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Compliance with follow-up and prognosis among patients with thin melanomas

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Abstract

The aim of this study was to report on the compliance with follow-up among patients with thin melanomas. We also examined the prognosis of patients with recurrent disease and whether there were any differences in prognosis associated with the time between the last follow-up examination and the onset of recurrence. A retrospective analysis of the records of 513 consecutive patients (50.3% males, mean age: 52.8±16.9 years) with thin melanomas (<1.5 mm Breslow thickness) was carried out. The estimated cumulative proportion of patients who still continued their follow-up examinations 5 years after diagnosis of the primary tumour was 55.3% (95% Confidence Interval (CI): 50.4–60.2%). The mean annual drop-out rate was 11.2%. The drop-out rate was similar for males and females and was not influenced by the patients' age or the tumour thickness. Among 263 patients who continued follow-up, 50.2% ($n=132$) were not compliant with the time schedule. 20 patients presented with recurrent disease after a median of 35.9 months (25–75% percentiles: 16.7–46.5 months). Six patients who did not have a follow-up examination within 1 year before the onset of recurrence presented with more advanced disease and had a worse prognosis (median survival: 12.5 months, hazard ratio: 3.5, 95% CI: 1.1–17.1, $P=0.04$), than those patients, who had a recent follow-up examination before the onset of recurrence ($n=14$, median survival: 22.3+ months). In the majority of recurrent cases with good prognosis, metastatic disease was confined to the regional lymph nodes and the presumptive diagnosis of metastatic disease was either made by palpation or by sonography of the regional lymph nodes. The observed drop-out rate of patients during the first 5 years of follow-up is substantial and does not depend on the patients' age, sex or on the tumour thickness. Although the frequency of recurrences among patients with thin melanomas is low, regular follow-up examinations including physical examination, as well as palpation and sonography of the regional lymph nodes, are essential.

Keywords: Melanoma; Recurrent disease; Follow-up; Compliance

1. Introduction

The worldwide rising incidence of melanoma has been mainly attributed to an increase in the frequency of thin melanomas [1]. According to the data available in the literature, the frequency of recurrences in patients with thin melanomas is generally low, ranging from 4 to 11% [2–8]. Guidelines for the follow-up of patients with thin melanomas exist, but given the low frequency of recurrences, it has been questioned, whether follow-up of these patients is worthwhile [2,7,9–16]. No data exist on the compliance with follow-up among patients with melanoma and it is unclear, whether regular follow-up examinations provide any benefit for the patient [2,9,13].

The aim of this study was to report on the compliance with follow-up and on the frequency and patterns of recurrence among patients with thin melanomas. We also wanted to compare the prognosis of patients with recurrent disease, who had a recent follow-up examination before the onset of metastatic disease, with those patients, who did not.

2. Patients and methods

We retrospectively reviewed the records of 513 consecutive patients who were seen and followed according

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to the surveillance protocol at the Department of Dermatology at the University of Vienna. We included patients with invasive primary cutaneous melanomas thinner than 1.5 mm Breslow thickness, who had their first visit between March 1993 and December 1996. Patients with *in situ* melanomas ($n=120$) were excluded from further analysis. Patients with metastatic disease at the time of diagnosis of the primary tumour ($n=7$) and patients with primary melanomas of any other site than the skin ($n=3$) were also excluded.

All patients received initial staging comprising clinical examination, complete blood count and routine chemistry, chest X-ray, abdomen and peripheral lymph node sonography.

Follow-up examinations included a total skin examination, palpation and sonography of the regional lymph nodes, complete blood count, routine blood chemistry, sonography of the abdomen, as well as a chest X-ray. For the first 5 years after diagnosis, these examinations were scheduled every 6 months. After 5 years, the follow-up interval was extended to 1 year. All files were regularly reviewed and reminder letters were sent to patients who did not come to a scheduled follow-up visit. Patients were considered to be lost to follow-up if they did not respond to these written reminders and did not come to further follow-up visits. Patients who responded to the reminders and stated that they will continue follow-up visits at another institution were not considered to be lost to follow-up, but no further follow-up data were available for them.

Patients were considered to be compliant with the follow-up regimen if they had at least one annual follow-up examination. Patients who had follow-up intervals of more than one year were considered as non-compliant. Patients who developed metastatic disease were stratified into two groups depending on whether or not they had a follow-up-examination within one year before the onset of recurrence.

2.1. Statistical analysis

Data are presented as means and standard deviations (S.D.), unless otherwise specified. Comparisons of continuous variables were performed with the *t*-test or with the Mann–Whitney-*U*-test, as appropriate. For the comparison of proportions, the Chi-square test or the Fisher's Exact test were used. For estimation of the drop-out rates and disease-specific survival rates, life tables and the method according to Kaplan and Meier were used. The reported survival times refer to the survival times since the onset of recurrence. To test for homogeneity among the various groups of patients, we used the log-rank test. The Cox proportional-hazards model was used for multivariate analysis.

Data were analysed with Statistical Package for the Social Sciences (SPSS) statistical software package (SPSS, Chicago, IL). All *P* values given are two-tailed and a *P* value of <0.05 was regarded as statistically significant.

3. Results

3.1. General data

A total of 513 patients (50.3% males, mean age: 52.8 ± 16.9 years) with thin melanomas (<1.5 mm Breslow thickness) were included in the analysis. The median Breslow thickness was 0.6 mm (25–75% percentiles: 0.4–0.9 mm). The anatomical level of invasion (Clark level) was level II in 140 (27.3%) cases, level III in 264 (51.5%) cases and level IV in 98 (19.1%) of cases. Clark level for various reasons was not recorded in 11 (2.1%) cases. The series included 376 (73.3%) superficial spreading melanomas, 92 (17.9%) lentigo maligna melanomas, 22 (4.3%) nodular melanomas and 5 (1.0%) acral lentiginous melanomas. The histological type was not classified in 18 (3.5%) cases. The melanomas were located on the trunk in 246 (48.0%) patients, on the lower extremities in 145 (28.3%) patients and on the upper extremities in 69 (13.5%) patients. Fifty-three (10.3%) melanomas were located in the head and neck region.

3.2. Compliance with follow-up

A total of 201 patients were lost to follow-up during the 5 five years after diagnosis and 49 patients stopped their follow-up examinations at our institution, but continued follow-up at another institution. The estimated cumulative proportion of patients who still continued the follow-up examinations 5 years after the diagnosis of the primary tumour was 55.3% (95% Confidence Interval (CI): 50.4–60.2%; Fig. 1). The mean annual drop-out rate was 11.2%. The drop-out rate during the first 5 years of follow-up did not change substantially with regard to the duration of follow-up. The drop-out rate was similar for males and females (adjusted hazard ratio for drop-out: 0.86, 95% CI: 0.63–1.18, $P=0.26$) and was not influenced by the age of the patient (adjusted hazard ratio: 1.01, 95% CI: 0.996–1.02, $P=0.35$) or the tumour thickness (adjusted hazard ratio: 0.60, 95% CI: 0.35–1.03, $P=0.07$). Of 263 patients who were not lost to follow-up, 132 patients (50.2%) extended their follow-up interval to more than 1 year at least once during the follow-up period.

3.3. Frequency of subsequent second melanomas

8 patients developed subsequent second melanomas after the diagnosis of the first melanoma. One patient developed two further melanomas. The subsequent melanomas consisted of four *in situ* melanomas and six invasive melanomas. The median Breslow thickness of

the subsequent melanomas was lower than the invasion thickness of the first melanomas. (0.28 versus 0.50 mm, $P = 0.04$).

3.4. Patterns and frequency of recurrence

Over a median observation period of 3.7 years (25–75% percentiles: 2.3–5.0 years), 20 patients (3.9%) developed metastatic disease (13 males, mean age: 51.3±19.5 years). The median time interval until the onset of metastatic disease was 35.9 months (25–75% percentiles: 16.7–46.5 months). A Cox proportional hazard model that included the Breslow thickness, Clark level, anatomical site, age, gender and compliance with follow-up as independent variables showed that only the Breslow thickness was significantly associated with recurrent disease (hazard ratio: 11.6, 95% CI: 3.1–44.0, $P < 0.001$).

The characteristics of the individual patients with recurrences are given in Table 1. The majority of recurrences were detected by physical examination, lymph node palpation or lymph node sonography. These examinations led to further diagnostic work-up and finally to the confirmation of the suspected diagnosis by histopathology. Complete blood counts and blood chemistry were unremarkable or showed mild-non-specific abnormalities in 18 cases. In 2 cases with metastases of the lung and the liver, lactate dehydrogenase (LDH) was elevated.

3.5. Prognosis among patients with recurrent disease

Among the patients with recurrences, 14 patients had a follow-up examination within one year before the onset of metastatic disease. 4 patients (29%) presented with satellite or intransit metastases, 1 patient (7%) with a single retrobulbar metastasis, 7 patients (50%) had metastases confined to the regional lymph nodes and 2 patients (14%) had metastatic disease of inner organs. 6 patients did not have a follow-up examination within 1 year before the onset of metastatic disease; one of these patients (17%) presented with satellite or intransit metastases, three of these patients (50%) presented with metastases confined to the regional lymph nodes and the other patients (33%) with metastatic disease of inner organs. In patients with regional lymph node metastases who had a follow-up examination within 1 year before the manifestation of metastatic disease, the maximum diameter of the lymph node metastases as measured by sonography was smaller than in patients with lymph node metastases who did not have a recent follow-up examination (median: 16 mm versus 40 mm, $P = 0.03$).

Of the 14 patients who had a recent follow-up examination before the onset of metastatic disease, 4 (29%) died of melanoma-related metastatic disease. For these 14 patients, the median overall survival from the onset of recurrence was 22.3+ months.

All of the patients ($n = 6$) who did not have a recent follow-up examination before the onset of recurrence died of metastatic disease and had a significantly worse prognosis than patients with a recent follow-up examination before the onset of recurrence (median survival: 12.5 months, hazard ratio: 3.5, 95% CI: 1.1–1 7.1, $P = 0.04$, Fig. 2).

4. Discussion

In our cohort of patients with thin melanomas, the frequency of recurrences was approximately 4%, which is comparable to similar studies performed previously

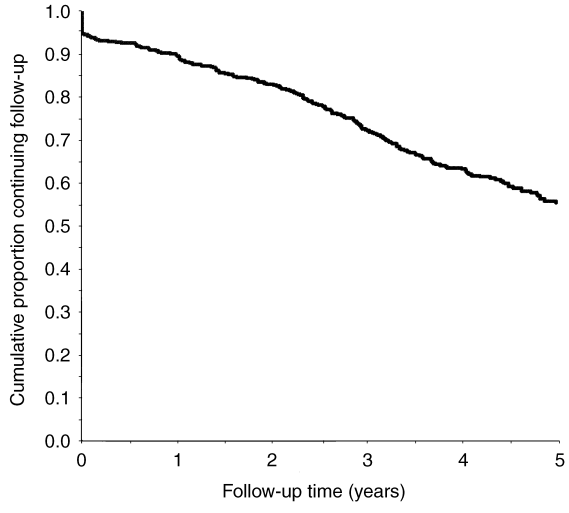

Fig. 1. Kaplan–Meier curve for the drop-out rate during follow-up. Follow-up times of patients who stated that they will continue follow-up at another institution are censored.

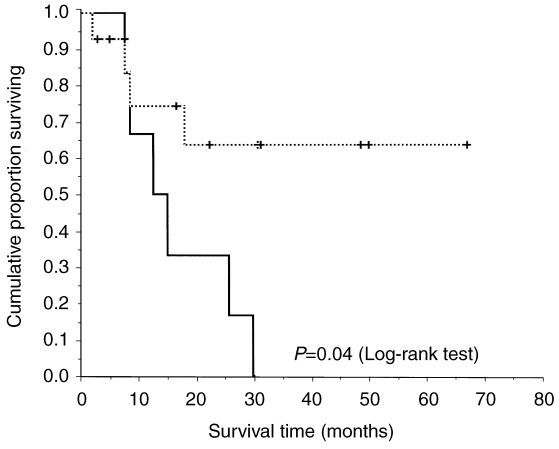

Fig. 2. The survival curves of patients with recurrences. The solid line indicates the group of patients who did not have a follow-up examination within 1 year before the onset of recurrence ($n = 6$). The dotted line indicates the group of patients who did have a follow-up examination within 1 year before the onset of recurrence ($n = 14$). The crosses indicate censored observations.

Table 1
Individual data of patients with recurrences

Histological type	Clark level	Breslow thickness (mm)	Age (years)	Sex	Site	Follow-up time[a] months	Melanoma-related death	Reason for stopping follow-up	Localisation of recurrence	Diagnosis of recurrence[b]	Maximum diameter of LNN (mm)	Number of involved LNN (n)	Symptoms recognised by patient
Patients who did not have a follow-up examination within 1 year before the onset of recurrence ($n=6$)													
LMM	III	0.83	75.2	M	Chest	7.7	Yes	Not compliant	Liver	Abdomen sonography			No
SSM	IV	1.00	66.0	M	Ear	29.8	Yes	Misdiagnosis	Skin	Physical examination			Yes
SSM	III	0.82	73.5	F	Lower leg	15.0	Yes	Not compliant	Regional LNN	Palpation of LNN	40	1	Yes
SSM	III	0.65	45.8	F	Back	25.7	Yes	Not compliant	Regional LNN	Palpation of LNN	32	>5	Yes
SSM	III	0.50	44.6	M	Abdomen	12.5	Yes	Misdiagnosis	Regional LNN, liver, lung	Palpation of LNN, abdomen sonography, chest X-ray			
SSM	III	0.35	43.0	M	back	8.6	Yes	Not compliant	Regional LNN	Palpation of LNN	50	>5	Yes
Patients who had a follow-up examination within 1 year before the onset of recurrence ($n=14$)													
SSM	III	1.34	47.8	M	Chest	8.5	Yes		Lung	Chest X-ray			No
SSM	III	0.80	84.6	F	Back	5.1	No		Skin	Physical examination			Yes
SSM	IV	1.20	24.9	M	Abdomen	7.7	Yes		Regional LNN	Palpation of LNN	24	3	No
LMM	IV	1.40	68.8	M	Face	2.9	No		Retrobulbar	Computer tomography			Yes
LMM	III	1.40	64.2	M	Back	17.9	Yes		Regional LNN	Sonography of LNN	15	1	No
SSM	IV	1.00	53.4	M	Back	2.1	Yes		Lung, bone	Chest X-ray			No
LMM	IV	1.30	61.6	F	Lower leg	7.6	No		Skin	Physical examination			Yes
SSM	IV	1.40	66.0	M	Back	22.3	No		Skin	Physical examination,			Yes
LMM	II	0.56	47.8	F	Face	16.6	No		Skin	Physical examination			No
SSM	III	1.04	42.5	F	Upper leg	31.2	No		Regional LNN	Sonography of LNN	7	1	No
SSM	II	0.68	36.1	M	Back	67.1	No		Regional LNN	Sonography of LNN	10	1	No
SSM	II	0.50	41.2	M	Lower leg	48.7	No		Regional LNN	Palpation of LNN	37	1	Yes
SSM	III	0.90	77.0	M	Back	50.0	No		Regional LNN	Palpation of LNN	26	2	No
SSM	III	1.07	39.5	F	Lower leg	30.6	No		Regional LNN	Palpation of LNN	16	1	Yes

SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma; LNN, lymph nodes.

[a] The follow-up time refers to the time interval between onset of recurrence and event (melanoma-related death) or the censoring event.

[b] This row indicates the type of examination at which the presence of metastases was suspected for the first time.

[2,6,13,17]. Although it has been stated, that regular follow-up of patients with thin melanomas is not worthwhile, our data do not support this view. Patients with recurrent disease, who had a follow-up examination within one year before relapse presented with less advanced disease and had a better survival than patients who did not have a recent follow-up examination [18]. As shown in Table 1, in almost all cases with favourable outcome, metastatic disease was confined to the skin or to the regional lymph nodes and the presumptive diagnosis of lymph node metastases was made during routine follow-up examination [19–21].

Patients without a follow-up examination within 1 year before the onset of recurrence mainly presented with bulky and clinically evident lymph node metastases or metastases of inner organs and had a worse prognosis. It is reasonable to argue that the difference in prognosis can be mainly attributed to the earlier diagnosis of asymptomatic metastatic disease in the context of a routine follow-up examination. This is in line with the observation by Poo-Hwu and colleagues [10], who found that patients with asymptomatic recurrences had a better prognosis than patients with symptomatic recurrences.

In contrast to physical examination and sonography of the regional lymph nodes, the value of chest X-ray and abdomen sonography for the follow-up of our patients with thin melanomas was questionable, which supports the observations made by Weiss and colleagues [16]. Complete blood counts and blood chemistry also had no impact on the diagnosis of recurrent disease in patients with thin melanomas.

We also showed that nearly half of the patients stopped their follow-up examinations during the first 5 years. The annual drop-out rate was constant during the first 5 years after diagnosis and was approximately 11% per year. Additionally, 50.2% of the patients who did not stop their follow-up examinations were not compliant with the follow-up regimen and extended their follow-up interval to more than 1 year.

Despite our finding that regular follow-up examinations are essential, the number of patients who were lost to follow-up or who were not compliant with the follow-up regimen is alarming. We did not identify factors to predict whether patients will be compliant with the follow-up regimen or not.

The limitations of our study are the retrospective design and the relatively small number of patients with recurrences. Moreover, in two patients, whose primary tumours were excised at another institution, misdiagnosis of the primary tumours was the reason that the patients did not have follow-up examinations until the manifestation of metastatic disease. In both cases, the correct diagnosis of melanoma was made retrospectively after metastatic disease had developed. It may be hypothesised, that patients who are unaware of the diagnosis of melanoma behave differently than patients who know about their diagnosis with regard to self-examinations and awareness of skin changes or swelling of the regional lymph nodes. Finally, we did not investigate the reasons for stopping follow-up, which should be a subject for future research.

References

1. Lipsker DM, Hedelin G, Heid E, Grosshans EM, Cribier BJ. Striking increase of thin melanomas contrasts with stable incidence of thick melanomas. *Arch Dermatol* 1999, **135**, 1451–1456.
2. Johnson RC, Fenn NJ, Horgan K, Mansel RE. Follow-up of patients with a thin melanoma. *Br J Surg* 1000, **86**, 619–621.
3. Woods JE, Soule EH, Creagan ET. Metastasis and death in patients with thin melanomas (less than 0.76 mm). *Ann Surg* 1983, **198**, 63–64.
4. Andersson AP, Dahlstrom KK, Drzewiecki KT. Prognosis of thin cutaneous head and neck melanoma (<1mm). *Eur J Surg Oncol* 1996, **22**, 55–57.
5. Karakousis CP, Emrich U, Rao U. Tumor thickness and prognosis in clinical stage I malignant melanoma. *Cancer* 1989, **64**, 1432–1436.
6. Mansson-Brahme E, Carstensen J, Erhardt K, Lagerlof B, Ringborg U, Rutqvist LE. Prognostic factors in thin cutaneous malignant melanoma. *Cancer* 1994, **73**, 2324–2332.
7. Brandt SE, Welvaart K, Hermans J. Is long-term follow-up justified after excision of a thin melanoma (less than or equal to 1.5 mm)? A retrospective analysis of 206 patients. *J Surg Oncol* 1990, **43**, 157–260.
8. Finley JW, Gibbs JF, Rodriguez LM, Letourneau R, Driscoll D, Kraybill W. Pathologic and clinical features influencing outcome of thin cutaneous melanoma: correlation with newly proposed staging system. *Am Surg* 2000, **66**, 527–531.
9. Jubelirer SJ. Surveillance testing in patients with primary malignant melanoma. *W V Med J* 1999, **95**, 80–81.
10. Poo-Hwu WJ, Ariyan S, Lamb L, *et al*. Follow-up recommendations for patients with American Joint Committee on Cancer Stages I–III malignant melanoma. *Cancer* 1999, **86**, 2252–2258.
11. Dicker TJ, Kavanagh GM, Herd RM, *et al*. A rational approach to melanoma follow-up in patients with primary cutaneous melanoma. Scottish Melanoma Group. *Br J Dermatol* 1999, **140**, 249–254.
12. Romero JB, Stefanato CM, Kopf AW, Bart RS. Follow-up recommendations for patients with stage I malignant melanoma. *J Dermatol Surg Oncol* 1994, **20**, 175–178.
13. Moloney DM, Gordon DJ, Briggs JC, Rigby HS. Recurrence of thin melanoma: how effective is follow-up? *Br J Plast Surg* 1996, **49**, 409–413.
14. Regan MW, Reid CD, Griffiths RW, Briggs JC. Malignant melanoma, evaluation of clinical follow up by questionnaire survey. *Br J Plast Surg* 1985, **38**, 1–14.
15. 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. *Hautarzt* 1994, **45**, 285–291.
16. 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**, 703–705.
17. Pontikes LA, Temple WJ, Cassar SL, *et al*. Influence of level and depth on recurrence rate in thin melanomas. *Am J Surg* 1993, **165**, 225–228.
18. 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**, 174–180.

19. Binder M, Kittler H, Steiner A, Dorffner R, Wolff K, Pehamberger H. Lymph node sonography versus palpation for detecting recurrent disease in patients with malignant melanoma. *Eur J Cancer* 1997, **33**, 1805–1808.
20. Uren RF, Howman-Giles R, Thompson JF, *et al*. High-resolution ultrasound to diagnose melanoma metastases in patients with clinically palpable lymph nodes. *Australas Radiol* 1999, **43**, 148–152.
21. Blum A, Schlagenhauff B, Stroebel W, Breuninger H, Rassner G, Garbe C. Ultrasound examination of regional lymph nodes significantly improves early detection of locoregional metastases during the follow-up of patients with cutaneous melanoma: results of a prospective study of 1288 patients. *Cancer* 2000, **88**, 2534–2539.