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The association between active tumor volume, total lesion glycolysis and levels of S-100B and LDH in stage IV melanoma patients

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ABSTRACT

Introduction: The Standardized Uptake Value (SUV) in single lesions on ^{18}F-FDG PET/CT scans and serum S-100B concentrations are inversely associated with disease-free survival in stage IV melanoma. The aim of this study was to assess the association between biomarkers (S-100B, LDH) and the PET-derived metrics $SUV_{mean/max}$, metabolic active tumor volume (MATV), and total lesion glycolysis (TLG) in stage IV melanoma in order to understand what these biomarkers reflect and their possible utility for follow-up.

Methods: In 52 stage IV patients the association between PET-derived metrics and the biomarkers S-100B and LDH was assessed and the impact on survival analyzed.

Results: S-100B was elevated (>0.15 μg/l) in 37 patients (71%), LDH in 11 (21%). There was a correlation between S-100B and LDH (R^2 = 0.19). S-100B was correlated to both MATV (R^2 = 0.375) and TLG (R^2 = 0.352), but LDH was not. Higher MATV and TLG levels were found in patients with elevated S-100B ($p < 0.001$) and also in patients with elevated LDH (>250 U/l) ($p < 0.001$). There was no association between the biomarkers and $SUV_{mean/max}$. Survival analysis indicated that LDH was the only predictor of melanoma-specific survival.

Conclusion: In newly diagnosed stage IV melanoma patients S-100B correlates with ^{18}F-FDG PET/CT derived MATV and TLG in contrast to LDH, is more often elevated than LDH (71% vs. 21%) and seems to be a better predictor of disease load and disease progression. However, elevated LDH is the only predictor for survival. The biomarkers, S-100B and LDH appear to describe different aspects of the extent of metastatic disease and of tumornecrosis.

Introduction

The introduction of effective systemic treatment options (BRAF/MEK inhibitors and immunotherapy) over the past decade has resulted in improved survival rates for stage IV melanoma patients with non-resectable disease [1,2]. Potentially curative surgery is achievable in less than 10% of stage IV patients with metastatic disease, and systemic therapies are most effective when the tumor burden is still low [3,4]. This has resulted in an increased urgency to identify recurrent disease in the follow-up of melanoma patients, especially those with stage III disease in whom the risk of recurrence in the first five years has been reported to be 19%, 36%, 55% and 90% for stage III A, B, C and D (AJCC 8th edition) [5]. In order to maximize stage IV treatment efficacy, stage III follow-up strategies are compared, tested, and may be updated in the future by adding biomarkers and/or standard radiological assessments with whole-body Computed Tomography (CT) or ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET scans). For example, in the prospective randomized TRIM study (NCT03116412) the role of imaging with PET/CT or CT scanning and laboratory tests (S-100B,

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ALP, LDH, and transaminases) during follow-up after radical surgery for stage IIB-C and III melanoma is being assessed.

Globally, there is no consensus in relation to the use of biomarkers in the follow-up of melanoma patients. The German and Swiss guidelines on melanoma follow-up and response evaluation do recommend monitoring of biomarkers (e.g. LDH, S-100B) as well as regular imaging (e.g. ^{18}F-FDG PET/CT) for surveillance [6,7]. In contrast, the NCCN and Australian guidelines do not recommend monitoring of biomarkers, because of insufficient evidence supporting the use of biomarkers in melanoma follow-up [8,9].

For S-100B, it has been shown that serum levels are correlated with melanoma stage [10–12]. Furthermore, S-100B has proved to be of prognostic significance in stage III patients and can be used as a selection tool for ^{18}F-FDG scanning [13,14]. Serum LDH is used as a biomarker together with ^{18}F-FDG PET/CT in evaluating the response of systemically treated stage IV melanoma patients and predicts the success of systemic ipilimumab therapy before the initiation of treatment. Stage IV patients with ≥2x the upper limit of normal LDH levels do not benefit from ipilimumab treatment in terms of survival and therefore, are not offered this treatment [15].

The abovementioned associations between LDH and S-100B with melanoma stage and behavior suggest that there is an association between melanoma biomarkers and active melanoma tumor load. The extent of disease in stage IV melanoma patients is best determined by whole-body ^{18}F-FDG PET/CT, which reveals different metrics reflecting physical tumor volume (metabolic active tumor volume (MATV)), biological tumor activity ($SUV_{mean/max}$ and total lesion glycolysis (TLG = MATV x SUV_{mean})).

The aim of the present study was to provide new insights into the role of biomarkers in the follow-up of melanoma patients, by studying the associations between the biomarkers S-100B and LDH and ^{18}F-FDG PET/CT-derived metrics (i.e. MATV, $SUV_{mean/max}$, and TLG) in melanoma patients with newly diagnosed stage IV disease. Unraveling these associations could lead to a better understanding of what these markers reflect and whether and, if so, how they can be useful in melanoma follow-up.

Methods

Study population

This retrospective study included data for all newly diagnosed stage IV melanoma patients that were retrieved from a prospectively-collected cohort database at the Department of Surgical Oncology of the University Medical Center Groningen (UMCG).

Selected patients (n = 60) were >18 years of age with histologically-proven stage IV cutaneous melanoma according to the American Joint Committee on Cancer (AJCC) 8th edition [16–18], with a baseline ^{18}F-FDG PET/CT scan performed between 2010 and 2015, and S-100B and LDH blood samples taken prior to (median of 1 week; interquartile range (IQR) 0.5–1.5) or just after the ^{18}F-FDG PET/CT scan (median of 2 weeks, IQR 1–3). Patients were excluded if there were multiple small metastases in a single organ (e.g. liver, lung) that made proper analysis impossible (n = 3), or if there was no adherence to the European Association of Nuclear Medicine (EANM) ^{18}F-FDG PET/CT scan protocol (n = 5) [19,20]. Final analyses were performed on 52 patients.

Patient- and tumor characteristics including sex, age, Breslow thickness, site of the primary melanoma, melanoma type and ulceration were collected from medical records, as well as the laboratory results for serum S-100B and LDH (Table 1).

Data collection was conducted according to the declaration of Helsinki ethical principles for medical research involving human subjects [21]. The Medical Ethics Review Board of the University Medical Center Groningen (METc UMCG) approved the study (METc 2019/515, Research Register number 201900627).

Table 1
Patient and tumor characteristics.

Characteristics		All patients, N = 52
Sex	Male	30 (58)
	Female	22 (42)
Age (years) at diagnosis		64 [53; 69]
Breslow (mm)		2.8 [1.65; 4.75]
Region primary	Head/Neck	8 (15)
	Trunk	25 (48)
	Lower extremity	16 (31)
	Upper extremity	3 (6)
Melanoma type	Superficial spreading	28 (65)
	Nodulair	14 (33)
	Other	1 (2)
	Missing	9
Ulceration	Yes	16 (40)
	No	24 (60)
	Missing	12
BRAF mutation	Yes	26 (55.3)
	No	21 (44.7)
	Missing	5
S-100B[a]	Elevated	37 (71)
	Normal	12 (29)
LDH[b]	Elevated	11 (21)
	Normal	41 (79)

Data are displayed as n (%) or median [interquartile range].
LDH lactate dehydrogenase.
All blood samples were taken prior to or just after ^{18}F-FDG PET/CT scan.
[a] S-100B values > 0.15 μg/l are considered elevated.
[b] LDH values > 250 U/l are considered elevated.

^{18}F-FDG PET/CT and delineation technique

^{18}F-FDG PET/CT scans were performed and reconstructed according to the EANM procedure guideline [19,20] using a hybrid PET/CT scanner (Siemens Biograph mCT 40 and 64 slices). Both systems were from the same vendor and from the same generation; the acquisition and reconstruction protocols were harmonized, and the systems were cross-calibrated. Patients were advised to fast for at least 4–6 h prior to scanning. One hour prior to the PET/CT, patients were injected with ^{18}F-FDG (3 MBq/kg). For the imaging, patients were examined in the supine position and scanned for 1–3 min per bed position based on their body weight.

A delineation analysis software program developed in-house (ACCURATE) was used to determine the ^{18}F-FDG PET/CT-derived metrics [22]. All lesions that could not be attributed to physiological uptake of ^{18}F-FDG were assumed to be metastases. This was double-checked with the documentation of the nuclear physician and radiologist. Volumes of interest (VOIs) were automatically drawn using 50% of the SUV_{peak} contour, corrected for local background [23]. For each patient, and for every metastatic lesion, 5 metabolic parameters were extracted: SUV_{mean}, SUV_{max} (voxel with the highest SUV value), the SUV_{peak} (using a 1 mL sphere containing the highest average value), Metabolically Active Tumor Volume (MATV), and Total Lesion Glycolysis (TLG; the product of SUV_{mean} and MATV) [24,25]. All parameters were corrected for Lean Body

Mass (LBM) as recommended by Boellaard et al. [20], using Janmahasatian's formula [26]. For SUV metrics the median and maximum values for all the patient's lesions were calculated. For example, if a patient has four lesions, the SUV_{peak} was calculated for each individual lesion, then the median SUV_{peak} was calculated from these four SUV_{peak} values. For MATV and TLG, when there was more than one lesion, values were summed. All the metrics were log-transformed to approximate a normal distribution.

Statistical analysis

Variables were summarized with frequencies and percentages, with median and interquartile range (IQR) for continuous variables or, when normally distributed, with mean ± SEM. Inferential statistics were performed using Fisher's exact, Mann-Whitney U or T-tests as appropriate to compare variables. The relationship between the ^{18}F-FDG PET/CT-derived metrics and the biomarkers S-100B and LDH were assessed using scatter plots and Pearson correlation.

Receiver operating characteristic (ROC) curves were used to explore the relationship between patient survival and the biomarkers S-100B and LDH.

S-100B and LDH levels per patient were categorized as normal (S-100B<0.15μg/l and LDH<250U/l) or elevated (S-100B>0.15μg/l and LDH>250U/l). Kaplan Meier curves were then constructed describing the melanoma-specific survival, defined as the time from stage IV melanoma diagnosis until last follow-up visit or death. The log-rank test was used for statistical comparison of the groups. For all statistics, a p-value < 0.05 was considered statistically significant, without correction for multiple comparisons. SPSS version 23.0 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) was used for statistical analyses.

Results

Population

Of the 52 patients with newly diagnosed stage IV melanoma 30 were male (58%) and 22 female (42%) with a median age of 64 years [IQR 53; 69]. The median Breslow thickness of their primary melanomas was 2.8 mm [IQR 1.65; 4.75]. The melanomas were located on the trunk in 25 patients (48%), followed by a lower extremity in 16 (31%), the head/neck region 8 (15%) and an upper extremity 3 (6%). BRAF mutation was present in 26 patients (55%). Twenty-eight melanomas were of the superficial spreading type (65%) and 16 were ulcerated (40%). The biomarker S-100B was elevated in 37 (71%) and LDH in 11 (21%) at the time of the initial diagnosis of stage IV disease (Table 1). All patients with an elevated LDH had elevated S-100B levels simultaneously. The total number of metastatic lesions per patient ranged from 1 to 66. The median number of lesions per patient was 8 [IQR 3; 14](Appendix A).

Patient and tumor factors associated with high biomarker levels

For S-100B, there were no patient or tumor characteristics that showed an association with elevated serum levels (Table 2). For LDH, older patients (≥65 years) had more frequently elevated LDH values: 32% versus 12.5% for younger patients (<45 years) ($p = 0.048$). Patients who were BRAF-negative more frequently had an elevated LDH compared to BRAF positive-patients (38.1% vs 11.5% ($p = 0.043$)). The other factors did not show an association with LDH levels (Table 2).

Correlation between biomarkers and ^{18}F-FDG PET/CT-derived metrics

The correlation between LDH and S-100B was $R^2 = 0.191$. The R^2 between S-100B and the ^{18}F-FDG PET/CT-derived metrics (SUV_{mean}, MATV and TLG) was $R^2 = 0.019$, $R^2 = 0.374$ and $R^2 = 0.351$ respectively. Both MATV and TLG were significantly correlated ($p \leq 0.01$). No significant correlation was found for the ^{18}F-FDG PET/CT-derived metrics (SUV_{mean}, MATV and TLG) and the biomarker LDH with $R^2 = 0.046$, $R^2 = 0.025$ and $R^2 = 0.019$ respectively. The associations between LDH and S-100B, and MATV and S-100B are displayed in Fig. 1 and Fig. 2. A complete overview of all the correlations between the biomakers LDH and S-100B and the ^{18}F-FDG PET/CT-derived metrics are shown in Table 3 and Appendix B.

ROC analysis of the relationship between survival and biomarker elevation

ROC analysis showed an AUC of 0.563 for S-100B, and 0.693 for LDH (Fig. 3).

Melanoma-specific survival

The 52 patients in this cohort had a median follow-up of 24.9 months (range 2.6–86.0). Of these patients, 33 (63%) died of melanoma, and 4 of other causes (3 of an unknown cause and 1 of pleomorphic sarcoma). Median survival for patients with normal LDH (<250U/l) was 28.9 months [IQR 13.5; 45.8] vs. 6.7 months [IQR 4.3; 37.3] for patients with an elevated LDH (>250U/l) ($p = 0.019$). Median survival for patients with normal S-100B (<0.15 μg/l) was 23.0 months [IQR 11.9; 42.8] vs. 26.1 months [IQR 6.7; 45.1] for patients with an elevated S-100B (>0.15 μg/l) ($p = 0.709$). Kaplan Meier analyses showed that an elevated LDH values (LDH>250U/l) was significantly associated with shorter melanoma-specific survival ($p = 0.026$). However, classification of patients based on a normal (<0.15 μg/l) or elevated (>0.15 μg/l) level of S-100B was not associated with different survival (Fig. 4a and 4b).

Discussion

The goal of the study was to clarify the association between the biomarkers, S-100B and LDH, and tumor load in patients with newly stage IV melanoma, and to re-assess the value of these biomarkers in follow-up. We found a correlation between the values of both biomarkers (S-100B and LDH), while the ^{18}F-FDG PET/CT-derived metrics MATV and TLG were found to be correlated only with S-100B and not with LDH. S-100B was elevated in 71% and LDH in 21% of the newly-diagnosed stage IV melanoma patients, with all patients having an elevated LDH also having an elevated S-100B levels. However, LDH seemed to be the best predictor of survival. An explanation could be that S-100B and LDH describe different aspects of the lesion. When LDH eventually becomes elevated, the disease is already at a further stage of progression, with some tumor necrosis and the prognosis is worse. It might be that S-100B is already elevated in an earlier stage of disease when there is no tumor necrosis. So, S-100B seems to be more a disease proliferation marker and LDH a reflection of tumor necrosis.

An association between the biomarker S-100B and tumor load has previously been suggested by others [12,27]. However, in most of these studies the melanoma stage was used to estimate tumor load. Previous studies of the use of biomarkers including S-100B and LDH for melanoma follow-up have suggested that S-100B, in particular, might be associated with tumor load and could, therefore, be useful in follow-up to detect recurrences in asymptomatic

Table 2
Disease-related characteristics, stratified by S-100B (S-100B normal/S-100B elevated) or LDH (LDH normal/LDH elevated).

Characteristics		N	S-100B <0.15 N = 15	S-100B > 0.15 N = 37	p-value	LDH <250 N = 41	LDH >250 N = 11	p-value
Sex	Male	30	9 (60)	21 (56.8)	1.000[a]	25 (61)	5 (45.5)	0.495[a]
	Female	22	6 (40)	16 (43.2)		16 (39)	6 (54.4)	
Age (years)	<45	8	3 (20)	5 (13.5)	0.414[a]	7 (17.1)	1 (9.1)	0.199[a]
	45–64	19	7 (46.7)	12 (32.4)		17 (41.5)	2 (18.2)	
	≥64	25	5 (33.3)	20 (54.1)		17 (41.5)	8 (72.2)	
	Median [IQR]		62 [47; 67]	65 [54; 71]	0.192[b]	62 [51; 68]	69 [62; 74]	**0.048**[b]
Breslow (mm)	<2,00	18	5 (38.5)	13 (40.6)	1.000[a]	14 (40)	4 (40)	1.000[a]
	≥2,00	27	8 (61.5)	19 (59.4)		21 (60)	6 (60)	
	Missing	7	2	5		6	1	
	Median [IQR]		3.3 [1.4; 4.3]	2.7 [1.7; 5.0]	0.764[b]	3.3 [1.6; 5.0]	2.2 [1.6; 3.7]	0.503[b]
Region primary	Head/Neck	8	2 (13.3)	6 (16.2)	0.660[a]	6 (14.6)	2 (18.2)	0.867[a]
	Trunk	25	9 (60)	16 (43.2)		20 (48.8)	5 (45.5)	
	Lower extremity	16	1 (6.7)	2 (5.4)		2 (4.9)	1 (9.1)	
	Upper extremity	3	3 (20)	13 (35.1)		13 (31.7)	3 (27.3)	
Melanoma type	Superficial spreading	28	9 (69.2)	19 (63.3)	1.000[a]	22 (64.7)	6 (66.7)	0.178[a]
	Nodulair	14	4 (30.8)	10 (33.3)		12 (35.3)	2 (22.2)	
	Other	1	0 (0)	1 (3.3)		0 (0)	1 (11.1)	
	Missing	9	2	7		7	2	
Ulceration	Yes	16	7 (58.3)	9 (32.1)	0.166[a]	13 (41.9)	3 (33.3)	0.717[a]
	No	24	5 (41.7)	19 (67.9)		18 (58.1)	6 (66.7)	
	Missing	12	3	9		10	2	
BRAF mutation	Yes	26	7 (63.6)	19 (52.8)	0.731[a]	23 (63.9)	3 (27.3)	**0.043**[a]
	No	21	4 (36.4)	17 (47.2)		13 (363.1)	8 (72.7)	
	Missing	5	4	1		5	0	

Data are displayed as n (%), median [interquartile range].
S-100B (μg/l), *LDH* Lactate dehydrogenase, (U/l).
Values in **bold** are considered significant ($p < 0.05$).
[a] Fisher exact test.
[b] Mann-Whitney *U* test.

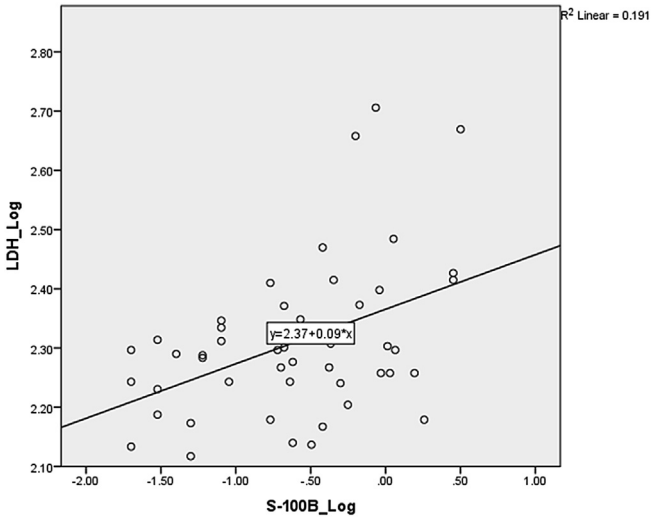


Fig. 1. Association between LDH and S-100B.

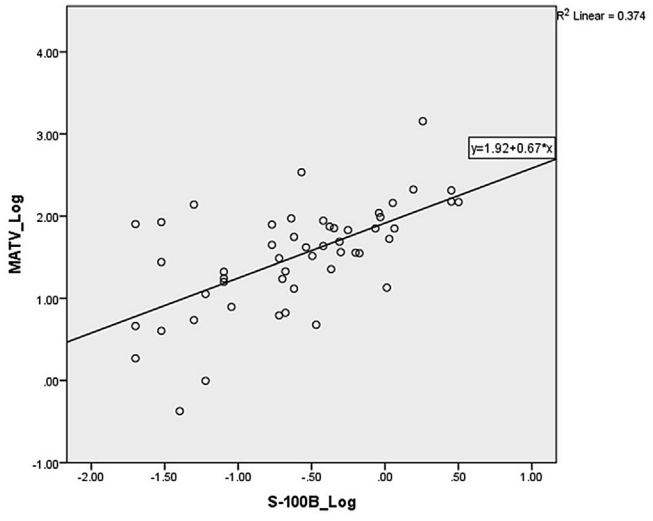


Fig. 2. Association of the metabolically active tumor volume (MATV) and S-100B.

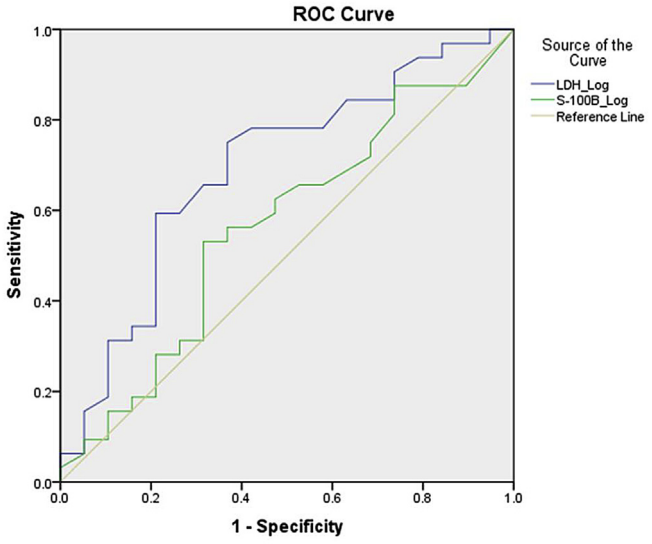
patients [12,14,28–32]. However, there were frequent false-positive and false-negative measurements.

^{18}F-FDG PET/CT is today's most accurate imaging modality for metastatic staging in melanoma combining the diagnostic possibilities of ^{18}F-FDG PET and CT [33,34]. The advantage of the combination is that it provides both metabolic and morphologic information. Beside this, it has also been suggested that the use of both SUV and MATV combined (TLG) could be of prognostic value [20,35]. However, subtraction of these data from scans is a time-consuming process. In the near future (semi-)automatic tumor selection and quantification might be possible and is a prerequisite for further implementation into clinical routine praxis.

Table 3
All correlations between PET derived metrics and biomarkers LDH and S-100B.

	LDH_Log	S-100B_Log	SUV_mean_LBM2_ Median_Log	MATV_Log	TLG_LBM2_ SUM_Log
LDH_Log	1	**0.437****	−0.023	0.160	0.139
S-100B_Log	**0.437****	1	0.140	**0.612****	**0.593****
SUV_Mean_LBM2_ Median_Log	−0.023	0.140	1	−0.043	0.238
MATV_Log	0.160	**0.612****	−0.043	1	**0.938****
TLG_LBM2_ Sum_Log	0.139	**0.593****	0.238	**0.938****	1

LDH lactate dehydrogenase; *SUV* Standard Uptake Value; *LBM2* Lean Body Mass; *MATV* Metabolic Active Tumor Volume; *Log* Log-transformed.
**Pearson correlation significant at the 0.01 level (2-tailed).



Area Under the Curve	
LDH_Log	0.693
S-100B_Log	0.563

Fig. 3. ROC Curve for death of disease based on S-100B or LDH.

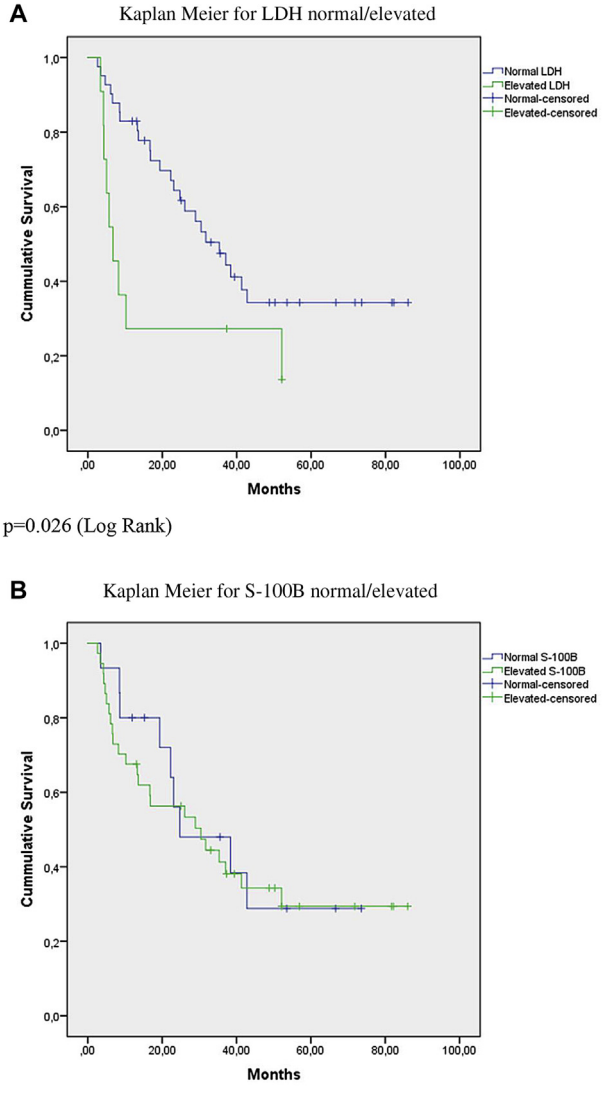


Fig. 4. a - Kaplan Meier for LDH normal/elevated p = 0.026 (Log Rank). b - Kaplan Meier for S-100B normal/elevated p = 0.715 (Log Rank).

Recent studies have indicated that MATV and TLG are accurate prognostic markers for progression-free and recurrence-free survival in patients with cervical cancer and cutaneous melanoma [36,37]. In addition, MATV and TLG are stronger predictors of overall and melanoma-specific survival than SUV_{max} [20,38]. Kruijff et al. showed that, for clinically stage III melanoma patients, SUV_{mean} and S-100B were not correlated, but S-100B was a good predictor of disease-free survival. However, until now little has been known about the prognostic value of MATV and TLG and their relation to biomarkers in stage IV melanoma disease [39,40].

For LDH, there seems to be a trend towards more elevated levels in elderly patients. This positive association between age and LDH in cancer has been noted previously, but the explanation is unclear [41]. It is well established that LDH has important prognostic value in stage IV melanoma patients and it was, therefore, incorporated in the 7th Edition AJCC staging system in 2001 [42]. We found 30–40% higher MATV and TLG values for the 11/52 patients with an elevated LDH (mean: 461U/I and median: 295U/I versus normal LDH with mean: 185U/I and median: 189U/I) which could partly account for the worse prognostic estimates. This is in line with the recent study of De Heer et al. who showed that patients with elevated LDH have higher MATV and SUV values [25]. LDH levels may rise because of increasing tumor load in later stages of disease with more tumor necrosis, which might explain the poor prognosis and poor treatment responses. Because of their known poor response to systemic treatment, stage IV patients with a high LDH are often excluded from immune- and/or targeted treatment [4].

In case of S-100B, it might be melanoma metabolically activity and proliferating tumor cells in advance of tumor necrosis that make the biomarker rise earlier [25]. In this study, S-100B was elevated in 37 patients (71%) and LDH in only 11 (21%) patients. This suggests that either S-100B is a more sensitive marker than LDH in the follow-up of melanoma patients or that they reflect different phases of disease progression.

TLG might be one of the better parameters to reflect actual tumor burden, as both FDG-uptake and tumor size are combined and when corrected for lean body mass it reflects "real" tumor burden even more accurately [20]. In addition, in lung cancer, TLG is known to be an independent predictor of survival [38]. TLG was marginally associated with elevated S-100B levels, whereas LDH was not. However, in the present study, LDH was the only predictor of survival. This also suggests that LDH and S-100B reflect different stages of disease progression.

In the literature there is no description of a standard cut-off for S-100B due to variations between different immunoassays and/or due to investigators choice [43,44]. The present study used the same cut-off of 0.15 as used in 'S-100B as an extra selection tool for FDG PET/CT scanning in follow-up of AJCC stage III melanoma patients' [14]. Some other studies used 0.10 or 0.09 as cut-off [45]. When using 0.10 as cut-off for the present analyses, no significant differences are found in the results. Also when using a 0.09 cut-off, as used by Brouard et al. [43], the results do not change; reclassifying only one case as having an elevated S-100B instead of being normal.

Future studies could focus on the role of S-100B and LDH in evaluating the biomarker response of stage IV melanoma patients receiving systemic therapy. Perhaps ^{18}F-FDG PET/CT scans could be substituted for biomarker measurements if further studies demonstrate persistent correlation between S-100B and/or LDH and tumor volume metrics over subsequent response evaluation scans during systemic treatment of stage IV patients. Only those with stage IV disease who are suitable for systemic therapy and have previously shown elevated S-100B biomarkers might be candidates for such biomarker response evaluation in the future.

In order to effectively use S-100B in follow-up, it would be of great help to know which subgroup of patients will show elevation of their serum S-100B when there is melanoma recurrence. Unfortunately, the present study did not identify any patient or tumor characteristic that predicted a high sensitivity of S-100B in follow-up. This could be explained by the low sample size and the fact that this is a retrospective study. An option to identify suitable S-100B responders could be to evaluate the S-100B change after surgery with curative intent in patients with advanced stage III disease. Patients with S-100B elevation in association with metastatic melanoma and who have a decrease in S-100B after potentially curative surgery are designated as S-100B responders. These patients might be good candidates for follow-up with S-100B measurements to detect recurrent disease.

Reduction of follow-up and therapy evaluation scans will not only have a positive effect on healthcare costs, patient anxiety, and risk for second malignancies due to radiation, but will also decrease the risk of incidental findings and false positive scan results, which are found in a least half of asymptomatic stage III melanoma patients and even lead to unnecessary invasive procedures [46].

Conclusion

The associations between the biomarkers S-100B and LDH in the serum and tumor load, as assessed by MATV/TLG on ^{18}F-FDG PET/CT scans, suggests that S-100B is correlated with disease progression (higher tumor burden) in contrast to LDH. However, LDH has a predictive value for survival in contrast to S-100B. Both LDH and S-100B seem to describe different aspects of the metastatic disease, tumor proliferation and tumor necrosis. Future research should focus on the possibility of using S-100B and LDH monitoring in appropriate patients with resected stage III disease as a useful alternative to routine follow-up with ^{18}F-FDG PET/CT scans.

Synopsis

In newly diagnosed stage IV melanoma patients, S-100B seems to be a better predictor of disease load and disease progression while elevated LDH is the only predictor for survival. The biomarkers, S-100B and LDH appear to describe different aspects of the extent of metastatic disease and of tumornecrosis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.07.011.

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