Hazard rates for recurrent and secondary cutaneous melanoma: An analysis of 33,384 patients in the German Central Malignant Melanoma Registry

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Background: Knowledge about the risk for recurrence and secondary cutaneous melanoma (CM) is an important basis for patient counseling and planning of follow-up examinations.

Objectives: This study aimed to analyze stage- and time-dependent hazard rates (HR) and discusses current surveillance recommendations.

Methods: Follow-up data of 33,384 patients with incident CM in stages I to III (American Joint Committee on Cancer 2002) were recorded by the German Central Malignant Melanoma Registry in 1976 through 2007. Survival was based on Kaplan-Meier estimates and HRs were calculated.

Results: Recurrences were recorded in 4999 patients (stage I, 7.1%; stage II, 32.8%; and stage III, 51.0%). Ten-year recurrence-free survival was 78.9% (95% confidence interval 73.1-90.5); in stage I, 89.0%; stage II, 56.9%; and stage III, 36.0%. Whereas HR for recurrent CM showed a constantly low level less than or equal to 1:125 per year for stage IA, clearly higher HRs of greater than or equal to 1:40 were recorded in stage IB for the first 3 years and generally in stages II to III. Of all patients 2.3% developed secondary melanomas, with a consistently low HR of less than 1:220 per year.

Limitations: As German recommendations discontinued regular follow-up examinations after 10 years, no information can be given beyond this time point. Follow-up data of longer than 5 years were available in 41.4% of patients.

Conclusion: For patients at stage IA with thin melanoma and low HR for recurrent CM the need for surveillance remains questionable. For patients with higher HR greater than 1:40 per year, intensified surveillance strategies should be taken into account. (J Am Acad Dermatol 2012;66:37-45.)

Key words: cutaneous melanoma; hazard rates; recurrences; survival analysis.

Between the 1940s and the 1980s, the incidence of invasive cutaneous melanoma (CM) increased rapidly in populations of predominantly Caucasian origin.[1] More recent studies showed that this trend is still continuing in many European countries, Canada, the United States, Australia, and New Zealand.[2] Data from the US Surveillance, Epidemiology, and End Results (SEER) registry showed that CM was the most rapidly increasing malignancy in both sexes in the United

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States between 1973 and 1981 with an annual percentage change of 6.1.[3] During the time period 1981 to 2007, the annual percentage change in incidence was still 2.6 in the United States and the age-adjusted incidence rate was 25.6 per 100,000 men per year and 16.2 per 100,000 women per year for the 2003 to 2007 time period. For 2009, 68,720 new diagnoses and 8650 deaths attributed to CM were forecasted for the United States.[3,4]

Long-term surveillance is an essential part of the management of this disease. Two goals are guiding practically all schedules that have been proposed in the literature: first, the early detection of recurrences, and, secondly, the early detection of secondary melanomas. So far, only few analyses of hazard rates (HR) for melanoma recurrences and occurrence of secondary melanomas have been published. HR may provide a more rational basis for the stage-dependent planning of surveillance schedules, however, scheduling time periods and frequencies of examinations will remain to a certain extent arbitrary. As cost-effectiveness becomes an important goal in medical decision making, accurate data on the stage- and time-dependent hazards may enable rational approaches.

CAPSULE SUMMARY

- Few analyses of hazard rates for recurrent and secondary melanoma have been published.
- As cost-effectiveness becomes an important goal in medical decision making, accurate data on stage- and time-dependent hazards may enable rational approaches for follow-up recommendations.
- For patients with low hazard rates (<1:125 in stage IA), the need of surveillance remains questionable; reduced follow-up seems appropriate.
- For patients with high hazard rates (>1:40 in stages II-III and in stage IB for years 1-3), intensified surveillance should be considered.

Since the early 1990s several suggestions for follow-up schedules of patients with melanoma have been suggested for international consensus.[5-10] Most studies recommended a minimum of yearly visits for 10 years, more frequent follow-up visits for thicker tumors and/or advanced stages, and a reduction of the frequency of visits over time. Long-term or even lifelong follow-up examinations were recommended varying in frequency from once to 4 times per year.[11-13] One study found that most secondary melanomas occurred in the first 2 years after the primary diagnosis.[11]

The aims of this study were to determine the HR of: (1) melanoma recurrences; and (2) secondary melanomas according to the stages of the American Joint Committee on Cancer (AJCC) melanoma classification. The analysis was performed using the large data set from the German Central Malignant Melanoma Registry (CMMR) with more than 30,000 patients with follow-up data collected during a period of 30 years. Based on these results, recommendations for stage- and time-dependent surveillance of patients with melanoma were discussed.

METHODS

Patients

This analysis included patients with incident primary CM diagnosed between January 1976 and December 2007, who had a follow-up time of at least 3 months. All melanomas in stages I to III at primary diagnosis were included in this analysis. Data from 84 clinical centers (of these 50 with current follow-up data) in Germany, Austria, and Switzerland were collected by the German-based CMMR. The data of the CMMR are not population based. Nevertheless, these data can be considered to be representative because patients of a respective area that is serviced by one center are recorded almost completely. In Germany, the majority of patients are referred to the hospitals and cooperative surveillance of the patients between the dermatologist in private practice and the hospital is routinely performed. The CMMR records about 35% to 50% of all patients with melanoma in Germany. All patients had given their written informed consent to have their data on primary tumor and follow-up recorded within the CMMR.

Tumor characteristics and case histories were recorded in a standardized manner. Ulceration was diagnosed by histopathology. Histopathological reports of the responsible dermatohistopathologist of the respective hospitals were documented within the current study. Patients were staged or restaged retrospectively according to the AJCC 2002 staging system.[14,15] Since 1996 sentinel lymph node biopsies were routinely performed in CM of more than 1.0-mm tumor thickness in most of the centers. Patients at stage III were routinely offered therapeutic lymph node dissection. All patients were free of detectable disease at the time when included into the study.[16] Second melanoma was diagnosed clinically by physical examination and dermatoscopy. Lesions suspicious for second melanoma were completely excised and histologically diagnosed. Histologic reports had to state clearly that the excised lesions were

Abbreviations used:

AJCC:	American Joint Committee on Cancer
CI:	confidence interval
CM:	cutaneous melanoma
CMMR:	Central Malignant Melanoma Registry
HR:	hazard rate
IQR:	interquartile range
RFS:	recurrence-free survival
SEER:	Surveillance, Epidemiology, and End Results

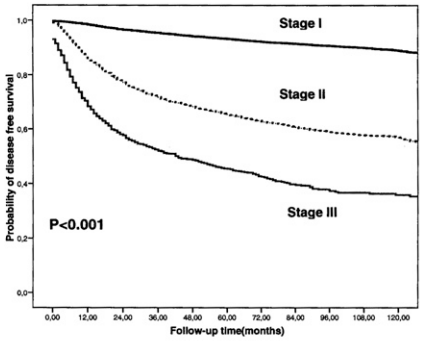
considered to be second primary melanomas and not cutaneous metastases.

In Germany, Austria, and Switzerland follow-up examinations are recommended every 3 months during the first 5 years after resection of the primary tumor, and every 6 months from the sixth to the tenth year after surgery. Follow-up examinations usually comprise a physical whole body skin examination and, once or twice per year, a lymph node ultrasound, imaging techniques, and blood examinations of the tumor marker protein S100ß and lactate dehydrogenase in patient with CM of a tumor thickness of 1.00 mm or greater.[16,17] Follow-up schedules are finished at 10 years after primary diagnosis, last recurrence, or secondary CM. Therefore, only a few patients who developed a secondary melanoma or a recurrence continue follow-up examinations beyond that time point.

Statistical analysis

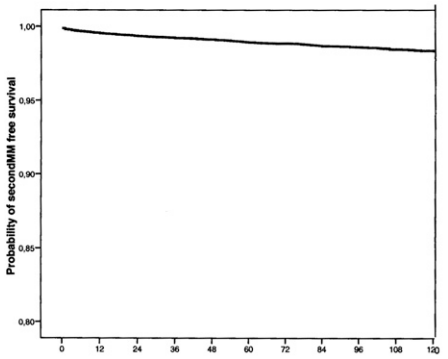
Statistical analysis was conducted using statistical software (SPSS 17, SPSS Inc, Chicago, IL). Numeric variables were described by mean values and SD or median values and interquartile range (IQR), depending on their distributions. Follow-up time was defined from the date of primary excision to the date of last follow-up or death (overall survival), or the date of primary excision to the date of the first recurrence (recurrence-free survival [RFS]), or the date of primary excision to the date of diagnosis of the subsequent secondary melanoma (secondary melanoma–free survival). In 1.8% of cases date of primary excision was not recorded and date of diagnosis was used for these calculations. Follow-up times were described as median values with IQR. All patients included in the current analysis had a follow-up time of at least 3 months. Linear regression analysis was used to judge the relationship between follow-up times cut at 120 months and the HR for the emergence of recurrences.

Survival analyses included only deaths caused by CM. Kaplan-Meier analyses were performed to estimate overall survival and RFS. Five- and 10-year survival probabilities and 95% confidence intervals



Rates of recurrence free survival	0 yr	1 yr	3 yr	5 yr	10 yr
Stage I	99.7%	98.4%	95.3%	93.2%	89.0%
Stage II	99.1%	86.2%	71.8%	65.5%	56.9%
Stage III	93.0%	68.3%	52.0%	56.9%	36.0%

A



Time to second melanoma	0 yr	1 yr	3 yr	5 yr	10 yr
	100.0%	99.9%	99.7%	99.4%	97.7%

B

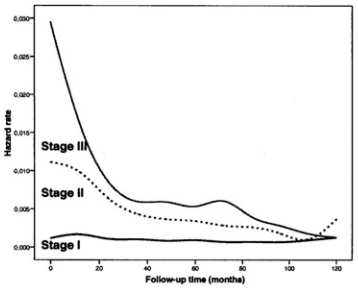
Fig 1. A, Probability of recurrence-free survival after primary cutaneous melanoma (CM) diagnosis according to stages. **B**, Probability of secondary melanoma–free survival after primary CM diagnosis.

(CI) were provided in Fig 1. HR and 95% CI for recurrences and for secondary melanoma were calculated using life table procedures (SPSS 17, SPSS Inc). Results in relation to length of follow-up are given (Fig 2). "Hazard" is the instantaneous risk of an event happening (eg, death, recurrence, or secondary melanoma) at a certain point in time and is calculated by the number of patients having the event divided by the number of patients effectively under risk at that point in time. All HR were presented per person-years.

RESULTS

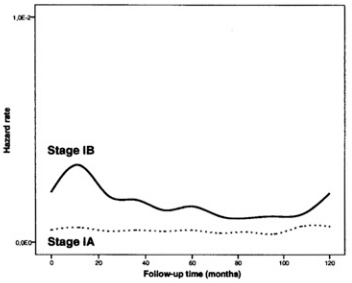
Description of sample

The sample of 33,384 patients with primary CM or locoregional metastasis after complete resection and with documented follow-up consisted of 45.1% male patients and the mean age at diagnosis was 54.0 years (SD ± 16.8) (Table I). The median tumor thickness was 1.00 mm (IQR 0.52-2.00). Of these



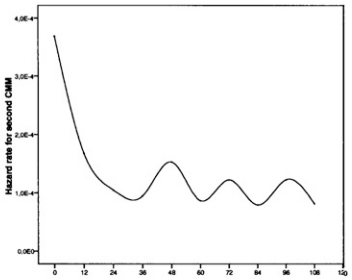
Hazard rates and 95% confidence intervals (per person-year)				
Stage	**1 year**	**3 years**	**5 years**	**10 years**
I	0.014 (0.0125, 0.0156)	0.0129 (0.0112, 0.0147)	0.0100 (0.0082, 0.0118)	0.0110 (0.0077, 0.0143)
II	0.1335 (0.1250, 0.1421)	0.0759 (0.0676, 0.0843)	0.0438 (0.0358, 0.0518)	0.0126 (0.0051, 0.0200)
III	0.3545 (0.3234, 0.3856) All stages different	0.1016 (0.0770, 0.1263) Stage I differs from II and III	0.0709 (0.0437, 0.0982) Stage I differs from II and III	0.0213 (0.0, 0.0508) Stages not different
Cumulative hazard function (person-year)				
Stage I	0.01606	0.04785	0.07028	0.11639
Stage II	0.14866	0.33190	0.42309	0.56364
Stage III	0.38069	0.65358	0.78842	1.02289
Number of patients at risk of first recurrence				
Stage I	20850	14731	10160	2741
Stage II	5999	3551	2297	654
Stage III	998	536	303	78

A



Hazard rates and 95% confidence intervals (per person-year)				
Stage	**1 year**	**3 years**	**5 years**	**10 years**
Ia	0.0066 (0.0053, 0.0080)	0.0060 (0.0045, 0.0075)	0.0060 (0.0042, 0.0077)	0.0087 (0.0050, 0.0124)
Ib	0.0269 (0.0234, 0.0305) Stages different	0.0252 (0.0211, 0.0292) Stages different	0.0172 (0.0132, 0.0212) Stages different	0.0150 (0.0086, 0.0214) Stages not different
Cumulative hazard function (person-year)				
Stage Ia	0.00724	0.02080	0.03354	0.06451
Stage Ib	0.03141	0.09522	0.13491	0.20805
Number of patients at risk of first recurrence				
Stage Ia	13257	9430	6529	1731
Stage Ib	7593	5301	3631	1010

B



Hazard rates and 95% confidence intervals (per person-year)				
	1 year	**3 years**	**5 years**	**10 years**
Second melanoma	0.0045 (0.0038, 0.0053)	0.0013 (0.0008, 0.0018)	0.0019 (0.0012, 0.0026)	0.0010 (0.0001, 0.0018)
Cumulative hazard function (person-year)				
Second melanoma	0.00471	0.00807	0.01101	0.01737
Number of patients at risk of secondary melanoma				
Overall	28761	19834	13442	3773

C

Fig 2. Hazard rates (per person-year) for recurrences according to stages (**A**); for recurrences according to stages IA and IB (**B**); and for secondary melanoma (**C**).

patients, 71.4% were in stage I, 23.6% were in stage II, and 5.0% were in stage III.

Overall, patients had a median follow-up time of 49 months (IQR 23-91). Follow-up information was available for 41.4% of patients for a period of 5 years or more. The disease-related mortality was 7.6% (n = 2539). Patients who died from CM had a median follow-up time of 34 months (IQR 19-60), whereas censored cases had a median follow-up time of 51 months (IQR 24-95). The melanoma-specific 5-year survival was 91.9% (95% CI 91.5-92.2) and the melanoma-specific 10-year survival was 87.2% (95% CI 86.6-87.8).

RFS according to Kaplan-Meier analyses

Recurrences were recorded in 4999 patients (15.3%; stage I, 7.1%; stage II, 32.5%; and stage III, 51.0%) (Table II). The median RFS time was 44 months (IQR 19-85). The 10-year RFS was 78.9% (95% CI 73.1-90.5) overall, 89.0% for stage I, 56.9% for stage II, and 36.0% for stage III melanoma cases ($P < .001$) (Fig 1 and Table II). Of all initial recurrences 37.4% were locoregional, 39.5% affected the regional lymph nodes, and 23.0% were classified as distant metastases.

HR for the first recurrences according to stage of disease

HR, 95% CI, and number of patients at risk were provided for years 1, 3, 5, and 10 (Fig 2, *A* and *B*) and for the detailed course of 10 years (Table III). When CIs overlapped, results were not considered significant at the 5% level. For stage I melanoma, the HR remained at a low level during the entire follow-up

Table I. Description of clinical characteristics of invasive cutaneous melanoma of 33,384 patients recorded by Central Malignant Melanoma Registry of German Society of Dermatology between 1976 and 2007

Clinical characteristics	CMMR (n = 33,384)
Age at diagnosis, y	
Mean (± SD)	54.0 (± 16.8)
≤ 30	7.6%
31-40	12.6%
41-50	17.5%
51-60	22.8%
61-70	22.0%.
71-80	13.4%
>80	4.1%
Gender	
Male	45.1%
Female	54.9%
Tumor thickness, mm	
Median (IQR)	1.00 (0.52-2.00)
≤ 1.00	52.6%
1.01-2.00	23.3%
2.01-4.00	15.9%
>4.00	8.2%
Level of invasion	
II	21.3%
III	37.3%
IV	35.1%
V	4.1%
Missing values	n = 723 (2.2%)
Histologic subtype	
SSM	59.5%
NM	19.5%
LMM	8.1%
ALM	3.6%
Others	3.3%
Missing values	n = 2338 (7.0%)
Body site	
Head, scalp, and neck	13.3%
Trunk	39.7%
Upper extremities	16.0%
Lower extremities	31.0%
Missing values	N=102
Ulceration	11.5%
Missing values	n = 8274
Stage at primary diagnosis	
IA	45.3%
IB	26.1%
IIA	12.9%
IIB	7.9%
IIC	2.7%
IIIA	1.0%
IIIB	3.6%
IIIC	0.4%

ALM, Acral lentiginous melanoma; *CMMR*, Central Malignant Melanoma Registry; *IQR*, interquartile range; *LMM*, lentigo maligna melanoma; *NM*, nodular melanoma; *SSM*, superficial spreading melanoma.

Table II. Follow-up times and Kaplan-Meier survival probabilities to recurrences and secondary melanoma of invasive cutaneous melanoma of 33,384 patients recorded by Central Malignant Melanoma Registry of German Society of Dermatology between 1976 and 2007

Recurrences and secondary melanoma	
Median follow-up time, mo (IQR)	49 (23-91)
Stage I	53 (25-96)
Stage II	41 (20-82)
Stage III	33 (16-63.75)
Death caused by CM	7.6%
Median follow-up time to first recurrence, mo (IQR)	44 (19-85)
Stage I	51 (23-93)
Stage II	31 (13-69)
Stage III	19 (7-48)
Time to first recurrence, mo	
≤ 12	16.6%
13-24	15.3%
25-48	21.3%
49-60	8.6%
60-120	27.8%
>120	10.4%
First recurrence (n = 5100; 15.3%)	
Locoregional metastases	37.4%
Regional lymph node metastases	39.5%
Distant soft tissue metastases	8.6%
Visceral metastases	14.4%
First recurrence by stage	
Stage I (n = 23,842)	7.1%
Stage II (n = 7866)	32.5%
Stage III (n = 1676)	51.0%
Median follow-up time to second melanoma, mo (n = 783; 2.3%) (IQR)	21 (4-61)
Time to second melanoma, mo	
≤ 12	40.5%
13-24	13.9%
25-48	12.6%
49-60	8.0%
60-120	13.9%
>120	11.0%

CM, Cutaneous melanoma; *IQR*, interquartile range.

(Fig 2, *A*). Although in stage 1A the HR remained stable (≤1:125, ie, 1 case/125 persons/y for 10 years) (Table III), an increased HR was observed in stage IB during the first 36 months (1 case/37 persons/y in year 1 to 1 case/40 persons/y in year 3) (Table III) with overlapping 95% CI after 10 years (Fig 2, *B*). For stage II melanoma, a decline from a HR of 1 case per 7 persons per year in the first year to 1 case per 13 persons per year in the third year could be observed. HRs decreased further after the third year and were below 1 case per 40 persons per year after 8 years (Fig 2, *A*). For stage III melanoma, a

Table III. Hazard Rates for first recurrences and secondary melanoma of 33,384 patients recorded by Central Malignant Melanoma Registry of German Society of Dermatology between 1976 and 2007

Postdiagnosis, y	Stage I	Stage IA	Stage IB	Stage II	Stage III	Second CM
1	1:71	1:152	1:37	1:7	1:3	1:222
2	1:50	1:125	1:24	1:8	1:5	1:476
3	1:78	1:167	1:40	1:13	1:10	1:769
4	1:81	1:152	1:44	1:19	1:14	1:909
5	1:100	1:167	1:58	1:23	1:14	1:526
6	1:90	1:152	1:52	1:24	1:16	1:833
7	1:122	1:200	1:71	1:29	1:14	1:667
8	1:120	1:179	1:77	1:32	1:21	1:833
9	1:127	1:217	1:72	1:46	1:30	1:667

Results are presented as 1 recurrence or secondary cutaneous melanoma per number of person-years.
CM, Cutaneous melanoma.

sharp decline was observed from a HR of 1 case per 3 persons per year in the first year to 1 case per 10 persons per year after 3 years and reached a level of 1 case per 30 persons per year after nine years. From 3 years of follow-up onward, stage II and III CIs overlapped and showed no significant differences for the development of recurrences (Fig 2, *A*). After 10 years of follow-up HR of all 3 stages did not differ significantly. The hazard to develop a recurrence statistically significantly decreased with the follow-up time for stages I, II, and III and for stage IB ($P <$ .05, respectively); the decline for stage IA was not significant ($r = -0.16$; $P = .654$). Cumulative HR are presented in the tables below Figs 1 and 2.

Linearity was checked graphically and seemed in broad terms fulfilled. The analysis was conducted to support the observation that HR were decreasing with increased time of follow-up statistically.

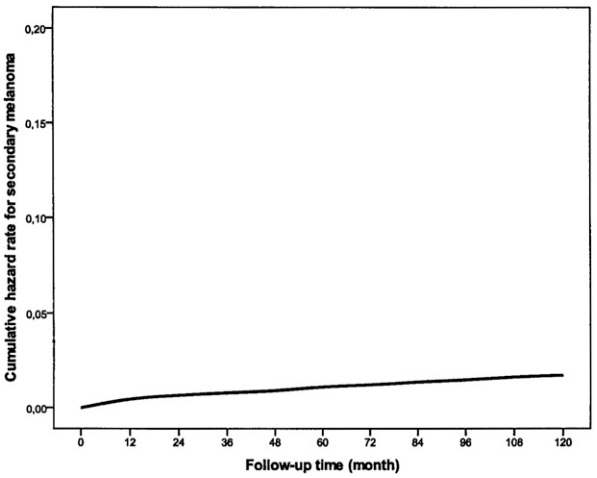


Fig 3. Cumulative hazard function (per person-year) for secondary melanoma.

Secondary melanoma

A total of 723 (2.3%) secondary melanomas were diagnosed during regular follow-up of the 33,384 patients with primary CM. The characteristics of secondary melanoma were calculated in 522 of 723 cases and were the following: the median tumor thickness of secondary melanoma was 0.3 mm, and second CM were detected more early than the primary melanoma. Concerning Clark level of invasion 33.6% of the secondary melanoma were detected as in situ melanoma, 24.3% were level II, 27.5% were level III, and 14.6% were level IV. Concerning the histologic subtype, 81.4% were superficial spreading melanoma, 3.2% were nodular melanoma, 10.4% were lentigo maligna melanoma, 1.0% were acrolentiginous melanoma, and 3.8% were others. The median follow-up time to the diagnosis of the second CM was 21 months (IQR 4-61). The 10-year secondary melanoma–free survival was 95.6% (95% CI 96.1-95.0). Of all secondary melanomas 40.5% were detected within 1 year and 54.4% were detected within the first 2 years after diagnosis of the primary CM (Table II). About 25% of secondary melanomas were diagnosed after the fifth year of follow-up. The HR for secondary melanoma decreased from 1 case per 222 persons per year to 1 case per 769 persons per year after 3 years of follow-up (Fig 2, *C*, and Table III). The decline in the HR was borderline significant ($r = -0.63$; $P = .049$). HR, 95% CI, and number of patients at risk are given for years 1, 3, 5, and 10 (Fig 2, *C*). CIs overlapped and were not considered significant on the 5% level. Fig 3 shows the cumulative HR for secondary melanoma.

DISCUSSION

This study analyzed HR for recurrences and secondary melanomas on the basis of a large data set with long-term follow-up information. The data allowed calculation of HR of recurrences stratified by the different stages of CM with CI, which may have an impact on melanoma follow-up schedules.

The analysis of HR for recurrences of melanoma disease during the follow-up time allowed us to determinate patients at risk for different time points. In the current study HR below 1 recurrence per 125 persons per year were observed in stage IA CM during the entire period of 10-year follow-up. For stage II and III melanomas increased HR (1 recurrence/7 persons/y and 1 recurrence/3 persons/y, respectively, for year 1) were found in the first 3 years after diagnosis with a slow decrease thereafter. HR showing values of more than 1 recurrence per 40 persons per year during the entire follow-up time showed an increased risk of developing recurrences during that time frame.

In stage III CM increased HR for recurrences (between 1 recurrence/3 persons/y and 1 recurrence/30 persons/y) were demonstrated until the end of the 10-year time period. After 10 years our analysis did not detect any significant differences in HR among stages I, II, and III. However, sample sizes were reduced after this follow-up period. Therefore, the current study was not able to give advice for the time period beyond 10 years, as the German recommendations always included discontinuation of regular follow-up examinations at this time point. Follow-up information beyond 10 years was anecdotal in the CMMR and consisted mainly of patients with late recurrences. To our knowledge, there is only one published study[10] dealing with HR for recurrences of CM, as recurrences are usually not comprised in cancer registries. Therefore these rates cannot be compared with those of other countries or the SEER database or even large European registries. Concerning the recurrences of CM, rates of 17% to 23% have been described in the literature[5,7,16,18-23]; the rates of secondary CM occurrence vary between 2% and 7%.[6,24,25] But similar to the recurrence situation, so far no HR for the occurrence of secondary CM have been published. Concordant with our results, Poo-Hwu et al[10] showed that the estimated 6-month HRs for death or recurrence after the first follow-up visit were 0.0044, 0.0088, and 0.0278, respectively, for patients with stage I, II, and III disease or roughly a ratio of 1:2:6.3, showing similar hazard functions than the current study, although when Poo-Hwu et al[10] did their analysis, routine sentinel lymph node biopsy had not been performed in all patients with CM greater than or equal to 1.0-mm tumor thickness and therefore patients with micrometastases were regarded as stage I/II.

HRs for secondary CM were less than 1 case per 222 persons per year during the entire 10-year follow-up period and reached values of less than 1 case per 500 persons from year 5 onward. Similar to these results, Goggins and Tsao[11] reported that most secondary CM occurred in the first few months after primary CM diagnosis and that the frequency declined subsequently. On the other hand, secondary CM were detected even more than 30 years after the primary diagnosis, which argues for a lifelong risk for secondary CM.[6,11,13]

This analysis has some limitations: 58.6% of patients had a follow-up time of less than 5 years; for 41.4% of patients follow-up information was available for 5 years or more. Current German recommendations discontinue regular follow-up examinations after 10 years. Hence, no information could be provided beyond 10 years of follow-up. Data of patients with CM and dysplastic nevus syndrome were not documented within the CMMR.

Implications for follow-up schedules

Naturally, follow-up schedules cannot be deducted from HR calculations. Other considerations have to be taken into account such as the clinical scope and efficiency of examinations and also cost-effectiveness aspects. Nevertheless, the analysis of HR plays a role in the scheduling of follow-up examinations, particularly for its distribution into more intense and less intense periods. In the following, the relative impact of these different aspects for scheduling follow-up examinations is discussed in more detail.

Planning follow-up service requires us to make some basic decisions that depend on clinical considerations and experience. There are two main clinical goals of follow-up examinations: (1) early detection of newly developing secondary melanomas; and (2) the diagnosis of melanoma recurrences in an early phase of development. Currently, time periods scheduled to reach these goals are based on clinical experience and on opinion and have to be investigated in future more thoroughly.

The following time periods for the different clinical goals have been proposed in the literature. First, for early detection of secondary melanomas, in long-term surveillance, once yearly screenings seem to be sufficient. More frequent examinations in 3- to 6-monthly intervals may be advantageous during the first year. Second, for the diagnosis of melanoma recurrences in an early phase mainly 3- and 6-monthly intervals have been proposed. Seemingly, longer intervals such as 1 year may leave the tumor too much time to grow and detection in an early phase of development can no longer be expected. More frequent examinations seem mainly to be indicated during periods of high risk for development of melanoma recurrences, whereas less frequent examinations should be applied to periods of lower risk.

Table IV. Proposal for type and frequency of follow-up examinations for patients with cutaneous melanoma according to stages (American Joint Committee on Cancer, 2002)

Stage	Years 1-3	Years 4-8	Ultrasound + S100	Other imaging techniques
Stage IA	1-2×	1×	No	No
Stage IB	2-4×	2×	Yes	No
Stage II	4×	4×	Yes	No
Stage III	4×	4×	Yes	Yes

Aspects of the cost-effectiveness of follow-up examinations relate more to the kind of technical examinations because of the high costs of imaging procedures than to the pure frequency of follow-up examinations.

The analysis of HR for secondary melanoma and for recurrences may mainly help us to answer two questions: (1) how long should we conduct follow-up examinations?; and (2) if we should plan periods with increased frequencies of follow-up examinations. Both questions have to be answered for the two different clinical goals of melanoma follow-up separately.

First, for the detection of subsequent melanomas, we found increased HR particularly in the first year. Thereafter, HR stabilized on a low level. The seeming increase during years 9 and 10 may already be a selection bias for persons developing subsequent primary melanomas related to a low rate of patients still being followed up. After the first year, once yearly screening examinations may be sufficient to detect newly developing primary melanomas. There were no hints that the risk may diminish after 8 or 10 years of follow-up, therefore, further continuation of screening examinations may be an individual decision taking into account features such as multiple moles and dysplastic nevus syndrome.

Second, the diagnosis of melanoma recurrences in an early phase is confronted with different HR in different clinical stages and pronounced changes of HR over time after the first diagnosis of primary melanoma. In the stages II and III, clearly increased HR were observed over the first 3 years. At least in stages II and III more frequent examinations, for example in 3-monthly intervals, should be considered. HR in stage IB were likewise elevated in comparison with stage IA during the first 2 years, but its level did by far not reach the levels in stage II and III. Therefore, twice yearly follow-up examinations may be sufficient for stage IA during the first years; for stage IB two to four visits per year could be considered in the first 3 years after diagnosis. There was a constantly low level of HR in stage I except for a slight elevation during the first 2 years. After a period of 8 years, HR decreased for patients at stage II and III to the magnitude of stage I. A seeming elevation after this time period in the ninth and tenth year could be a result of selection bias for those patients who represented with recurrences, in relationship to the low number of patients still under observation. Therefore, a total period of 8 years seems to be sufficient to detect melanoma recurrences.

Based on these considerations, we proposed a time schedule for follow-up examinations for patients with melanoma differentiated by clinical stages, which is provided in Table IV. Certainly, this follow-up schedule was influenced by national traditions of melanoma follow-up and also by personal opinions. Nevertheless, implications of HR analysis have been related now systematically to the timely structure of screening examinations under the two aspects of detection of subsequent primary tumor and of melanoma recurrences. This schedule could be suitable to initiate a more rational discussion on follow-up schedules and to determine those areas on which future investigations on melanoma follow-up should focus.

Conclusions

This study aimed at proposing a surveillance strategy for CM based on empirical evidence in the form of HR for recurrences and secondary melanomas. Nevertheless, decisions relating to the frequency of examinations and follow-up time remain somewhat arbitrary. This study showed that HR for first recurrences were higher then 1 case per 40 persons per year in stage IB during the first 3 years, in stages II in the first 8 years after primary melanoma diagnosis, and in stage III for the entire 10 year follow-up period.

Based on these results, we propose that patients at high risk with HR of more than 1 recurrence per 40 persons per year should be considered in an intensified follow-up schedule. Reduced surveillance seems appropriate for patient groups with HR of less than 1 recurrence per 40 persons per year. For patients at stage IA with HR of less than 1 recurrence per 125 persons per year during the entire follow-up period, the need of surveillance remains debatable, and should mainly focus on the detection of secondary or multiple primary melanomas. For patients with elevated risk for secondary CM, ie, with dysplastic nevus syndrome, continuation of annual examinations beyond the 10-year time period should be considered.

REFERENCES

1. Grin-Jorgensen CM, Rigel DS, Friedman RJ. The worldwide incidence of malignant melanoma. 2nd ed. Philadelphia: JB Lippincott Company; 1992. p. 27-39.
2. Lens MB, Dawes M. Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma. Br J Dermatol 2004;150:179-85.
3. Ries L, Melbert D, Krapcho M. SEER cancer statistics review, 1975-2000. Bethesda (MD): National Cancer Institute; 2008.
4. Altekruse SF, Kosary C, Krapcho M. SEER cancer statistics review, 1975-2007. National Cancer Institute; 2010. Available from: http://seer.cancer.gov/csr/1975_2007/. Accessed June 7, 2011.
5. Baughan CA, Hall VL, Leppard BJ, Perkins PJ. Follow-up in stage I cutaneous malignant melanoma: an audit. Clin Oncol (R Coll Radiol) 1993;5:174-80.
6. Brobeil A, Rapaport D, Wells K, Cruse CW, Glass F, Fenske N, et al. Multiple primary melanomas: implications for screening and follow-up programs for melanoma. Ann Surg Oncol 1997; 4:19-23.
7. Dicker TJ, Kavanagh GM, Herd RM, Ahmad T, McLaren KM, Chetty U, et al. A rational approach to melanoma follow-up in patients with primary cutaneous melanoma: Scottish Melanoma Group. Br J Dermatol 1999;140:249-54.
8. Kalady MF, White RR, Johnson JL, Tyler DS, Seigler HF. Thin melanomas: predictive lethal characteristics from a 30-year clinical experience. Ann Surg 2003;238:528-35.
9. Moloney DM, Gordon DJ, Briggs JC, Rigby HS. Recurrence of thin melanoma: how effective is follow-up? Br J Plast Surg 1996;49:409-13.
10. Poo-Hwu WJ, Ariyan S, Lamb L, Papac R, Zelterman D, Hu GL, et al. Follow-up recommendations for patients with American Joint Committee on Cancer stages I-III malignant melanoma. Cancer 1999;86:2252-8.
11. Goggins WB, Tsao H. A population-based analysis of risk factors for a second primary cutaneous melanoma among melanoma survivors. Cancer 2003;97:639-43.
12. Johnson TM, Hamilton T, Lowe L. Multiple primary melanomas. J Am Acad Dermatol 1998;39:422-7.
13. Kang S, Barnhill RL, Mihm MC Jr, Sober AJ. Multiple primary cutaneous melanomas. Cancer 1992;70:1911-6.
14. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localized primary cutaneous melanoma. Lancet Oncol 2005;6:608-21.
15. Kleeberg UR. Wishful thinking, unicentric empiricism and the everyday world of the medical melanomologist. Melanoma Res 1997;7(Suppl):S143-9.
16. Garbe C, Paul A, Kohler-Spath H, Ellwanger U, Stroebel W, Schwarz M, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. J Clin Oncol 2003;21: 520-9.
17. Orfanos CE, Jung EG, Rassner G, Wolff HH, Garbe C. Position and recommendations of the Malignant Melanoma Committee of the German Society of Dermatology on diagnosis, treatment and after-care of malignant melanoma of the skin. Status 1993/94 [in German]. Hautarzt 1994;45:285-91.
18. Cohn-Cedermark G, Rutqvist LE, Andersson R, Breivald M, Ingvar C, Johansson H, et al. Long-term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8-2.0 mm. Cancer 2000; 89:1495-501.
19. Garbe C. A rational approach to the follow-up of melanoma patients. Recent Results Cancer Res 2002;160:205-15.
20. Soong SJ, Harrison RA, McCarthy WH, Urist MM, Balch CM. Factors affecting survival following local, regional, or distant recurrence from localized melanoma. J Surg Oncol 1998;67: 228-33.
21. Francken AB, Accortt NA, Shaw HM, Colman MH, Wiener M, Soong SJ, et al. Follow-up schedules after treatment for malignant melanoma. Br J Surg 2008;95:1401-7.
22. Hofmann U, Szedlak M, Rittgen W, Jung EG, Schadendorf D. Primary staging and follow-up in melanoma patients—monocenter evaluation of methods, costs and patient survival. Br J Cancer 2002;87:151-7.
23. Weiss M, Loprinzi CL, Creagan ET, Dalton RJ, Novotny P, O'Fallon JR. Utility of follow-up tests for detecting recurrent disease in patients with malignant melanomas. JAMA 1995; 274:1703-5.
24. Berwick M, Dubin N, Luo ST, Flannery J. No improvement in survival from melanoma diagnosed from 1973 to 1984. Int J Epidemiol 1994;23:673-81.
25. DiFronzo LA, Wanek LA, Morton DL. Earlier diagnosis of second primary melanoma confirms the benefits of patient education and routine postoperative follow-up. Cancer 2001; 91:1520-4.