Metastatic Patterns, Clinical Outcome, and Malignant Phenotype in Malignant Cutaneous Melanoma

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The objective of this population-based study was to assess metastatic pathways and outcomes vs. selected clinical and histopathologic features of the primary tumor in patients with recurrent cutaneous malignant melanoma. At a median follow-up time of 11 years, 569/2493 patients with recurrence were identified. We demonstrated a 5-year survival rate of 82% and 30% among those with a primary local or regional recurrence, respectively. Patients with primary distant skin, distant lymph node, or pulmonary metastases had a significantly better survival compared with those with CNS, bone, visceral, liver, or multiple sites of first distant metastases. The metastatic pathways were similar with regard to histogenetic type, primary tumor thickness, Clark's level of invasion, and primary tumor ulceration. Different histogenetic types, as assessed by light microscopy, imply different risks of recurrence. However, once the recurrence is manifest, the metastatic pathways are uniform, as well as prognosis, and survival.

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Of the patients with cutaneous malignant melanoma, approximately 25–35% subsequently will get recurrent disease (1–6). Well-documented risk factors for developing a recurrence have been primary stage, primary tumor thickness, and ulceration of the primary tumor (3, 7, 8). The use of molecular biological techniques has resulted in a correlation between integrin expression, and other adhesion molecules, and the subsequent development of metastases (9, 10). Once a recurrence has been diagnosed, most studies have shown that features of the primary tumor are no longer useful in predicting survival. Many studies have shown that it is mainly the number of positive nodes that contributes significant prognostic information after lymph node recurrence (7, 11). Survival after distant recurrence has been shown to be dependent on metastatic site, the extent of metastases, and the possibility of eradicating gross disease (1, 2, 12–14). Vascularity (angiogenesis), and tumor markers such as S-100 protein, and c-myc oncoprotein have recently been shown to provide useful prognostic information (15–17). The impact of the disease-free interval on survival has also been debated, but contrasting opinions prevail (6, 7, 18, 19).

The objective of this population-based study was to assess metastatic pathways and outcomes vs. selected clinical and histopathologic features of the primary tumor among patients with recurrent cutaneous malignant melanoma.

MATERIAL AND METHODS

Patients

Since 1976 all new melanoma cases in the Stockholm–Gotland region (population 1.7 million) have been prospectively registered in a regional cancer registry. This registration comprises clinical and histopathologic parameters such as age at diagnosis, gender, site of the primary tumor, stage of disease, pigmentation, surgical treatment, histopathologic type, thickness according to Breslow, Clark's level of invasion, regression, ulceration, and mitotic index. All histopathologic slides are routinely reviewed by experienced pathologists. During 1976–1987 surgery of the primary lesion was made with an at least 1-cm margin for cutaneous melanoma ≤ 0.8 mm thick, unless the melanoma was located in a technically difficult area. Most of the thicker melanomas were surgically re-

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sected with a 2- or 5-cm margin, often including split-thickness skin grafting, because of an ongoing clinical trial. Elective lymph node dissection was not routinely performed. Physical examinations took place mainly in one institution. The routine work-up included history and physical examination, chest x-ray and liver function studies. Other diagnostic studies were performed only as indicated based on clinical symptoms. The initial clinical staging procedure was based on the original three-stage system (20, 21). Stage I was defined as primary tumor $\pm$ satellites within 5 cm of the primary tumor. Stage II encompassed regional lymph node metastases and/or in-transit metastases (i.e., cutaneous or subcutaneous metastases 5 cm from the primary tumor and in-transit to the regional lymph node basin). Stage III included disseminated disease beyond the regional lymph node basin. During follow-up a local recurrence was defined as a recurrence in the scar or transplant. In-transit recurrence comprised a subcutaneous or cutaneous metastasis between the scar and the regional lymph node station. Lymph nodes were classified as regional according to the American Joint Committee on Cancer staging of cancer. Locoregional recurrence and distant metastases were diagnosed using cytology, histopathology, or unequivocal diagnostic radiologic imaging. Clinical follow-up examinations were scheduled every 3 months during the first 5 years and once yearly thereafter up to 10 years from the primary diagnosis. Since 1989 physical examinations were scheduled only for a total of 5 years, except for patients with melanoma in situ and for those with primary tumors with thickness ≤ 0.8 mm, for whom clinical control for registration and information only was performed once and twice, respectively. Once a recurrence was diagnosed, or if the patient was primarily in stage II or III the follow-up schedule was intensified. Examining physicians report to the registry at every single check up. Local recurrence, in-transit metastases, regional lymph node metastases, disseminated disease, and death are reported to the registry and recorded prospectively.

During 1976–1987, 2516 consecutive patients with primary cutaneous malignant melanoma (382 melanoma in situ) were registered in this population-based regional cancer registry. Follow-up information was obtained through the clinical records and the regional cancer registry. All patients were also checked against the Swedish National Cancer Registry (founded in 1958) and the Swedish Cause of Death Registry. The closing date for follow-up was December 31, 1994. Less than 1% of the patients were lost to follow-up owing to emigration. Twenty-three patients were excluded because of a diagnosis of melanoma registered in the National Cancer Registry before the initiation of the regional melanoma registry, and thus not followed according to the guidelines described. At a median follow-up time of 11 years (range 7–18 years), a total of 569 patients (23%) with recurrence was identified among the remaining 2493 patients. There were significant differences in proportions between the melanoma population without recurrence, and the group with recurrence, respectively, at the $p < 0.001$ level in terms of age, gender, stage, primary tumor thickness, histogenetic type, Clark's level of invasion, and presence of tumor ulceration. There were no differences in terms of multiple primary melanomas or regression of the primary tumor. Stage II patients were more common among patients with recurrence (9% vs. 2%). Primary tumor thickness was median 2.7 mm (range 0.3–30) for the patients with recurrence vs. median 1.1 mm (range 0.1–30) for those without recurrence.

For the purpose of this study the clinical records of all the patients with disease recurrence were reviewed with regard to the following parameters, which are not routinely registered: the chronologic pattern of all metastases (the registry routinely only comprises the first event of each type of locoregional recurrence and the first two sites of distant metastases), and treatments after recurrence. Hierarchical analysis was performed in describing the metastatic pathways in Fig. 4. 'Hierarchical' means that the direction of recurrence is described in the order of local to in-transit recurrence to regional lymph node recurrence and finally to distant metastases. The pathway is described in a one-way manner; i.e., if one patient had a regional lymph node recurrence as first event, in-transit recurrence as second and third events, and distant recurrence as a fourth event, we would have neglected the in-transit recurrences in describing the metastatic pattern. Furthermore, if simultaneous recurrences to more than one location were diagnosed, these recurrences would be described according to the most advanced location. Treatment of disseminated melanoma varied over time, at the discretion of the responsible physician. Either local and/or systemic treatment was initiated for 35% of the patients at the time of the diagnosis of the first distant metastases.

Statistical methods

Differences in proportions were analyzed with the χ^2 homogeneity test. Putative prognostic factors for the risk of melanoma death among patients with recurrent melanoma were analyzed using Cox's proportional hazards regression model (22). Both uni- and multivariate models were used. Differences with a p-value < 0.05 (two-sided) were considered to be statistically significant. Among the 569 patients with disease recurrence, 7 patients were diagnosed at autopsy. The univariate analyses were restricted to those 531 patients (93%) who had only one primary melanoma. Cox's proportional hazards regression model was also used for uni- and multivariate analyses including those 410 patients with stage I primary melanoma for whom information was available on all selected parameters.

The survival distributions were estimated and plotted using actuarial methods constructed according to a life-

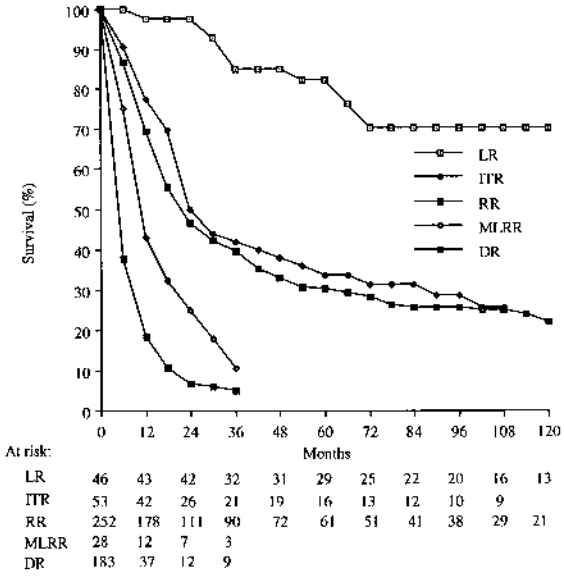

Fig. 1. Melanoma survival in 562 patients with recurrent malignant melanoma according to type of first recurrence; LR (local recurrence), ITR (in-transit recurrence), RR (regional lymph node recurrence), MLRR (multiple simultaneous locoregional recurrence), DR (distant recurrence). Time was calculated from diagnosis of recurrence, event was melanoma death. (Excluded are 7 patients with post-mortem diagnosis only.)

table technique in Figs. 1–3. Death caused by melanoma was the event of interest in calculating the melanoma survival for different subsets of patients. Deaths from unrelated causes were treated as censored observations.

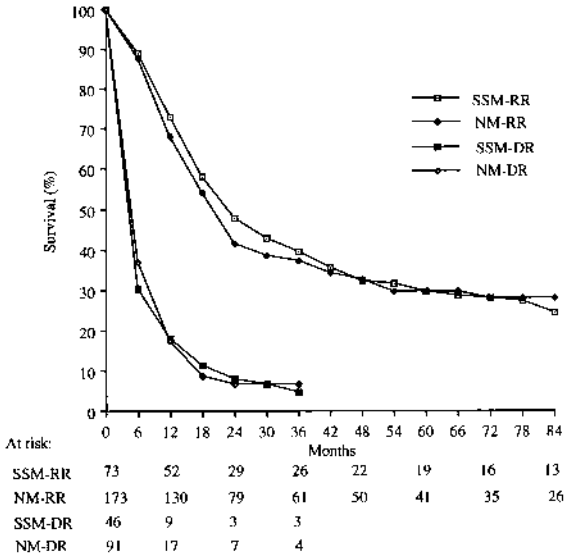

Fig. 2. Melanoma survival according to histogenetic type (SSM vs. NM) and type of first recurrence; RR (in-transit and regional lymph node recurrence) vs. DR (distant recurrence) in 383 patients with one primary melanoma. Time was calculated from diagnosis of recurrence, event was melanoma death. (Excluded are 7 patients with post-mortem diagnosis only.)

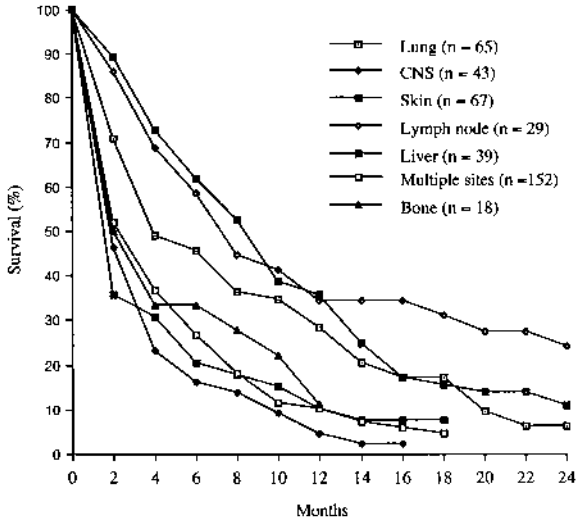

Fig. 3. Melanoma survival in all 413 patients with distant metastases at any time according to type of first distant metastases. Time was calculated from first distant metastases. (Excluded are 15 patients with post-mortem finding only.)

Time was calculated from diagnosis of first recurrence. In Fig. 3 time was calculated from diagnosis of the first distant metastases irrespective of any previous recurrence. Patients with first recurrence found at post-mortem were excluded ($n = 7$) and in Fig. 3, a total of 15 patients was excluded for the same reason. Distributional comparisons were made with the logrank test with a p-value < 0.05 considered to be statistically significant (23).

RESULTS

Survival and prognostic factors

Survival. Melanoma-specific survival for patients with recurrent melanoma was 25% at 5 years after the first recurrence and 18% by 10 years. However, when relating survival to type of first recurrence, we demonstrated a 5-year survival rate of 82% among those with a primary local recurrence, compared with about 30% surviving 5 years after a primary regional in-transit, or lymph node recurrence. When the first recurrence was to a distant site, or simultaneous multiple locoregional recurrences, only a few patients survived for more than 3 years (Fig. 1).

The melanoma survival was identical among patients with NM vs. SSM tumors, in relation to first recurrence being a regional or a distant recurrence (Fig. 2).

Patients with distant skin, distant lymph node, or pulmonary metastases had a significantly better survival outcome ($p < 0.0001$) compared with those with CNS, bone, visceral, liver or multiple sites of first distant metastases (Fig. 3).

Prognostic factors. When the clinical features and histopathologic parameters of the primary tumor were tested individually by a Cox's univariate analysis, gender, initial

Table 1

Cox's univariate analysis of prognostic factors for mortality attributable to melanoma in 531 patients with one primary invasive cutaneous melanoma and recurrence

Parameter	Patients/Events	Unadjusted rate ratio (95% C.I.)	p-value
Age (years)			
<50	148/113	1.0	
≥50	383/296	1.2 (1.0–1.5)	0.0902
Gender			
Male	300/250	1.0	
Female	231/159	0.7 (0.6–0.9)	0.0004
Stage			
Stage I	477/359	1.0	
Stages II and III	54/50	2.2 (1.6–3.0)	<0.0001
Site			
Trunk	258/214	1.0	
Extremities, head and neck	273/195	0.7 (0.6–0.8)	0.0002
Histogenetic type #			
SSM, UM, LMM, ALM	382/294	1.0	
NM	137/109	1.1 (0.9–1.3)	0.5818
MIS	12/6		
Tumor thickness (mm)			
<2.0	174/123	1.0	
≥2.0	325/264	1.3 (1.0–1.5)	0.0226
Unavailable	32/22		
Clark's level of invasion			
Level I	12/6		
Levels II and III	226/165	1.0	
Levels IV and V	261/211	1.2 (1.0–1.5)	0.0468
Unavailable	32/27		
Ulceration			
Present	253/206	1.0	
Absent	218/153	0.7 (0.5–0.8)	0.0003
Unavailable	60/50		
Disease-free interval (years)			
<5	467/367	1.0	
≥5	64/42	0.8 (0.6–1.1)	0.1789
Type of first event			
Locoregional recurrence	357/241	1.0	
Distant metastases	174/168	4.4 (3.6–5.4)	<0.0001

SSM: superficial spreading melanoma; NM: nodular melanoma; LMM: lentigo maligna melanoma; ALM: acral lentiginous melanoma; UM: unclassifiable melanoma MIS: melanoma in situ.

clinical stage, primary tumor site, presence of ulceration in the primary tumor, and type of first recurrence, all yielded significant prognostic information after recurrence with regard to melanoma survival (Table 1). Having had a distant vs. a locoregional recurrence as first event was the clinical feature having the most adverse effect on melanoma survival. Furthermore, being primarily in clinical stages II and III, having primary trunk location, presence of ulceration in the primary tumor, and male gender were all statistically significant prognosticators, indicating poor survival, whereas histogenetic type, age at recurrence, disease-free interval, primary tumor thickness, and Clark's level of invasion did not contribute any statistically significant prognostic information after recurrence with regard to melanoma survival. Table 2 shows the Cox's uni- and multivariate analyses of putative prognostic factors for melanoma death after diagnosis of first recurrence among 410 patients with an originally stage I primary malignant melanoma. In the multivariate analysis, age at recurrence, site of primary tumor, presence of ulceration in the primary tumor, disease-free interval, and type of recurrence remained independently significant. Disease-free interval, tumor thickness and histogenetic type were included in the multivariate analysis despite not being significant in the univariate analysis, because the objective of this study was to assess potential differences in metastatic behavior with regard to such factors.

Table 2

Cox's uni- and multivariate analysis of prognostic factors related to melanoma death in 410 patients with one primary melanoma stage I and recurrence

Parameter	Patients/Events	Univariate analysis	p-value	Multivariate analysis	p-value
		Hazard rate ratio (95% confidence interval)		Hazard rate ratio (95% confidence interval)	
Age (years)					
<50	112/80	1.0		1.0	
≥50	298/230	1.4 (1.1–1.8)	0.02	1.4 (1.1–1.8)	0.02
Gender					
Male	228/187	1.0		1.0	
Female	182/123	0.7 (0.6–0.9)	<0.01	1.0 (0.7–1.2)	0.70
Site					
Trunk	196/159	1.0		1.0	
Extremities, head and neck	214/151	0.7 (0.6–0.9)	<0.01	0.7 (0.6–0.9)	<0.01
Histogenetic type					
NM	107/81	1.0		1.0	
SSM, UM, LMM, ALM	303/229	1.1 (0.8–1.4)	0.55	1.2 (0.9–1.6)	0.15
Tumor thickness (mm)					
<2.0	158/111	1.0		1.0	
≥2.0	252/199	1.2 (0.9–1.5)	0.20	1.1 (0.9–1.4)	0.40
Ulceration					
Present	223/179	1.0		1.0	
Absent	187/131	0.7 (0.6–0.9)	<0.01	0.7 (0.6–0.9)	<0.01
Disease-free interval (years)					
<5	357/277	1.0		1.0	
≥5	53/33	0.8 (0.5–1.1)	0.16	0.5 (0.4–0.8)	<0.01
Type of first event					
Locoregional recurrence	293/198	1.0		1.0	
Distant metastases	117/112	4.4 (3.4–5.6)	<0.01	5.1 (4.0–6.6)	<0.01

Metastatic pathways vs. selected histopathologic features

In Fig. 4, the hierarchical metastatic pathways for the three largest groups of different histogenetic types of melanoma are depicted, and also the respective disease-free intervals for the first recurrences in each group. We observed that 48% of the patients with a primary nodular melanoma developed recurrent disease, 36% of those with unclassifiable melanoma, and 20% of the patients with SSM melanoma developed recurrent disease. The proportional distribution of first event (metastatic pathways) did not differ between patients with primary tumor of SSM, nodular, or unclassifiable type although there were numerical differences, nor did the mortality for those with recurrent disease differ significantly in relation to these histogenetic types of primary tumor. However, the median disease-free intervals were shorter in patients with primary nodular melanoma and local or distant recurrence, in comparison to patients with SSM, or unclassifiable melanomas.

The distribution of first recurrences in relation to stage is demonstrated in Table 3. In stage I patients, most of the first recurrences were to the regional lymph nodes. In stage II, however, the main types of first recurrence were distant metastases.

The distribution of metastases in relation to primary tumor thickness is shown in Table 4. Regardless of primary tumor thickness, the major first recurrence site was to the regional lymph nodes, except for the group of patients whose primary tumor thickness was unknown. There was no statistically significant difference in distribution of type of first event in relation to Clark's level of invasion (II and III vs. IV and V) in the primary tumor. (Data not shown.)

A mapping of primary tumor site in relation to type of first recurrence (Table 5) revealed a somewhat different pattern for patients with head and neck primaries, with a higher frequency of distant metastases as first recurrence, as opposed to regional lymph node metastases for trunk, and extremity melanoma ($p < 0.001$). Local recurrences were also more common among patients with head and neck melanoma. In-transit metastases as a first recurrence were most commonly found among patients with lower extremity melanoma.

Distant metastases were found in 428/569 patients with recurrent melanoma. There were no differences in distribu-

tion of distant metastatic sites whether the distant metastases was the first event, or if preceded by locoregional recurrences (Table 6). Nor could any relation to Clark's level of invasion, or ulceration of the primary tumor be found. (Data not shown.)

DISCUSSION

The aim of our study was to distinguish phenotypic features in patients with recurrent disease, and to assess the clinical outcomes after first recurrence. By exploring the pathways of recurrence and relating to different explanatory factors, we also sought to assess putative differences in the biologic properties of the primary tumor. It is clear that the metastatic potential can be correlated to well-known and reproducible parameters of the primary tumor (tumor thickness, presence of ulceration) and to some clinical parameters (clinical stage, gender) (13). When a recurrence has become manifest, is the clinical behavior dependent on these factors?

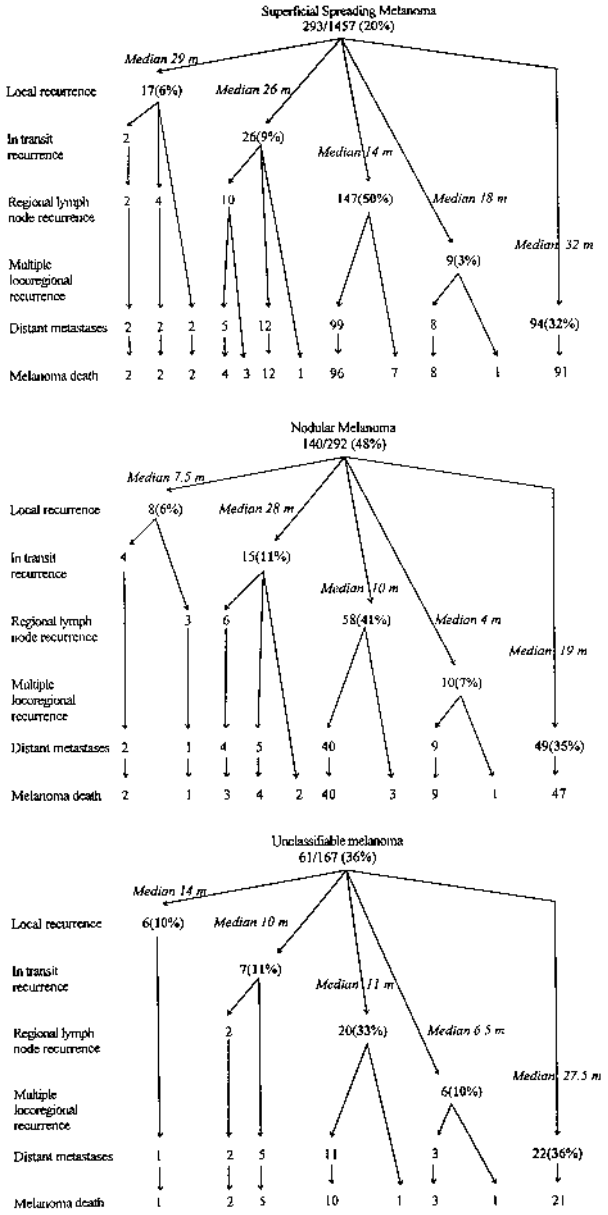

Fig. 4. Pathways of recurrence in patients with primary SSM, NM, or unclassifiable melanoma, and recurrent disease. For each pathway of first event the median disease-free interval in months is noted, and the number of patients (percent of all patients with recurrence within respective histogenetic group in parentheses).

Our results regarding the different clinical and histopathologic features of the source population and those with subsequent recurrence are in accordance with findings in the majority of other studies performed (24).

The most prominent prognosticator after recurrence was type of first recurrence, as is demonstrated in Fig. 1. Type of first recurrence as the strongest predictor of survival has also been shown by other authors (1, 4, 19, 25–27). The prognosis for patients with a local recurrence, within our strict definition, was relatively good in comparison to those with in-transit or regional node recurrence, which most likely reflects the fact that the definition of local recurrence in this study mainly refers to true local recurrences, also discussed in a review article by Buzzell & Zitelli (28) and shown in a former article by the authors (29).

We could show some survival advantage depending on the location of the first distant metastases, but few patients survive for more than 2 years after distant recurrence (Fig. 3). The observed difference in median survival for patients with skin, distant lymph nodes, or lung metastases in comparison to those with bone, liver, viscera or CNS metastases, was only 6 months. These dismal survival rates after distant recurrence have been described by several authors (7, 19, 30, 31) with median survival times rarely exceeding 12 months.

We noted that the length of the disease-free interval was related to several factors, and in our study a disease-free interval ≥ 5 years reached statistical significance in the multivariate analyses, although it appeared to be of less significance in the univariate analysis. A longer disease-free interval may well reflect a slower growing and less aggressive disease. There are different opinions regarding the impact of the disease-free interval (6, 7, 18, 19), but owing to variations in the definition of the disease-free interval, comparisons of these findings are difficult. Karakousis et al. (19) defined six different disease-free intervals and evaluated the median survival after recurrence according to stage. Considering all their patients no significant difference in survival after first recurrence was found, but for patients with lymph node metastases they found that the disease-free interval contributes statistically significant information with regard to survival. Crowley & Seigler (6) defined five different disease-free intervals and concluded that for the majority of the patients, survival after recurrence was independent of the disease-free interval.

Table 3

Distribution of first recurrence among 537 patients with one primary malignant melanoma according to stage at primary diagnosis

Type of first event	Stage I 482 (%)	Stage II 46 (%)	Stage III 9 (%)	Total no. of patients 537 (%)
Local recurrence	40 (8)	2 (4)	0	42 (8)
In-transit recurrence	42 (9)	7 (15)	0	49 (9)
Regional lymph node recurrence	230 (48)	9 (20)	0	239 (45)
Multiple locoregional recurrence	24 (5)	3 (7)	0	27 (5)
Distant metastases	146 (30)	25 (54)	9 (100)	180 (34)

The rise in incidence of melanoma is mainly attributable to an increase in the proportion of melanomas of SSM type, where most likely UV induction is the predominant etiologic factor, whereas the proportion of patients with nodular melanomas has remained fairly constant (database of the Stockholm–Gotland region 1976–1997). This gives rise to the question of whether these histogenetically different tumors with possible different etiologies also behave differently after first recurrence.

When investigating the metastatic pathways, we found the proportions of type of first recurrences in relation to histogenetic type to be similar, although we noted some differences with regard to the disease-free interval. Patients with nodular primary tumors had their first local and distant recurrences sooner than those with SSM primaries (Fig. 4), but survival after recurrence was not related to histogenetic type despite the seemingly biologic aggressive behavior of nodular melanomas. We could not demonstrate any prognostic significance of histogenetic type, either in the uni- or multivariate analysis. This partly concurs with large studies which have shown that histogenetic type contribute prognostic information for localized melanoma in univariate analyses, but not in multivariate analyses when tumor thickness was included in the model (13, 32).

Table 4

Type of first event in relation to primary tumor thickness in 505 patients with cutaneous malignant melanoma

First event	≤0.8 mm No. (%)	0.9–2.0 mm No. (%)	>2.0 mm No. (%)
Local recurrence, n = 36	7 (14)	8 (6)	21 (7)
In-transit recurrence, n = 48	2 (4)	9 (7)	37 (12)
Regional lymph node recurrence, n = 230	22 (44)	67 (49)	141 (44)
Multiple locoregional recurrence, n = 22	0	3 (2)	19 (6)
Distant recurrence, n = 169	19 (38)	50 (36)	100 (31)
Total, n = 505	50 (100)	137 (100)	318 (100)

In the Cox's multivariate analysis, several features contributed with independent prognostic information after first recurrence, but tumor thickness, being an important and unquestioned predictive factor in malignant melanoma, did not reach statistical significance in relation to survival after recurrence. This accords with the findings of Fusi et al. (1) and Markowitz et al. (2). The proportions of type of first recurrences were also unrelated to the thickness of the primary tumor, which is in contrast to Milton et al. (4) who concluded that site of first recurrence was related to tumor thickness: thick lesions gave rise to a higher proportion of recurrences in the vicinity of the scar, while thin lesions gave rise to regional or distant recurrences.

The multivariate analyses showed that both primary tumor ulceration and primary tumor site yielded independently significant prognostic information in recurrent disease. These parameters are also prognostic factors in stage I disease. The UV induction may have diverse mutagenic effects on different body sites. Surprisingly, we found age to be an independently prognostic factor in recurrent disease. Host factors might possibly be responsible for this finding. However, in stage I disease age is not a prognostic factor.

The different types of recurrence included in the analyses of metastatic pathways are probably correlated events. This implies that they may be regarded as competing risks. Apparent distributional differences in regard to type of first event may be related to problems of competing risks. Our analyses did not take such problems into account since the metastatic pathways for different subgroups appeared quite uniform. However, the observation that patients with head–neck melanomas had an increased frequency of distant metastases as first event may have been spurious since many of them were not at risk of developing a regional recurrence because about 30% had undergone a prophylactic neck dissection.

We suggest that once the multistep metastatic cascade is completed, the clinical behavior of the disease is quite uniform irrespective of the studied histopathologic and clinical factors associated with the development of recurrent disease. Nevertheless, clinical data such as these are the basis for future studies correlating the molecular biol-

Table 5

Type of first event in relation to site of primary tumor in 537 patients with recurrent malignant melanoma

First event	Trunk	Lower extremity	Head and neck	Upper extremity
Local recurrence, n = 42	9 (3)	13 (9)	15 (21)	5 (8)
In-transit recurrence, n = 49	21 (8)	21 (15)	5 (7)	2 (3)
Regional lymph node recurrence, n = 239	130 (50)	65 (46)	18 (26)	26 (39)
Multiple locoregional recurrence, n = 27	6 (2)	9 (6)	4 (6)	8 (12)
Distant metastases, n = 180	94 (36)	33 (23)	28 (40)	25 (38)
Total, n = 537	260 (100)	141 (100)	70 (100)	66 (100)

Table 6

Site of first distant metastasis in relation to type of first recurrence in 428 patients with cutaneous malignant melanoma and distant metastases at any time during the disease

First distant site	Locoregional recurrence first event n = 238 (%)	Distant metastasis first event n = 190 (%)	Total n = 428 (%)
Skin	43 (18)	24 (13)	67 (16)
Lung	30 (13)	35 (18)	65 (15)
CNS	19 (8)	24 (13)	43 (10)
Visceral	23 (10)	16 (8)	39 (9)
Lymph nodes	20 (8)	9 (5)	29 (7)
Bone	10 (4)	8 (4)	18 (4)
Multiple sites	85 (36)	67 (35)	152 (36)
Post-mortem finding	8 (3)	7 (4)	15 (4)

χ^2 test: ns (413 patients, post-mortem findings excluded).

ogy of recurrent cutaneous malignant melanoma and patient outcome.

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