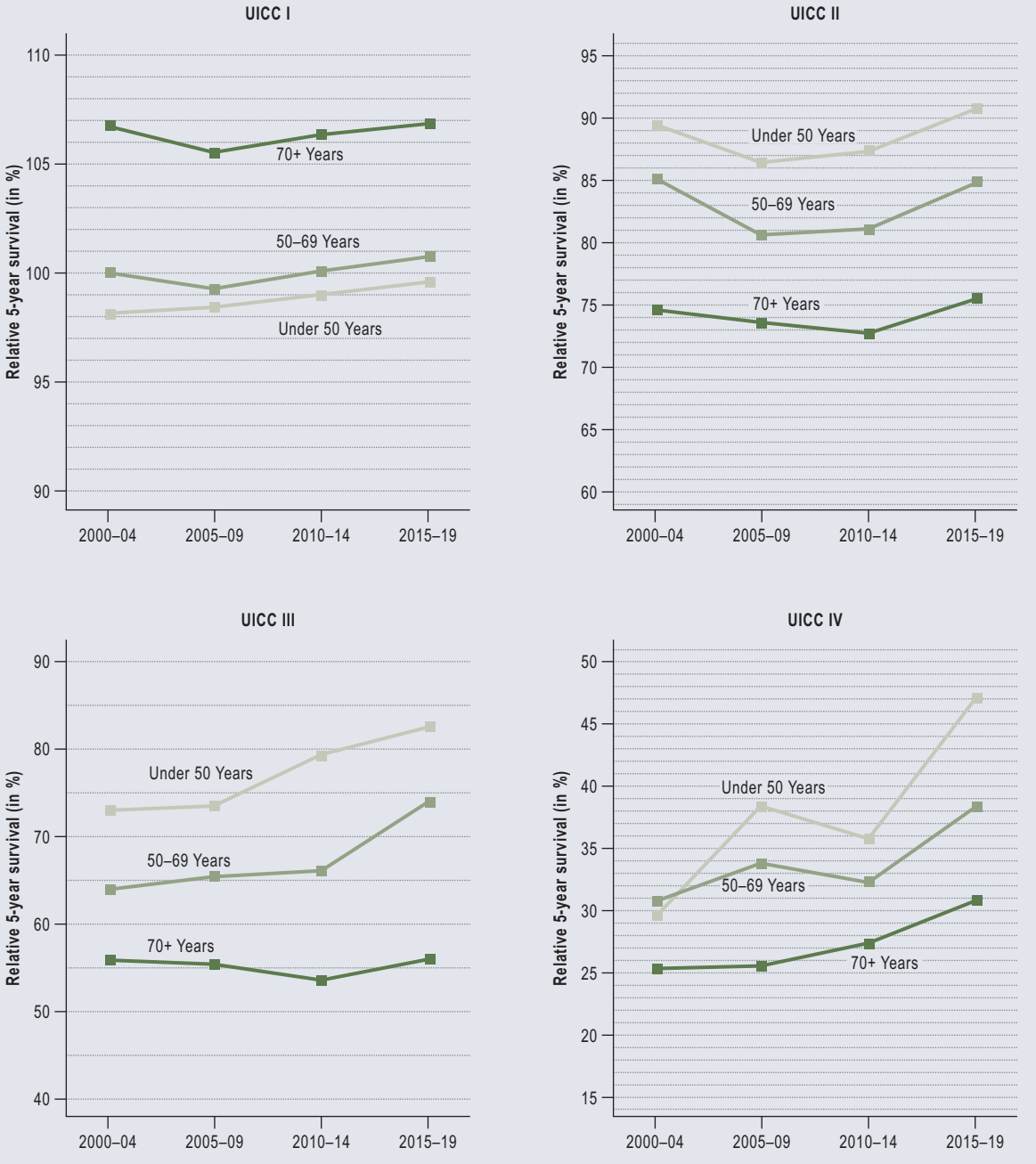
Although data quality improves the longer the cancer registry is kept, the present dataset suffers from a significant lack of information regarding tumor size (20%), lymph node metastasis (44%), and ulceration (30%), meaning that the UICC stage cannot be determined for 45% of the tumors. Therefore, the information that was lacking was replaced (multiple imputation by fully conditional specification, 10 imputed datasets) (8). In addition to the other TNM stage data, additional variables (age, sex, localization, year of diagnosis, histology, mortality risk in the form of the Nelson–Aalen estimator [9], life status [living, deceased], melanoma as cause of death) served as imputation predictors. Convergence was reached before the tenth iteration.

Relative 5-year survival (5YRS)

To investigate changes in survival over time, the 5YRS was calculated for four 5-year periods (2000–2004, 2005–2009, 2010–2014, 2015–2019) (10). The 'period' approach used also enables calculations for the current calendar year (11). The 5YRS compares the observed 5-year survival (that is, the proportion of patients that are still alive at 5 years post-diagnosis) with the expected survival (that is, the proportion of people of the same age and sex in the general population that are still alive after 5 years). A relative survival of 100% means that individuals with a cancer diagnosis have the same likelihood of still being alive at 5 years post-diagnosis as do comparable individuals in the general population. That is to say, their cancer does not cause additional mortality. A 5YRS of 80%, in contrast, means that in addition to the general mortality rate, 20% of cancer patients die as a result of their disease. The expected mortality rate was determined using the German mortality tables (12) according to the Ederer II method (13).

The 5YRS was calculated stratified according to the parameters sex, age group (16–49, 50–69, 70+ years), and tumor stage. For parameters according to which no stratification was performed in individual evaluations, the 5YRS was standardized for these in order to correct for differences between regions and over time: For the

Figure 2



Trends over time in relative 5-year survival for malignant melanoma of skin in four time periods, stratified according to UICC stage and age, standardized for sex
UICC, *Union internationale contre le cancer*

standardization of sex, a 1:1 weighting for women and men was used; for age, standardization of age according to Corazziari et al. was used (14). For tumor stage, the (rounded) percentage frequencies of the four UICC stages over the entire period were used as weightings (72%, 16%, 9%, and 3%, following the imputation of missing values).

The 5YRS was additionally modeled with a Poisson regression of melanoma excess mortality that was specifically developed for this area of application (15) to enable a statement on the significance of the (linear) trend over time. The independent variables taken into consideration included follow-up years (1–5), age group, sex, UICC stage, and the 5-year calendar period.

The age- and stage-standardized 5YRS in the German federal states were descriptively compared with one another based on the previous 10 years (2010–2019) in order to identify possible regional differences.

Results

A total of 301,486 individuals with a melanoma diagnosis were included *(Table, eSupplement Tables S1a, S1b).* The sex ratio was balanced (49.6% females). The median age of disease onset was 63.5 years (interquartile range 49.6–74.3 years) and continuously rose over time. Up until the third of the four 5-year calendar periods, the case numbers rose by approximately 30 000 per 5-year period and were around 100 000 from 2010–2014 onwards. Melanomas were most frequently diagnosed at an early stage (72% UICC I and 16% UICC II; following the replacement of missing data), with distant metastasis present in only 3% (UICC IV). Over the calendar periods, a slight shift in favor of earlier stages was seen.

The 5YRS in 2015–2019 was similar to or greater than that in 2000–2004 for all subgroups. For women as well as men, the 5YRS rose continuously following a dip in 2005–2009, while the gender gap that had emerged between the sexes in the interim had closed again. In the most recent period, the 5YRS was 94.7% (women) and 94.6% (men) *(Figure 1, eSupplement Tables S2a–S3b).*

The 5YRS also rose continuously in the three age groups following a period of stagnation or decline in the 2005–2009 period. Overall, the highest values were achieved in the 70+ age group (95.0% in 2015–2019). In the two younger age groups, the rises where particularly pronounced (from 92.5 to 95.1% in the under 50-year-olds and from 92.4 to 93.9% in the 50- to 69-year-olds).

Differing trends were seen in the UICC stages. Advanced melanomas (UICC III and IV) showed greater improvements compared to the more favorable UICC stages (UICC I and II). For example, the 5YRS rose by 4.7 percentage points in UICC III and by 7.7 percentage points in UICC IV between 2000–2004 and 2015–2019, whereas the 5YRS in UICC II remained at a similar level (– 1.7 percentage points) during these two periods. In UICC I, survival was virtually constant in all periods (+ 2 percentage points) and somewhat better compared to the general population (5YRS > 100%).

Figure 2 shows the survival trends according to age group in the various UICC stages. As a basic principle, 5YRS declines as the age group rises. Only in UICC stage I is the order reversed.

The regression model, which corrects for differences in sex, the three age groups, and UICC stage, shows a survival trend that rises significantly over the four time periods ($p < 0.001$). For the German federal states, the 5YRS ranges from 90.0 to 95.9% *(eSupplement Table S4).*

Discussion

The present analysis is the first to investigate trends in 5-year survival following a melanoma diagnosis in Germany over a time period of 20 years (2000–2019). By using modern analysis methods (period approach), it was possible to determine estimators for 5YRS that are current as well as comparable over time. When considering the four selected 5-year periods, one sees an overall statistically significant trend with an improvement in 5-year survival of approximately two percentage points for women and men. The largest rise in 5YRS can be seen between the 2010–2014 period and the most recent 2015–2019 period (1.4 percentage points). At the regional level, descriptive differences are seen in 5YRS that are comparable in terms of distribution to the EUROCARE-5 study in the country comparison (central and northern Europe) for 2000–2007 (16). Comparable survival trends can be seen in the Scandinavian countries. For example, relative 5-year survival in Denmark rose from 93% (2011–2015) to 95% (2016–2020) (17).

A variety of factors could be responsible for the observed improvements in survival. It is possible that the skin cancer screening introduced nationwide in 2008 had a fundamental effect on survival through the detection of melanomas at an earlier stage; the association between tumor stage and survival is well documented (18–21). However, if one looks at survival within a tumor stage (for example, UICC III), the trends over time are (largely) free from screening effects. The standardization of 5YRS to tumor stage that was undertaken also lessens a screening effect. Sex and age were additionally standardized (or stratified) in order that 5YRS at varying time points and between the sexes are readily comparable even in the case of different underlying stage and age distribution.

Another factor may be the introduction of new treatments, the primary indication for which lies in advanced stages. In studies, the checkpoint inhibitors approved in 2011 and subsequent treatment developments have led to a significant improvement in recurrence-free survival (4, 6, 22, 23). Indeed, the 5YRS in the 2010–2014 period is higher than in the 2005–2009 period and then increases even more strongly in all stage groups from 2010–2014 to 2015–2019. For UICC I, II, and III, the increases were by 1, 3, and 4 percentage points. The strongest improvement can be seen for the prognostically unfavorable stage IV: The 5YRS rose from 31% to 36%, corresponding to an absolute improvement of five percentage points. A similar rise in the less favorable stages III and IV was reported for the Netherlands. There, the 5YRS rose from 58% to 65% (stage III) and from 9% to 18% (stage IV) between 2004–2009 and 2010–2016 (24). A similar rise in 5YRS was also observed in the Nordic countries from 2016 to 2020 (25).

In addition to screening measures and new treatments, other factors relating to care and treatment—such as improved guideline compliance, shorter waiting times to

treatment initiation, or treatment in skin cancer centers—can also have a positive effect on survival.

Finally, changes in registration and the data situation—such as biases due to an increase in the number of registered cases or selective registration—may have an effect on the 5YRS. However, by standardizing for age and tumor stage, any such effects are considered to be of little relevance. Furthermore, the proportion of documented UICC stages increases over time, with staging information tending to be lacking for individuals with an unfavorable prognosis (26). Imputation counteracted this source of bias. It can be shown that the exclusion of individuals lacking a UICC stage leads to more irregular and less plausible trends in 5YRS (compare, for example, *eSupplement Table S3b* with *S8b*). Changes to the TNM classifications during the study period may also affect the composition of cases within the UICC stages over time. By reclassifying the stages using the available TNM data and the current edition of the TNM staging, it was possible to achieve sufficient comparability. However, the first study period still includes what tend to be smaller and thus prognostically more favorable melanomas in UICC I and in UICC II than in the later periods. As a result, despite standardizing for stage, survival estimates in the 2000–2004 period are still somewhat too favorable for registration reasons, as shown in sensitivity analyses *(eSupplement Tables S8a, S8b)*.

One particular age group-specific feature of 5YRS should be mentioned here. As a general rule, cancer mortality goes up with increasing age at diagnosis, meaning that absolute survival and the 5YRS go down. In addition, more intensive treatments are indicated at advanced stages, with the increased comorbidity in older individuals being reflected in poorer survival. Accordingly, the curves for the youngest age group (up to 50 years) in UICC stages II–IV were highest and those for the oldest age group (70+) lowest. Interestingly, the 70+ age group diagnosed in UICC stage I had better survival compared to the younger age groups. Several effects that increase the survival estimates are probably at play here. In higher age groups, screening more frequently leads to overdiagnosis and is more likely to be utilized by healthy individuals. Both distort survival (overdiagnosis and healthy screenee bias) in the direction of higher figures, which can be over 100% for UICC-I diagnoses and indicate better survival compared to the comparable normal population.

The strength of this analysis lies in its large case number, which can be considered as virtually complete for the whole of Germany from 2010 onwards, as well as in the high quality and currentness of the cancer registries' determination of life status.

Conclusion

The survival of melanoma patients has improved over the past 20 years. Starting from an already very good relative 5-year survival of 93% in the 2000–2004 period, this has improved to almost 95% in the current period (2015–2019). The most pronounced improvements were seen for advanced tumor stages in the 2010–2014 period to the current period. For the most unfavorable tumor stage (UICC IV), a rise in 5YRS from 31% to 36% was observed. This development coincided with the introduction of new treatments from 2011 onwards. Although the results do not permit direct conclusions to be drawn regarding causality, the association between the improvement in survival for tumors with a poor prognosis and the introduction of new treatments is the most plausible.

Conflict of interest statement
AK declares that he undertakes unpaid activity on the board of the Skin Cancer Council Germany (*Nationale Versorgungskonferenz Hautkrebs e.V.*). The remaining authors declare that no conflict of interests exists.

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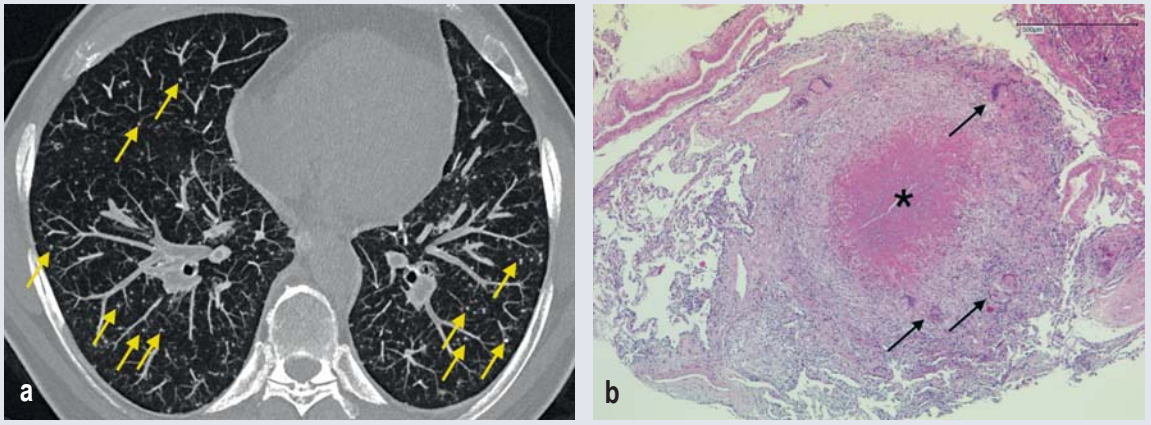
Supplementary material
eSupplement:
www.aerzteblatt-international.de/m2023.0242

CLINICAL SNAPSHOT

Miliary Pneumonia as a Complication of BCG Instillation



a) Axial MIP (maximum intensity projection) with 7 mm slice thickness in lung window reconstruction from plain thoracic computed tomography, showing miliary distribution of nodules (arrows).
b) Transbronchial biopsy from segments 8–10 of the right lung, showing a centrally necrotic granuloma (*) with histiocytic margin and occasional multinucleate giant cells (arrows) in the alveolar parenchyma.

A 55-year-old man presented with a 4-month history of progressive exertional dyspnea. He denied having a cough, but reported occasional night sweats. There were no cardiological abnormalities; lung function was unremarkable; laboratory tests showed a slightly elevated CRP concentration. Thoracic computed tomography carried out to exclude lung structure changes revealed a miliary distribution pattern (Figure a). Bronchoscopy then reinforced the suspicion by demonstrating necrotizing granulomas (Figure b) and Mycobacterium tuberculosis complex (PCR). The patient had previously received bacille Calmette–Guérin (BCG; M. bovis) instillation therapy to prevent the recurrence of non-invasive high-grade urothelial carcinoma. The QuantiFERON-TB-Gold-Plus test (M. tuberculosis) was negative, confirming that the pneumonia was caused by BCG. The instillation therapy had to be briefly interrupted after the induction phase owing to BCG prostatitis, with no demonstration of mycobacteria at that time, and maintenance therapy had been started 4 months before the patient presented to us. It can be stated that the cause of his exertional dyspnea was disseminated pulmonary infection with M. bovis. Systemic BCG infections can occur as complications of BCG instillation into the bladder (incidence 1–10:1000). The BCG instillations were discontinued and triple antitubercular treatment (isoniazid, rifampicin, ethambutol) was started.

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Supplementary material to the article

Longer Survival From Melanoma in Germany

A Registry-Based Time Series Study

by Nora Eisemann, Laura Schumann, Hannah Baltus, Louisa Labohm, Klaus Kraywinkel, Alexander Katalinic

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Supplement to the article “Longer Survival From Melanoma in Germany: A Registry-Based Time Series Study”

Overview

1. Sample size (main analysis)
2. Absolute 5-year survival (main analysis)
3. Relative 5-year survival (main analysis)
4. Comparison of German federal states
5. Comparison of individuals with complete vs. missing UICC stage
6. Case numbers (excluding patients without information on UICC stage)
7. Absolute 5-year survival (excluding patients without information on UICC stage)
8. Relative 5-year survival (excluding patients without information on UICC stage)
9. Sensitivity analysis (definition of T stage 1)

1. Sample size (Main analysis)

Table S1a: Sample size for all 5-year periods, in total and stratified according to sex, age group, and UICC stage

		5-year period			
		2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total					
		36 401	67 372	95 434	102 279
Sex					
	Women	19 237	34 185	47 198	48 947
	Men	17 164	33 187	48 236	53 332
Age group					
	<50 years	11 717	19 808	25 171	20 657
	50-69 years	15 383	26 731	35 087	39 609
	70+ years	9 301	20 833	35 176	42 013
Stage					
	UICC I	23 446	48 062	70 426	75 108
	UICC II	8 447	11 162	13 935	15 246
	UICC III	3 436	6 402	8 485	9 023
	UICC IV	1 072	1 746	2 588	2 902

Table S1b: Sample size for all 5-year periods, double-stratified by age group and UICC stage

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
UICC I	<50 years	8 648	15 934	20 747	16 967
	50-69 years	10 037	19 495	26 801	30 534
	70+ years	4 761	12 633	22 878	27 607
UICC II	<50 years	1 878	1 904	1 967	1 597
	50-69 years	3 417	3 994	4 341	4 662
	70+ years	3 152	5 265	7 627	8 987
UICC III	<50 years	937	1 620	2 024	1 722
	50-69 years	1 450	2 499	2 973	3 327
	70+ years	1 049	2 283	3 488	3 973
UICC IV	<50 years	254	351	433	371
	50-69 years	479	743	972	1 086
	70+ years	339	652	1 183	1 445

2. Absolute 5-year survival (main analysis)

Table S2a: Absolute 5-years-survival [in %] in the 5-year periods, total and stratified according to sex, age group and UICC stage

		5-year period			
		2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total					
		92.8	92.1	92.9	94.6
Sex					
	Women	92.9	92.9	93.6	94.6
	Men	92.6	91.3	92.2	94.5
Age group					
	<50 years	92.4	92.5	93.4	95.1
	50-69 years	92.3	91.2	91.9	93.9
	70+ years	94.5	93.5	93.8	94.9
Stage					
	UICC I	90.2	88.9	89.3	89.0
	UICC II	73.6	69.0	67.3	68.4
	UICC III	54.8	54.9	54.4	57.8
	UICC IV	25.4	28.7	27.2	31.2

Table S2b: Absolute 5-years-survival [in %] in the 5-year periods, double-stratified by age group and UICC stage

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
UICC I	<50 years	97.4	97.7	98.3	98.9
	50-69 years	94.7	93.9	94.9	95.9
	70+ years	79.0	78.5	80.9	81.5
UICC II	<50 years	88.6	85.4	86.2	89.9
	50-69 years	80.2	75.9	76.6	80.4
	70+ years	51.8	51.4	51.2	52.3
UICC III	<50 years	71.9	72.9	78.8	81.9
	50-69 years	60.3	61.9	62.7	70.4
	70+ years	40.3	39.5	38.7	40.5
UICC IV	<50 years	29.1	38.0	35.5	46.7
	50-69 years	29.3	32.1	30.8	36.5
	70+ years	19.5	19.4	20.8	23.2

3. Relative 5-year survival (main analysis)

Table S3a: Relative 5-years-survival [in %] in the 5-year periods, total and stratified according to sex, age group and UICC stage

		5-year period			
		2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total					
		92.8	92.2	93.0	94.7
Sex					
	Women	93.0	92.9	93.7	94.7
	Men	92.7	91.4	92.3	94.6
Age group					
	<50 years	92.5	92.5	93.5	95.1
	50-69 years	92.4	91.3	92.0	93.9
	70+ years	94.6	93.6	93.9	95.0
Stage					
	UICC I	101.5	101.2	102.5	103.5
	UICC II	83.1	79.2	78.6	81.5
	UICC III	62.2	62.8	62.7	67.0
	UICC IV	28.2	31.9	30.9	35.9

Table S3b: Relative 5-years-survival [in %] in the 5-year periods, double-stratified by age group and UICC stage

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
UICC I	<50 years	98.2	98.5	99.1	99.6
	50-69 years	100.1	99.3	100.1	100.8
	70+ years	106.8	105.6	106.4	106.9
UICC II	<50 years	89.5	86.4	87.3	90.8
	50-69 years	85.1	80.6	81.2	84.9
	70+ years	74.6	73.5	72.8	75.5
UICC III	<50 years	72.9	73.4	79.3	82.5
	50-69 years	63.9	65.4	66.0	73.7
	70+ years	55.9	55.4	53.6	55.8
UICC IV	<50 years	29.4	38.4	35.8	47.0
	50-69 years	30.9	33.9	32.4	38.3
	70+ years	25.4	25.6	27.3	30.9

4. Comparison of German federal states

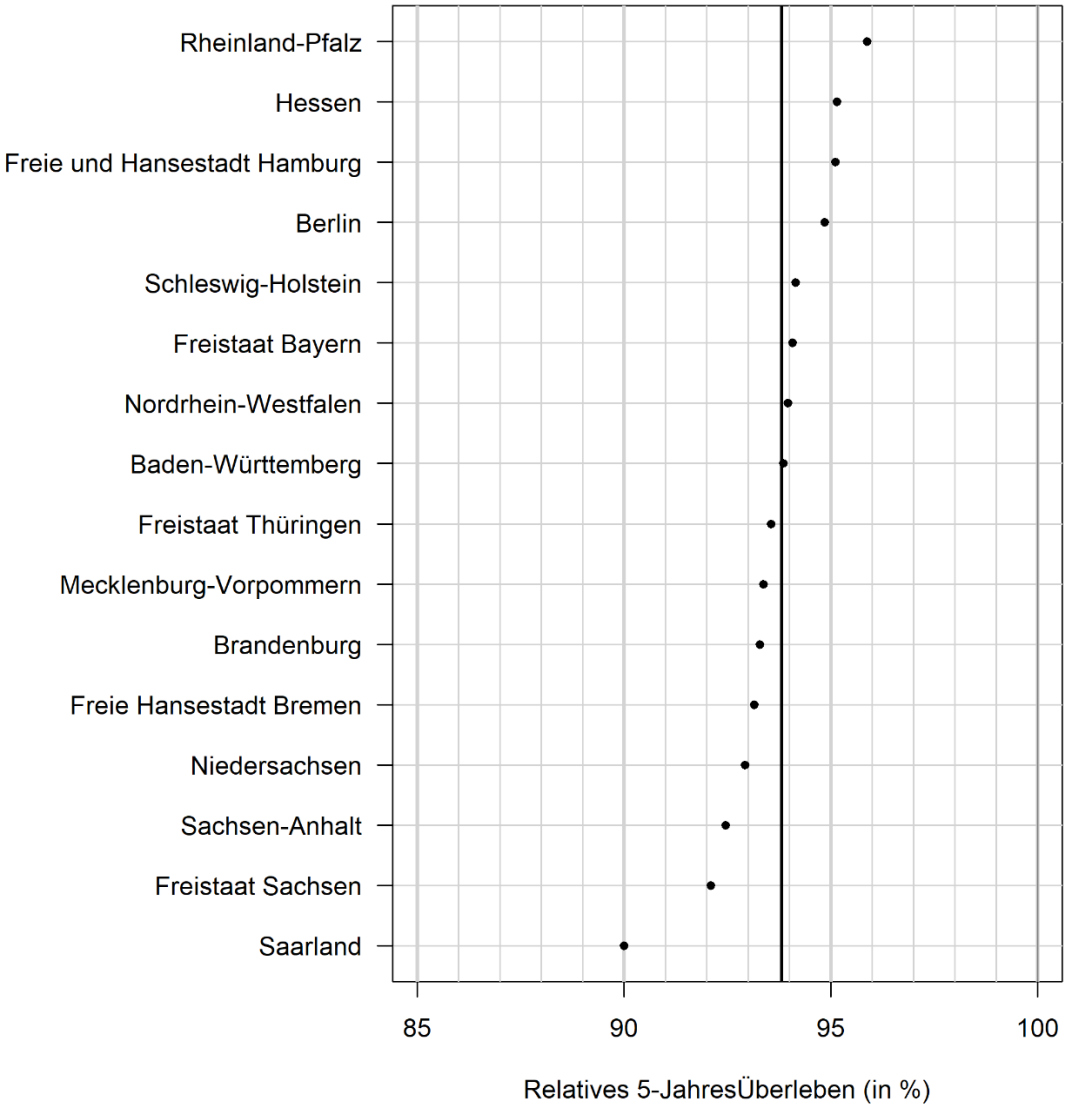

Figure S4: Relative 5-years-survival for malignant melanoma of the skin in 2010-2019, standardised for age, sex and UICC stage

5. Comparison of individuals with complete vs. missing UICC stage

Table S5a: Description of persons with missing UICC stage

	5-year period			
	2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total, N	17 111	32 382	43 550	43 674
Sex, N (%)				
Women	9 234 (54.0)	16 835 (52.0)	21 965 (50.4)	21 155 (48.4)
Men	7 877 (46.0)	15 547 (48.0)	21 585 (49.6)	22 519 (51.6)
Age group, N (%)				
<50 years	5 364 (31.3)	9 542 (29.5)	11 645 (26.7)	8 793 (20.1)
50-69 years	7 081 (41.4)	12 415 (38.3)	15 569 (35.7)	16 610 (38.0)
70+ years	4 666 (27.3)	10 425 (32.2)	16 336 (37.5)	18 271 (41.8)
T stage, N (%)				
T1	2 431 (14.2)	9 418 (29.1)	21 509 (49.4)	25 373 (58.1)
T2	4 303 (25.1)	2 545 (7.9)	3 192 (7.3)	2 970 (6.8)
T3	716 (4.2)	1 244 (3.8)	1 824 (4.2)	1 945 (4.5)
T4	546 (3.2)	1 177 (3.6)	1 805 (4.1)	2 044 (4.7)
T missing	9 115 (53.3)	17 998 (55.6)	15 220 (34.9)	11 342 (26.0)
N stage, N (%)				
N0	4 486 (26.2)	1 817 (5.6)	1 016 (2.3)	841 (1.9)
N+	0 (0)	0 (0)	0 (0)	0 (0)
N missing	12 625 (73.8)	30 565 (94.4)	42 534 (97.7)	42 833 (98.1)
Relative 5-years-survival	89.0 %	91.4 %	93.1 %	94.3 %

Table S5b: Description of persons with UICC stage

	5-year period			
	2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total, N	19 290	34 990	51 884	58 605
Sex, N (%)				
Women	10 003 (51.9)	17 350 (49.6)	25 233 (48.6)	27 792 (47.4)
Men	9 287 (48.1)	17 640 (50.4)	26 651 (51.4)	30 813 (52.6)
Age group, N (%)				
<50 years	6 353 (32.9)	10 266 (29.3)	13 526 (26.1)	11 864 (20.2)
50-69 years	8 302 (43.0)	14 316 (40.9)	19 518 (37.6)	22 999 (39.2)
70+ years	4 635 (24.0)	10 408 (29.7)	18 840 (36.3)	23 742 (40.5)
T-Stage, N (%)				
T1	10 541 (54.6)	20 196 (57.7)	29 921 (57.7)	32 585 (55.6)
T2	1 857 (9.6)	5 600 (16.0)	8 862 (17.1)	10 264 (17.5)
T3	4 111 (21.3)	4 510 (12.9)	6 073 (11.7)	7 186 (12.3)
T4	1 947 (10.1)	3 378 (9.7)	5 365 (10.3)	6 420 (11.0)
T missing	834 (4.3)	1 306 (3.7)	1 663 (3.2)	2 150 (3.7)
N-Stage, N (%)				
N0	16 444 (85.2)	30 020 (85.8)	44 542 (85.8)	50 210 (85.7)
N+	2 249 (11.7)	4 089 (11.7)	6 184 (11.9)	7 059 (12.0)
N missing	597 (3.1)	881 (2.5)	1 158 (2.2)	1 336 (2.3)
Relative 5-years-survival [1]	90.1 %	92.8 %	97.3 %	99.2 %

[1] Excluding all melanomas with distant metastases, as distant metastases lead directly to classification as UICC IV and therefore comparability with Table S5a would not be given.

6. Sample sizes (excluding patients without information on UICC stage)

Table S6a: Sample size in all 5-year periods, total and stratified according to sex, age group and UICC stage; after exclusion of all melanoma patients without information on UICC stage

		5-year period			
		2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total					
		19 290	34 990	51 884	58 605
Sex					
	Women	10 003	17 350	25 233	27 792
	Men	9 287	17 640	26 651	30 813
Age group					
	<50 years	6 353	10 266	13 526	11 864
	50-69 years	8 302	14 316	19 518	22 999
	70+ years	4 635	10 408	18 840	23 742
Stage					
	UICC I	11 617	23 733	35 540	39 377
	UICC II	4 663	6 028	8 604	10 311
	UICC III	1 938	3 483	5 152	6 015
	UICC IV	1 072	1 746	2 588	2 902

Table S6b: Sample size in all 5-year periods, double-stratified according to age group and UICC stage; after exclusion of all melanoma patients with missing UICC stage

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
UICC I	<50 years	4 435	7 860	10 501	9 192
	50-69 years	4 976	9 803	13 740	16 212
	70+ years	2 206	6 070	11 299	13 973
UICC II	<50 years	1 069	1 088	1 284	1 127
	50-69 years	1 975	2 271	2 837	3 336
	70+ years	1 619	2 669	4 483	5 848
UICC III	<50 years	595	967	1 308	1 174
	50-69 years	872	1 499	1 969	2 365
	70+ years	471	1 017	1 875	2 476
UICC IV	<50 years	254	351	433	371
	50-69 years	479	743	972	1 086
	70+ years	339	652	1 183	1 445

7. Absolute 5-year survival (excluding patients without information on UICC stage)

Table S7a: Absolute 5-years-survival [in %] in all 5-year periods, total and stratified according to sex, age group and UICC stage; after exclusion of all melanoma patients without information on UICC stage

		5-year period			
		2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total					
		94.1	94.3	93.8	94.9
Sex					
	Women	93.0	94.9	94.6	95.1
	Men	95.3	93.7	93.0	94.8
Age group					
	<50 years	93.2	92.9	93.3	94.9
	50-69 years	93.4	92.8	92.6	94.1
	70+ years	97.7	97.4	95.1	95.5
Stage					
	UICC I	91.9	91.2	90.3	89.3
	UICC II	74.5	72.2	69.9	70.7
	UICC III	56.9	57.5	53.9	58.6
	UICC IV	25.4	28.7	27.2	31.2

Table S7b: Absolute 5-years-survival [in %] in all 5-year periods, double-stratified according to age group and UICC stage; after exclusion of all melanoma patients with missing UICC stage

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
UICC I	<50 years	98.0	98.2	98.5	99.0
	50-69 years	95.7	95.2	95.5	96.0
	70+ years	82.8	82.7	82.8	82.1
UICC II	<50 years	89.2	87.1	86.6	90.3
	50-69 years	81.7	78.1	79.0	81.6
	70+ years	52.0	56.3	55.0	56.2
UICC III	<50 years	74.8	71.3	75.6	78.8
	50-69 years	61.1	64.2	61.4	69.6
	70+ years	44.7	43.5	39.5	44.5
UICC IV	<50 years	29.1	38.0	35.5	46.7
	50-69 years	29.3	32.1	30.8	36.5
	70+ years	19.5	19.4	20.8	23.2

8. Relative 5-year survival (excluding patients without information on UICC stage)

Table S8a: Relative 5-years-survival [in %] in all 5-year periods, total and stratified according to sex, age group and UICC stage; after exclusion of all melanoma patients without information on UICC stage

		5-year period			
		2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Total					
		94.6	94.5	93.8	94.9
Sex					
	Women	93.9	95.2	94.6	95.1
	Men	95.3	93.7	93.1	94.8
Age group					
	<50 years	93.6	93.0	93.4	94.9
	50-69 years	93.8	92.9	92.7	94.1
	70+ years	97.8	97.6	95.0	95.5
Stage					
	UICC I	102.9	102.8	102.9	103.0
	UICC II	83.7	81.1	78.5	81.3
	UICC III	63.4	64.7	61.1	67.1
	UICC IV	28.2	31.9	30.9	35.9

Table S8b: Relative 5-years-survival [in %] in all 5-year periods, double-stratified according to age group and UICC stage; after exclusion of all melanoma patients with missing UICC stage

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
UICC I	<50 years	99.0	98.7	99.1	99.6
	50-69 years	101.2	100.1	100.3	100.6
	70+ years	109.5	109.0	106.8	105.8
UICC II	<50 years	89.9	87.3	85.7	89.8
	50-69 years	86.3	82.1	81.9	83.5
	70+ years	73.6	76.2	72.5	76.7
UICC III	<50 years	75.5	71.9	76.2	79.4
	50-69 years	64.4	67.7	64.6	73.0
	70+ years	59.4	57.8	51.8	58.4
UICC IV	<50 years	93.6	93.0	93.4	94.9
	50-69 years	93.8	92.9	92.7	94.1
	70+ years	97.8	97.6	95.0	95.5

9. Sensitivity analysis (definition of T stage 1)

TNM classification 5 uses different boundaries for the T stage than the following TNM classifications. Only stage T4 contains melanomas of the same extent everywhere, so that T4 is not considered in the following.

In 2000-04, 44.9% of cases were reported according to TNM-5, in 2005-09 still 4.8%, in 2010-14 2.9% and in 2015-19 only 0.4%.

Of the cases reported in 2000-04 according to one of the later TNM classifications, 60.2 % were in stage T1, 22.2 % in T2 and 17.1 % in T3. In contrast, 48.9 % of tumours coded according to TNM-5 were in stage T1, 27.9 % in T2 and 23.1 % in T3. Only the period 2000-04 is considered, as national skin cancer screening also led to shifts in the stages in the later years.

In sensitivity analyses, the proportion of TNM-5-classified T2 cases that exceeded the expected frequency was shifted to T1. The same procedure was applied to the T3 cases. This resulted in the same percentage distribution across the T stages as occurred in the later TNM classifications in the same period. The cases to be deferred were selected in two ways:
A: random selection
B: random selection of persons whose melanomas were presumably rather small for their class, i.e. for whom neither lymph node nor distant metastases had been reported and for whom no death certificate notification had yet been received.

Table S9a: Relative 5-years-survival [in %] in all 5-year periods, total and stratified according to sex, age group and UICC stage; sensitivity analyses with regard to the tumour diameter boundaries in TNM-classification-5

	5-year period			
	2000-2004	**2005-2009**	**2010-2014**	**2015-2019**
Sensitivity analysis A				
Total				
	92.2	92.0	93.0	94.7
Sex				
Women	92.4	92.8	93.7	94.7
Men	91.9	91.2	92.2	94.6
Age group				
<50 years	92.2	92.4	93.5	95.1
50-69 years	91.9	91.2	92.0	93.9
70+ years	93.3	93.4	93.8	95.0
Stage				
UICC I	100.9	101.1	102.5	103.5
UICC II	81.7	78.8	78.6	81.5
UICC III	62.2	62.8	62.7	67.0
UICC IV	28.2	31.9	30.9	35.9
Sensitivity analysis B				
Total				
	92.2	92.0	93.0	94.7
Sex				
Women	92.4	92.8	93.7	94.7
Men	91.9	91.2	92.2	94.6
Age group				
<50 years	92.2	92.4	93.5	95.1
50-69 years	91.9	91.2	92.0	93.9
70+ years	93.3	93.4	93.8	95.0
Stage				
UICC I	101.8	101.3	102.5	103.5
UICC II	79.0	78.0	78.5	81.5
UICC III	62.2	62.8	62.7	67.0
UICC IV	28.2	31.9	30.9	35.9

Table S9b: Relative 5-years-survival [in %] in all 5-year periods, double-stratified according to age group and UICC stage; sensitivity analyses with regard to the tumour diameter boundaries in TNM-classification-5

		5-year period			
Stage	**Age group**	**2000-2004**	**2005-2009**	**2010-2014**	**2015-2019**
Sensitivity analysis A					
UICC I	<50 years	98.1	98.5	99.1	99.6
	50-69 years	99.7	99.2	100.1	100.8
	70+ years	105.4	105.4	106.3	106.8
UICC II	<50 years	88.3	86.0	87.2	90.7
	50-69 years	83.8	80.1	81.1	84.9
	70+ years	72.8	73.2	72.8	75.5
UICC III	<50 years	72.9	73.4	79.3	82.5
	50-69 years	63.9	65.4	66.0	73.7
	70+ years	55.9	55.4	53.6	55.8
UICC IV	<50 years	29.4	38.4	35.8	47.0
	50-69 years	30.9	33.9	32.4	38.3
	70+ years	25.4	25.6	27.3	30.9
Sensitivity analysis B					
UICC I	<50 years	98.4	98.6	99.1	99.6
	50-69 years	100.4	99.4	100.1	100.8
	70+ years	107.4	105.7	106.4	106.9
UICC II	<50 years	85.2	84.9	87.0	90.7
	50-69 years	80.7	79.1	80.9	84.8
	70+ years	72.6	72.9	72.6	75.4
UICC III	<50 years	72.9	73.4	79.3	82.5
	50-69 years	63.9	65.4	66.0	73.7
	70+ years	55.9	55.4	53.6	55.8
UICC IV	<50 years	29.4	38.4	35.8	47.0
	50-69 years	30.9	33.9	32.4	38.3
	70+ years	25.4	25.6	27.3	30.9