

Serum markers lactate dehydrogenase and S100B predict independently disease outcome in melanoma patients with distant metastasis

B Weide^{*,1,4}, M Elsässer^{1,4}, P Büttner², A Pflugfelder¹, U Leiter¹, TK Eigentler¹, J Bauer¹, M Witte³, F Meier¹ and C Garbe^{1,2}

¹Department of Dermatology, Center for Dermatocology, University Medical Center, Liebermeisterstrasse 25, Tübingen 72076, Germany; ²Skin Cancer Research Group, School of Public Health, Tropical Medicine and Rehabilitation Sciences, James Cook University, Townsville, Queensland 4811, Australia; ³Department of General and Transplant Surgery, University Medical Center, Hoppe-Seyler-Street 3, Tübingen 72076, Germany

BACKGROUND: Established prognostic factors are of limited value to predict long-term survival and benefit from metastasectomy in advanced melanoma. This study aimed to identify prognostic factors in patients with distant metastasis.

METHODS: We analysed overall survival of 855 institutional melanoma patients with distant metastasis by bivariate Kaplan–Meier survival probabilities and multivariate Cox hazard regression analysis.

RESULTS: Serum lactate dehydrogenases (LDH), S100B, the interval between initial diagnosis and occurrence of distant metastasis, the site of distant metastases, and the number of involved distant sites were significant independent prognostic factors in both bivariate and multivariate analyses. Visceral metastases other than lung (hazard ratio (HR) 1.8), elevated S100B (HR 1.7) and elevated LDH (HR 1.6) had the highest negative impact on survival. Complete metastasectomy was likewise an independent prognostic factor in multivariate analysis. This treatment was associated with favourable survival for patients with normal LDH and S100B values (5-year survival, 37.2%).

CONCLUSION: The serum markers LDH and S100B were both found to be prognostic factors in melanoma patients with distant metastasis. Furthermore, complete metastasectomy had an independent favourable prognostic impact in particular for the patient subgroup with normal LDH and S100B values.

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The prognosis of melanoma patients with distant metastasis is poor with a median survival of 9 months (Neuman *et al*, 2008). The American Joint Committee on Cancer (AJCC) 2009 staging system includes the site of involved organs and serum lactate dehydrogenase (LDH) to classify stage IV into the M categories: M1a (soft tissue metastasis), M1b (pulmonary involvement), and M1c (involvement of other visceral organs or elevated LDH) (Balch *et al*, 2009). Lactate dehydrogenase has been part of the AJCC staging system since the sixth edition released in 2001 (Balch *et al*, 2001), as it had been identified as an independent prognostic factor before start of systemic treatment for unresectable disease by different research groups (Sirott *et al*, 1993; Eton *et al*, 1998; Manola *et al*, 2000). Nevertheless, differences in survival according to M categories are small and current factors do neither allow the identification of patients with the worst prognosis nor those with the chance for long-term survival.

In addition to LDH, S100B is another prognostic serum factor for melanoma patients (Deichmann *et al*, 1999; Hauschild *et al*,

1999; Mohammed *et al*, 2001; Schmidt *et al*, 2005; Smit *et al*, 2005; Egberts *et al*, 2008; Tarhini *et al*, 2009). However, the role of S100B in interaction with LDH has not yet been well defined in patients with distant metastasis. All studies which addressed this question involving multivariate Cox regression analysis were performed in small patient cohorts ranging from 64 to 145 patients (Deichmann *et al*, 1999; Hauschild *et al*, 1999; Mohammed *et al*, 2001; Schmidt *et al*, 2005; Smit *et al*, 2005; Egberts *et al*, 2008). In all six studies, both serum markers were found to predict the patients' prognosis significantly in bivariate analyses. However, during multivariate analyses, only either LDH or S100B remained a significant prognostic factor; interestingly, three times LDH and three times S100B. It seems possible that the findings of a significant impact for only one serum marker per study depended on the relatively small sample sizes. Therefore, an investigation of this question in a large collective of stage IV patients is required.

Several research groups have reported favourable survival for patients after complete metastasectomy of distant metastases (Ollila *et al*, 1996; Leo *et al*, 2000; Meyer *et al*, 2000; Wood *et al*, 2001; Essner *et al*, 2004; Neuman *et al*, 2007; Wasif *et al*, 2011) with 5-year survival rates up to 41% (Ollila *et al*, 1996). Nevertheless, the impact of this procedure is still unclear, because a randomised trial has never been published and the majority of analyses comprised selected subgroups only. The decision, whether a patient is selected for complete metastasectomy, is apart from

*Correspondence: Dr B Weide;

E-mail: benjamin.weide@med.uni-tuebingen.de

⁴These authors contributed equally to this work.

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technical feasibility, influenced by prognostic factors, the age of the patient, and co-morbidities. This leads to a selection bias of prognostically favourable patients for surgery (Ollila, 2006).

The present study investigated prognostic factors in a cohort of 855 melanoma patients with distant metastases and thorough follow-up. The main aim was to clarify the prognostic impact of the serum markers LDH and S100B, adjusting for all potential and established prognostic factors like the number of distant sites and the organ involvement. Furthermore, the impact of complete metastasectomy and its interaction with the other significant prognostic factors has been examined.

PATIENTS AND METHODS

Patients

Patients with distant metastasis treated between 1996 and 2010, at the University Department of Dermatology in Tübingen, Germany, were identified in the Central Malignant Melanoma Registry (CMMR) database, which prospectively records patients from more than 60 dermatological centres in Germany. Of 1140 stage IV patients with follow-up, those with unknown primary melanoma at the time of initial diagnosis ($n=204$), ocular ($n=45$), or mucosal localisation ($n=36$) were excluded, resulting in a final sample size of 855 after individual file review. All patients had given their written informed consent to have their data recorded by the CMMR. The aims and methods of data collection by the CMMR have previously been reported in detail (Lasithiotakis *et al*, 2007). Staging algorithms according to national surveillance guidelines were used (Garbe *et al*, 2007). These algorithms consider the individual risk of relapse for each patient based on prognostic factors considered in the AJCC classification. Stage II patients are followed-up via clinical inspections, lymph node ultrasound, and the evaluation of S100B. Stage III patients are additionally staged once a year by whole body by computerised tomography scan.

Data obtained for each patient included gender, age at stage IV diagnosis (<60 vs ≥ 60 years), stage at initial diagnosis (I/II vs III vs IV), the time interval between initial diagnosis and stage IV diagnosis (<36 vs ≥ 36 months), the date of the last follow-up, and the date and cause of death, if applicable. The following characteristics of the primary tumour were analysed: anatomical localisation (axial vs extremities), Breslow's tumour thickness (≤ 2 vs >2 mm), Clark's level of invasion (I–III vs IV vs V), ulceration, histopathological signs of regression, and subtype (superficial spreading melanoma vs nodular melanoma vs lentigo maligna melanoma vs acral lentiginous melanoma). At the time of stage IV diagnosis, the following variables were evaluated: site of visceral involvement (soft tissue metastasis vs pulmonary involvement vs other visceral sites), the number of involved distant sites (distant soft tissue, lung, CNS, liver, intestine, bone, other visceral sites), serum LDH (normal vs $>$ upper limit of normal (ULN)), and S100B (normal vs $>$ ULN). S100B was detected using the Sangtec S100 ELISA (Diasorin Inc., Stillwater, OK, USA; ULN = $0.15 \mu\text{g l}^{-1}$) until December 2003 and thereafter by the Elecsys S100 electrochemiluminescence immunoassay (Roche Diagnostics AG, Rotkreuz, Switzerland, ULN = $0.10 \mu\text{g l}^{-1}$) according to the instructions of the manufacturers.

The first treatment after diagnosis of stage IV melanoma was categorised as either complete metastasectomy vs all other treatment modalities, for example, systemic treatment, irradiation, or best supportive care. In our analysis, complete metastasectomy was defined as a surgical procedure following the intention of complete resection (even if the surgical outcome finally was an incomplete resection) of all clinically or radiographic suspect lesions. In case of brain metastases, stereotactic irradiation was classified as a surgical excision. At our institution, a patient is selected for surgical treatment if there is a high probability of

complete resection of all detectable tumour manifestations according to national guidelines (Garbe *et al*, 2008). The decision is usually made after tumour board discussion accounting for the number of involved distant sites (ideally <3 for metastasectomy), technical feasibility, and treatment-related risks.

Statistical analysis

The closest clinically relevant cutoff was used for categorisation of characteristics instead of the median value for age (cutoff at 60 instead of median 62 years), Breslow's tumour thickness of the primary melanoma (2.0 instead of median 2.5 mm), and time interval (3 years instead of 2.5 years). The categorisation of the body site of the primary melanoma was performed as described before by studies based on the AJCC database (Soong *et al*, 2010). As only 3 of the 24 patients had primary melanomas with Clark levels I or II, these were analysed as one group together with those with Clark level III. Categorical variables were dummy coded to adhere to the linearity assumption of multivariable regression analysis. Follow-up time was defined from the date of diagnosis of stage IV disease to the date of last follow-up or death. Estimates of cumulative survival probabilities according to Kaplan–Meier were described together with 95% confidence intervals and compared using two-sided log-rank test statistics. Median survival times (MST) are presented. For the analysis of overall survival, patients who were alive at the last follow-up were censored, although patients who had died were considered an 'event'.

Multivariable Cox proportional hazard models were used to determine independent prognostic factors. All characteristics described above were considered in multivariable analysis. Missing values were assessed independently as a separate group for each variable except for LDH and S100B. Patients with missing LDH or S100B were excluded from multivariable testing. Forward and backward stepwise procedures of the multivariable modelling process were conducted. Results of the Cox models were described by means of hazard ratios (HRs) together with 95% confidence intervals; P -values were based on the Wald test.

Confounding was assessed by checking the effect of each remaining non-significant variable, which was not in a model, on factors in the model. If changes in the estimate of factors in the model of 5% or more occurred, the variable was considered a confounder. Throughout the analysis, P -values less than 0.05 were considered as statistically significant. All statistical analyses were carried out using the SPSS Version 19 (IBM SPSS, Chicago, IL, USA).

RESULTS

Description of sample

Patients' characteristics are shown in Table 1. A total of 855 patients (56.4% male) with primary cutaneous melanoma were included in the survival analysis at the time of stage IV diagnosis. The median age was 62 years (inter quartile range (IQR) 50–71 years). The median follow-up for patients who died was 9 months (IQR: 5–16) and 25 months (IQR: 10.5–64.5) for patients who were alive at the last date of observation. The MST according to Kaplan–Meier was 11 months. Cumulative survival rates were 46.5 (1 year), 22.9 (2 years), 10.3 (5 years), and 7.9% (10 years). Based on the site of distant metastases, the majority of patients (54.9%) was aligned to the M1c category (M1a = 18.5%; M1b = 26.7%). An elevated serum S100B or LDH was observed in 55% or 28% of patients, respectively. Metastasectomy, as a first treatment for distant metastases, was performed in 220 patients. In 77% of patients with metastasectomy, distant metastasis occurred at only one distant site; 16% of patients had two and 7% more than two involved sites. Soft tissue metastases, pulmonary lesions, and brain metastases were removed in 49%, 31%, and 24%, respectively. Metastasectomy of liver lesions was performed in 4% and in intestinal metastasis in 6%.

Table 1 Descriptive statistics and 2-year survival rates according to Kaplan–Meier for 855 melanoma patients with distant metastasis

Prognostic factor	n	%	% Dead	2-year survival rate (95% CI) (%)	P ^a
<i>Age at time of stage IV diagnosis</i>					
< 60 years	375	43.9	84.8	23.0 (18.5; 27.5)	0.905
≥ 60 years	480	56.1	83.3	22.9 (19.0; 26.8)	
<i>Sex</i>					
Male	482	56.4	84.2	21.4 (17.5; 25.3)	0.118
Female	373	43.6	83.6	24.8 (20.3; 29.3)	
<i>Body site of primary</i>					
Axial	513	60	84.6	19.6 (16.1; 23.1)	0.005
Extremities	342	40	83	27.8 (22.9; 32.7)	
<i>Breslow's thickness of primary</i>					
≤ 2 mm	348	40.7	82.8	22.2 (17.7; 26.7)	0.921
> 2 mm	464	54.3	85.1	23.1 (19.2; 27.0)	
Missing	43	5	84	26.4 (13.1; 39.7)	
<i>Histologic subtype of primary</i>					
SSM	370	43.3	82.4	23.3 (18.8; 27.8)	0.522
Nodular	243	28.4	84.8	23.8 (18.3; 29.3)	
LMM	38	4.4	86.8	17.8 (5.1; 30.5)	
ALM	88	10.3	87.5	27.0 (17.4; 36.6)	
Missing	116	13.6	83.6	18.4 (11.0; 25.8)	
<i>Clark's level of invasion</i>					
Level I–III	149	17.4	83.9	21.3 (14.4; 28.2)	0.978
Level IV	436	51.0	83.9	22.6 (18.5; 26.7)	
Level V	83	9.7	85.5	23.7 (14.5; 32.9)	
Missing	187	21.9	83.4	24.5 (18.0; 31.0)	
<i>Ulceration of primary</i>					
Yes	317	37.1	81.7	21.7 (16.8; 26.6)	0.644
No	408	47.7	85.8	25.3 (21.0; 29.6)	
Missing	130	15.2	83.8	17.8 (10.7; 24.9)	
<i>Regression of primary</i>					
Yes	56	6.5	87.5	12.6 (3.6; 21.6)	0.103
No	567	66.3	84.7	25.3 (21.6; 29.0)	
Missing	232	27.1	81.5	19.5 (14.0; 25.0)	
<i>Stage at primary diagnosis</i>					
Stage I/II	577	67.5	83.5	23.7 (20.2; 27.2)	0.438
Stage III	232	27.1	84.9	22.4 (16.7; 28.1)	
Stage IV	46	5.4	84.8	16.9 (5.5; 28.3)	
<i>Time interval between initial diagnosis and stage IV</i>					
≤ 36 months	491	57.4	86.8	18.9 (15.4; 22.4)	0.001
> 36 months	364	42.6	80.2	28.4 (23.5; 33.3)	
<i>Site of distant metastasis</i>					
Soft tissue only	158	18.5	73.4	43.3 (35.3; 51.3)	< 0.001
Lung	228	26.7	82	28.4 (22.3; 34.5)	
Other visceral	469	54.9	88.5	13.3 (10.2; 16.4)	
<i>Number of involved distant sites</i>					
1	448	52.4	77.9	32.8 (28.3; 37.3)	< 0.001
2	200	23.4	89	16.6 (11.3; 21.9)	
≥ 3	207	24.2	92.3	7.9 (4.2; 11.6)	
<i>LDH</i>					
Normal	502	58.7	79.3	27.1 (23.0; 31.2)	< 0.001
Elevated	228	26.7	93.9	8.4 (4.7; 12.1)	
Missing	125	14.6	84.8	32.6 (24.2; 41.0)	
<i>S100B</i>					
Normal	269	31.5	74.7	36.8 (30.7; 42.9)	< 0.001
Elevated	339	39.6	88.8	10.4 (6.9; 13.9)	
Missing	247	28.9	87.4	24.8 (19.3; 30.3)	
<i>First treatment in stage IV</i>					
Metastectomy	220	25.7	67.3	39.8 (32.9; 46.7)	< 0.001
Other treatment	635	74.3	89.8	17.3 (14.2; 20.4)	

Abbreviations: 95% CI = 95% confidence interval; LDH = lactate dehydrogenase.
^aTwo-sided log-rank excluding missing values.

Survival analysis according to Kaplan–Meier

Both factors included in the AJCC staging system (site of distant metastases and LDH) were correlated with survival. If distant lesions were limited to soft tissue, MST was 20 months, although it was shorter for patients with pulmonary involvement (14 months, $P=0.002$ in log-rank test) or other visceral lesions (7 months; $P<0.001$; Figure 1A). Serum S100B had a strong impact on

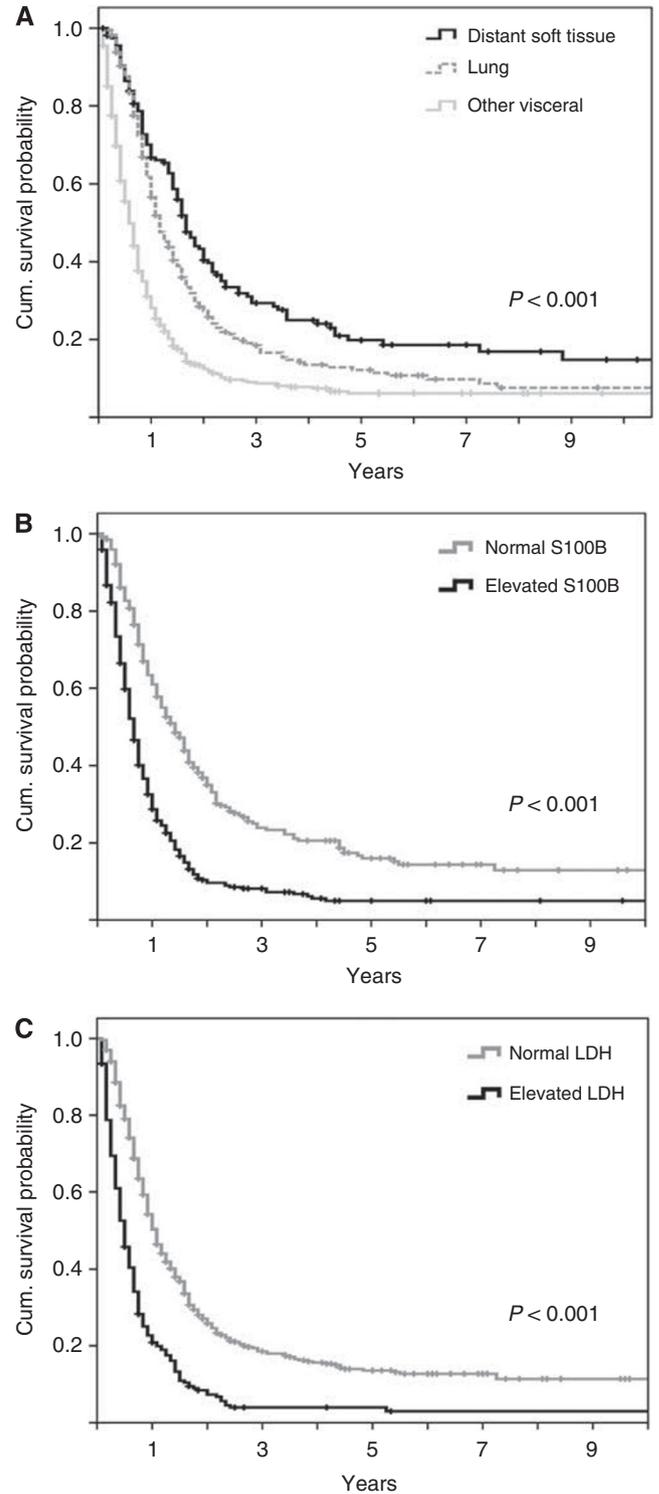


Figure 1 Bivariate analysis of 885 patients. Kaplan–Meier survival curves according to (A) the site of metastasis, (B) serum S100B, and (C) serum LDH. Censored events are indicated by vertical lines.

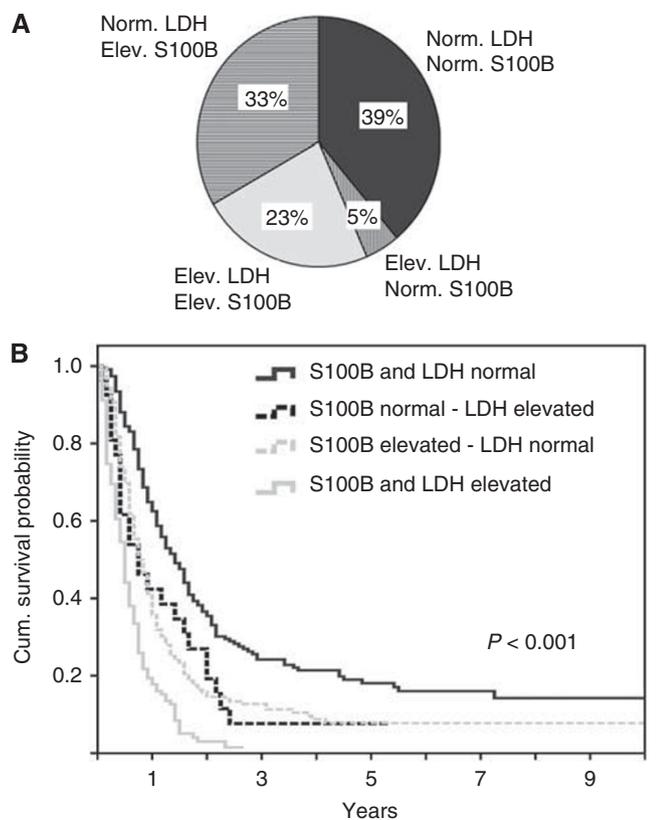


Figure 2 Combined analysis of LDH and S100B in 586 patients. **(A)** Proportions of subgroups with different pattern of LDH and S100B values. Elev. = elevated; Norm. = normal. **(B)** Kaplan-Meier survival curves for patients according to different combinations of S100B and LDH.

survival ($P < 0.001$; Figure 1B). Patients with normal LDH had a MST of 13 months, and those with elevated LDH had a MST of 6 months ($P < 0.001$; Figure 1C). The degree of elevation of both serum markers was also prognostically relevant (Supplementary Figure 1). A higher than two-fold elevation of S100B or LDH was associated with a remarkably worse prognosis compared with an elevation lower than two-fold (MST 3 vs 7 months for LDH and 7 vs 10 months for S100B, both $P < 0.001$). A longer survival since stage IV diagnosis was observed, if the site of the primary melanoma was located on the extremities compared with axial lesions ($P = 0.005$), if the interval between initial diagnosis and stage IV diagnosis was > 36 months ($P = 0.001$) and if only few distant sites were involved ($P < 0.001$). Patients who underwent complete metastasectomy of their initial distant metastases had a significantly longer MST compared with patients receiving other treatments (17 vs 9 months; $P < 0.001$). No differences in prognosis were evident for age, gender, stage at initial diagnosis, or histopathological characteristics of the primary melanoma (Table 1). Patients with combined elevation of S100B and LDH had an unfavourable prognosis. The 2-year survival rate was 3.1% in contrast to patients with normal values in one or both serum analyses (Figure 2). Median survival times of patients with brain metastases was 6 months. Significant survival differences for this subgroup of patients were observed according to the initial treatment, S100B, LDH and the number of involved distant sites (Supplementary Table 1).

Multivariable Cox proportional hazard analysis

Patients with missing values for LDH or S100B were excluded resulting in a sample size of 586 patients for the multivariate Cox

Table 2 Results of the Cox proportional hazard analysis excluding the initial treatment of distant metastasis

Prognostic factor	Sample size (n = 586)	% Dead	Hazard ratio (95% CI) ^a	P-value
LDH				
Normal	423 (72.2%)	78.5	1	
Elevated	163 (27.8%)	92.6	1.6 (1.3, 2.0)	$P < 0.001$
S100B				
Normal	255 (43.5%)	74.1	1	
Elevated	331 (56.5%)	88.8	1.7 (1.4, 2.1)	$P < 0.001$
Time interval between initial diagnosis and stage IV diagnosis				
≤ 36 months	336 (57.3%)	86.3	1.3 (1.1, 1.6)	$P = 0.004$
> 36 months	250 (42.7%)	77.2	1	
Site of distant metastasis				
Soft tissue only	105 (17.9%)	67.6	1	
Lung (+ soft tissue)	158 (27.0%)	81.6	1.6 (1.2, 2.2)	$P = 0.002$
Other visceral	323 (55.1%)	87.6	1.8 (1.3, 2.5)	$P < 0.001$
Number of involved distant sites				
1	300 (51.2%)	75.0	1	
2	138 (23.5%)	87.7	1.1 (0.88, 1.5)	$P = 0.323$
≥ 3	148 (25.3%)	92.6	1.7 (1.3, 2.3)	$P < 0.001$

Abbreviations: 95% CI = 95% confidence interval; LDH = lactate dehydrogenase. ^a95% CI; the model was adjusted for the confounding effects of ulceration of primary tumour and age of patients at primary diagnosis.

regression analyses. All variables except the initial treatment in stage IV disease were included in the first analysis (Table 2). In the final model, elevated LDH and S100B, an interval between initial diagnosis and stage IV diagnosis ≤ 36 months, lung, or other visceral sites of distant metastasis and a higher number of involved distant sites than two, were significant factors that independently increased the risk to die. Visceral metastases other than lung (HR 1.8), elevated S100B (HR 1.7), three or more involved metastatic sites (HR 1.7) and elevated LDH (HR 1.6) were the factors with the highest negative impact on survival.

In a second analysis, the first treatment after occurrence of distant metastasis was additionally included (Table 3) to the established Cox model (Table 2). A treatment other than complete metastasectomy was found to represent an independent prognostic factor (HR 1.3; $P = 0.023$). All other factors remained basically unchanged except the number of involved distant sites. The HR decreased to 1.5 if the patient had three or more involved sites. In patients with normal values of LDH and S100B, the difference in survival according to the initial treatment of distant metastasis was highest. The 5-year survival rate was 37.2% if complete metastasectomy was performed, although it was 9.5% for patient receiving other treatments ($P < 0.001$; Figure 3A). This association between complete metastasectomy and favourable survival was still evident if only one serum marker, either S100B or LDH, was elevated ($P = 0.023$; Figure 3B), but no prognostic impact was observed in patients with elevation of both markers (Figure 3C). The independent prognostic impact of LDH, S100B, the time interval between initial diagnosis and stage IV diagnosis, the site and the number of involved sites in model 1 and additionally of the first treatment in model 2 was also evident if age and tumour thickness were included as continuous variables in the Cox regression analysis.

DISCUSSION

The present analysis showed for the first time that the serum markers LDH and S100B are both independent prognostic factors

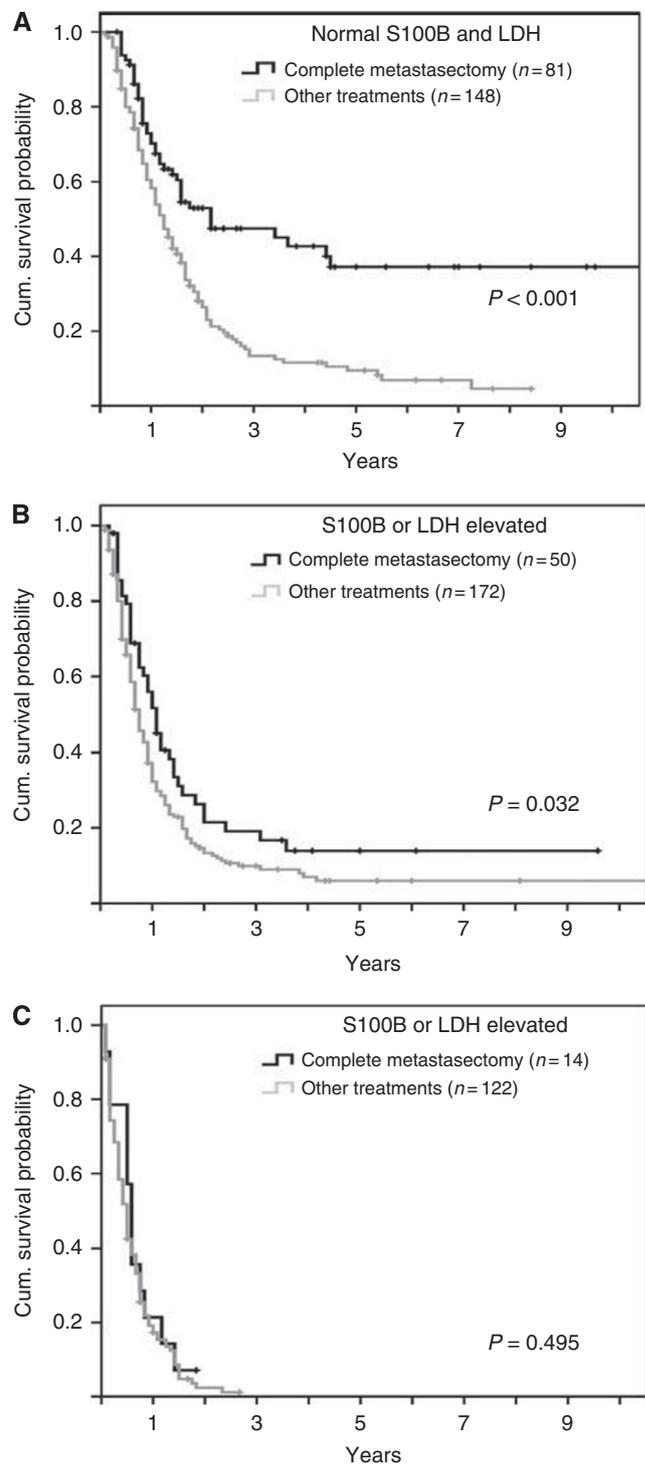
Table 3 Results of the Cox proportional hazard analysis additionally accounting for the initial treatment of distant metastasis

Prognostic factor	Sample size (n=586)	% Dead	Hazard ratio (95% CI) ^a	P-value
LDH				
Normal	423 (72.2%)	78.5	1	
Elevated	163 (27.8%)	92.6	1.6 (1.3, 2.0)	<i>P</i> <0.001
S100B				
Normal	255 (43.5%)	74.1	1	
Elevated	331 (56.5%)	88.8	1.7 (1.4, 2.1)	<i>P</i> <0.001
Time interval between initial diagnosis and stage IV diagnosis				
≤36 months	336 (57.3%)	86.3	1.3 (1.1, 1.6)	<i>P</i> =0.008
>36 months	250 (42.7%)	77.2	1	
Site of distant metastasis				
Soft tissue only	105 (17.9%)	67.6	1	<i>P</i> =0.010
Lung (+ soft tissue)	158 (27.0%)	81.6	1.5 (1.1, 2.0)	<i>P</i> <0.001
Other visceral	323 (55.1%)	87.6	1.8 (1.3, 2.5)	
Number of involved distant sites				
1	300 (51.2%)	75.0	1	
2	138 (23.5%)	87.7	1.1 (0.83, 1.4)	<i>P</i> =0.593
≥3	148 (25.3%)	92.6	1.5 (1.1, 2.1)	<i>P</i> =0.005
First treatment in stage IV				
Metastasectomy	145 (24.7%)	64.8	1	
Other treatment	441 (75.3%)	88.2	1.3 (1.04, 1.7)	<i>P</i> =0.023

Abbreviations: 95% CI=95% confidence interval; LDH=lactate dehydrogenase. ^a95% CI; the model was adjusted for the confounding effects of ulceration and histological subtype of primary tumour and age of patients at primary diagnosis.

in melanoma patients with distant metastasis, additionally to the extent, organ pattern, and the time course of the metastasis. The HRs for death were 1.6 for patients with elevated LDH and 1.7 for patients with elevated S100B. Accordingly, the MST differed largely between patients with both serum markers in the normal range with 18 months *vs* one serum marker elevated (either LDH or S100B) with 9 months or both factors elevated with 6 months. It should be stressed that the independent impact of both serum markers was confirmed in multivariate analysis adjusted for all potential and established prognostic factors. The finding of the independent impact of both serum markers on prognosis was surprising, because one would expect a parallel increase of both factors. However, in 33% of patients only S100B was elevated, whereas 23% of patients showed elevation of both serum markers at the time of first diagnosis of distant metastasis. In contrast, only 5% had an isolated increase of LDH. Lactate dehydrogenase is expressed ubiquitously in different healthy tissues. An elevated serum concentration of the intracellular enzyme is mainly based on cell lysis, for example, after myocardial infarction or haemolysis. Moreover, an increased serum LDH occurs in different tumour entities and indicates a high turn-over of tumour cells as well as necrosis in fast-growing tumours. It is associated with high tumour burden and seems to be particularly elevated in liver metastases for which no clear explanation can be given (Finck *et al*, 1983; Heimdal *et al*, 1989; Sirott *et al*, 1993).

S100B shows many differences to LDH. It is tissue specific and mainly expressed in glial cells of the brain, melanocytes, and other cell types, which are originally derived from the neural crest. Additionally, it is detectable in chondrocytes and dendritic cells. Most melanomas strongly express S100B. A functional role of this protein in melanoma is conceivable due to its capacity to interact with p53 and to activate STK38/NDR1, a protein kinase involved in cell survival and proliferation (Donato, 2001; Hergovich *et al*, 2006). It has been shown in cell culture experiments that it can be actively secreted upon metabolic stress (Gerlach *et al*, 2006) and it

**Figure 3** Impact of complete metastasectomy according to LDH and S100B. Kaplan-Meier survival curves for patients with (A) normal LDH and normal S100B (B) one elevated serum marker and (C) elevated LDH and elevated S100B. Censored events are indicated by vertical lines.

is likewise elevated in patients with neural diseases showing metabolic abnormalities like schizophrenia or depression (Schroeter and Steiner, 2009). Therefore, the biology of S100B is clearly different from LDH and this may explain the independent prognostic impact shown by both markers. A complete lack of S100B expression can be observed by immunohistochemistry in a small proportion of melanoma patients (Argenyi *et al*, 1994).

This downregulation of S100B might explain the normal serum S100B in spite of elevated LDH in 5% of our patients.

It is an interesting finding of the present study that complete metastasectomy was associated with a favourable prognosis. The subgroup of patients with no elevation of the two serum markers LDH and S100B in combination had the longest survival after complete metastasectomy. In general, it has to be considered that the association between metastasectomy and survival may be due to a selection bias of prognostically favourable patients towards surgery. As expected, a higher percentage of our patients with metastasectomy had soft-tissue metastases only and normal serum markers. The mean number of involved distant sites was lower with 1.3 compared with 2.1 in patients with other treatments (Supplementary Table 2). Therefore, we accounted for these factors in the multivariate analyses. Although the independent impact of complete metastasectomy was confirmed in the Cox regression analysis, we acknowledge that the true effect of this procedure can only be assessed in a prospective randomised controlled trial. Thus far, surgery of distant metastasis has frequently been found to be associated with favourable survival of selected patients subgroups (Ollila *et al*, 1996; Wood *et al*, 2001; Neuman *et al*, 2007), but only two research groups analysed the role of complete metastasectomy vs other treatments using Cox regression analyses in unselected patients with distant metastasis (Meyer *et al*, 2000; Wasif *et al*, 2011). Both groups found an independent positive impact on prognosis of this procedure but in both studies LDH was not available. The present study is the first that accounted for LDH as well as the site of distant metastasis in Cox regression analysis and therefore included both relevant factors of the current AJCC staging system (Balch *et al*, 2009). However, there could be other yet unknown prognostic factors that we have not adjusted for and which only a randomised study can control.

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