Metastatic Volume: An Old Oncologic Concept and a New Prognostic Factor for Stage IV Melanoma Patients

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Key Words

Melanoma · Metastatic volume · Distant metastases · Prognostic factor · Staging system · Survival time

Abstract

Background: The last melanoma staging system of the 2009 American Joint Committee on Cancer takes into account, for stage IV disease, the serum levels of lactate dehydrogenase (LDH) and the site of distant metastases. **Objective:** Our aim was to compare the significance of metastatic volume, as evaluated at the time of stage IV melanoma diagnosis, with other clinical predictors of prognosis. **Methods:** We conducted a retrospective multicentric study. To establish which variables were statistically correlated both with death and survival time, contingency tables were evaluated. The overall survival curves were compared using the Kaplan-Meier method. **Results:** Metastatic volume and number of affected organs were statistically related to death. In detail, patients with a metastatic volume $>15 \text{ cm}^3$ had a worse prognosis than those with a volume lower than this value (survival probability at 60 months: 6.8 vs. 40.9%, respectively). The Kaplan-Meier method confirmed that survival time was significantly related to the site(s) of metastases, to elevated LDH

serum levels and to melanoma stage according to the latest system. **Conclusion:** Our results suggest that metastatic volume may be considered as a useful prognostic factor for survival among melanoma patients.

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Introduction

Malignant melanoma shows a rapidly increasing incidence worldwide and is the most common cause of all skin cancer deaths [1].

Metastatic melanoma has an unfavourable prognosis, and treatment options are limited.

Only 9–26% of all melanoma patients with distant metastasis achieve a 5-year survival, with a median survival of less than 12 months [2–4].

An accurate and reliable staging to detect regional or distant metastases is therefore necessary to ensure an appropriate treatment and optimize patient survival, at least for a subgroup of these patients.

Previous studies have sought to identify, among patients classified as having stage IV disease, subgroups of patients with improved prognoses [4].

The most recent evaluation of prognostic factors for stage IV melanoma patients was performed during the development of the 2009 American Joint Committee on Cancer (AJCC) staging system. The only prognostic factors considered for stage IV patients, however, were lactate dehydrogenase (LDH) serum levels and the site of distant metastases. Balch et al. [2] did recognize the importance of the number of metastases, but this parameter was not included in the last revision because diagnostic tests to identify metastases varied widely between institutions.

Our aim was to compare the significance of metastatic volume, as evaluated at the time of stage IV melanoma diagnosis, with other clinical predictors of prognosis.

Materials and Methods

We conducted a retrospective study using clinical records from the Department of Dermatology, University of Rome La Sapienza, and from the Institute of Dermatology, University of Trieste. Records dated from July 1998 to April 2011 and concerned 239 patients with stage IV cutaneous melanoma.

The classification of patients was based on the first site of metastasis and on LDH serum levels in agreement with the AJCC 2009 staging system (M1a – skin, subcutaneous, or distant nodal disease; M1b – lung; M1c – non-pulmonary viscera or any distant metastases in patients with high LDH serum levels) [2].

Patients included in the study received treatments as follows: dacarbazine as first-line therapy (dacarbazine 250 mg/m² on days 1–5 every 28 days) [5]; the second-line therapies were: BOLD polychemotherapy (bleomycin 15 mg i.v. on days 1 and 4, vincristine 1 mg/m² i.v. on days 1 and 5, lomustine 80 mg/m² p.o. on day 1 and dacarbazine 200 mg/m² i.v. on days 1–5; the treatment was repeated every 4 weeks) [6], fotemustine [at doses of 100 mg/m² i.v. weekly for 3 consecutive cycles (induction phase) followed by a 5-week rest period, after which treatment was resumed with cycles of triweekly fotemustine at doses of 100 mg/m² as maintenance phase] [7] and CVD (vinblastine was used at a dose of 1.6 mg/m²/day for 5 days, dacarbazine was used at a dose of 800 mg/m² i.v. on day 1, and cisplatin was used at a dose of 20 mg/m²/day for 4 days starting on day 2 of chemotherapy; the courses of chemotherapy were repeated at 3-week intervals) [8].

Patients affected by ocular, anogenital, subungual melanoma, with unknown LDH serum level or treated with surgical resection of their isolated metastases were excluded from the study.

The date of the diagnosis of distant metastases was considered as 'time 0' for survival analysis.

To perform the statistical analysis, survival time was determined from the date of stage IV disease diagnosis until death or last follow-up.

For each patient the following data were recorded: sex, age at the time of stage IV melanoma diagnosis, LDH serum level, site and number of distant metastases, number of organs affected, melanoma stage according to AJCC 2009 and metastatic volume, which was measured by conventional and helical computed tomography scan (CT) with a minimum size of 10 mm by spiral CT scan and of 20 mm by non-spiral CT scan, to categorize the tumour

lesions and lymph nodes between measurable or non-measurable, according to the RECIST guideline. Each measurable metastasis was considered as a spherical formation whose diameter was the average of the minimum diameter and maximum diameter and the volumes calculated using the following formula: $\text{volume} = 4/3 \pi r^3$. Measurements were also performed considering measurable metastases as tri-axial ellipsoids, using the formula $4/3 \pi (a \times b \times c)$. The values obtained with the two methods were essentially superimposable. Intravenous iodinate non-ionic contrast, at the dosage of 2 mg/ml/kg, was used to perform the CT examination. Evaluation of images was performed independently by two radiologists; intra-observer agreement on the metastatic nature of the lesions considered was higher than 90%.

Patients were subdivided into 3 subgroups according to their age at the time of stage IV melanoma diagnosis (40 or under, 41–60 and over 60 years) and into 3 subgroups considering the sites of metastases: the first for patients with distant cutaneous, subcutaneous and lymph node metastases, the second for those with lung secondary localizations and the latter for patients affected by other visceral metastases.

LDH serum levels were dichotomized by ≤ 250 and >250 U/l and were determined using the mean value from blood samples taken with at least 24-hour intervals. Finally, the patients were classified into 3 groups on the basis of the number of affected organs (1, 2 and more than 2).

The receiver-operating characteristic curves were calculated to identify a cut-off that accurately dichotomized the variables metastatic volume and number of metastases.

To establish which variables were statistically correlated both with death and survival time, all data were entered into a Microsoft Excel spreadsheet and analysed as follows: contingency tables were evaluated by the log-rank test, and the overall survival curves were compared using the Kaplan-Meier method [9].

Assuming that the effects of the predictor variables are constant over time, the variables identified as statistically significant in the contingency tables were then analysed with a Cox proportional-hazard regression model to evaluate the most statistically significant.

Only p values <0.01 were considered. Statistical analysis was performed with MedCalc®, version 8.0.0.0 [10].

Results

We evaluated a total of 239 patients (141 male and 98 female), classified as having stage IV cutaneous melanoma. The median age was 63 years (range: 27–91). The median survival was 8.96 months (range: 1–139).

The cut-off values obtained by receiver-operating characteristic curves were 15 cm³ for metastatic volume and 4 for number of metastases (fig. 1); the sensitivity and the specificity were 78.5 and 58.1%, respectively, for metastatic volume, 70.6 and 53.2% for number of metastases.

The Kaplan-Meier method on our data series confirmed that, true to form, survival time was significantly related to the site(s) of metastases ($p < 0.0001$), elevated

Fig. 1. Graphs of receiver-operating characteristic curves show the sensitivity and specificity of the variables number of metastasis (a) and metastatic volume (b).

LDH serum levels ($p = 0.0063$) and to the last version of the AJCC Melanoma Staging System ($p < 0.0001$; fig. 2a–c).

Furthermore, the number of metastases ($p = 0.0003$), the number of affected organs ($p < 0.0001$) and, of interest to us, metastatic volume ($p < 0.0001$) were also factors statistically correlated with survival time (fig. 2d–f).

In fact, the Kaplan-Meier survival curves (fig. 2f) showed that patients with a metastatic volume greater than 15 cm^3 had a far worse prognosis when compared with those with a metastatic volume $\leq 15 \text{ cm}^3$ (survival probability at 20 months: 14.7 vs. 58.2%, respectively).

Of particular interest are the 2- and 5-year survival rates shown in table 1. Metastatic volume turned out to be the variable marking the greatest difference between subgroups as regards survival probability (40.9 vs. 6.8% at 60 months).

To evaluate the relationship between all statistically significant variables, we performed a multivariate analysis with the Cox proportional-hazard regression model. This showed statistical significance only for metastatic volume ($p = 0.0001$) with an instantaneous relative risk of 2.8753 (table 2; fig. 3).

Discussion

Since in 1947 Ackerman and Del Regato [11] had highlighted the need for a melanoma staging system, this has undergone a vast development. The TNM staging system adopted by the AJCC to classify different tumours using consensus criteria was proposed by McNeer and Das Gupta [12] and applied to melanoma staging in 1964. In 1977 the AJCC established the Clark level and the Breslow thickness as 2 important prognostic factors [13, 14]. Fur-

ther prognostic factors not previously considered, such as ulceration, the numbers of involved lymph nodes, the site of distant metastases and the increasing LDH serum levels, emerged in the course of the follow-up of large numbers of patients [15]. The seventh revision of the AJCC melanoma staging system, adopted in 2009 [2], considers as significant prognostic factors for stage IV melanoma patients only the site of metastases and LDH serum levels.

The objective of this study was to evaluate additional factors present at the time of a stage IV diagnosis that may influence prognosis. Because of the limited number of patients analysed, we considered only the variables with a p value < 0.01 as statistically significant. In univariate analysis, our results are in agreement with the 2009 AJCC staging system. Classifying patients in groups M1a, M1b and M1c evidences 3 clusters of patients with different prognoses (fig. 2c). Taken individually, other variables such as the sites of metastases (skin, subcutaneous and lymph node, lung and non-pulmonary viscera; fig. 2a) and elevated LDH serum levels (fig. 2b) also confirm to be statistically correlated with prognosis (table 1). Furthermore, the number of organs affected, the number of metastases and, remarkably, metastatic volume can be considered as factors predictive of survival in stage IV melanoma. The number of organs affected by distant metastases has previously been shown by several authors [4, 16–21] to be a statistically significant predictor of survival probability. Our data add strength to these findings. Patients with a single diseased organ have a 45% chance of 24-month survival; those with 2 diseased organs show a 20.9% probability, while patients with more than 2 affected organs have only a 9.1% chance of survival over the same period (fig. 2e).

The number of distant metastases was established as an important prognostic factor [2, 4, 17, 22] in the past,

Fig. 2. Survival curves comparing the sites of metastases (a), the LDH serum levels (b), the clusters of patients in accordance with the 2009 AJCC staging system (c), the number of metastases (d), the number of affected organs (e) and the metastatic volume (f). SQ = Subcutaneous.

and its validity was confirmed during a preliminary multivariate analysis using the AJCC Melanoma Staging Database. However, this parameter was not incorporated into the latest staging system because of considerable variability in the deployment of diagnostic tests. In order

to avoid a similar bias, our study relies only on bone window CT scan imaging.

To the best of our knowledge, no prior studies have considered metastatic volume as an independent variable when assessing the prognosis of stage IV melanoma

Table 1. Characteristics and predictors of survival in stage IV melanoma patients

Characteristic	Patients		Median survival, months	2-year survival, %	5-year survival, %	log-rank p
	n	%				
Sex						
Male	141	59.0	9.8	25.1	17.4	0.5489
Female	98	41.0	11.2	28.3	15.5	
Age at the diagnosis of stage IV melanoma						
≤40 years	26	10.9	9.4	27.5	18.3	0.3889
41–60 years	57	23.8	10.0	16.1	3.6	
>60 years	156	65.3	10.9	30.1	20.8	
Site of metastases						
Skin, SQ or distant nodes	55	23.0	16.5	39.6	26.2	<0.0001
Lung	58	24.3	16.7	39.8	19.9	
Non-pulmonary viscera	126	52.7	7.0	14.7	11.0	
LDH serum level						
≤250 U/l	133	55.6	11.9	31.5	17.7	0.0063
>250 U/l	106	44.4	8.0	19.9	15.6	
Melanoma stage (AJCC 2009)						
M1a	41	17.2	16.5	40.6	27.5	<0.0001
M1b	41	17.2	19.7	48.4	17.6	
M1c	157	65.7	7.9	17.4	13.5	
Number of affected organs						
1	89	37.2	19.7	45.0	28.5	<0.0001
2	84	35.2	8.9	20.9	15.2	
>2	66	27.6	6.2	9.1	3.6	
Number of metastases						
≤4	86	36.0	16.7	39.9	25.5	0.0003
>4	153	64.0	8.7	18.6	11.7	
Metastatic volume						
≤15 cm ³	75	31.4	30.9	55.7	40.9	<0.0001
>15 cm ³	164	68.6	7.9	13.7	6.8	
Therapy						
BOLD	132	55.2	9.7	23.5	14.1	0.1003
Muphoran	66	27.6	11.2	37.4	29.9	
CVD	41	17.2	12.0	20.3	8.7	

SQ = Subcutaneous; BOLD = bleomycin 15 mg i.v. on days 1 and 4, vincristine 1 mg/m² i.v. on days 1 and 5, lomustine 80 mg/m² p.o. on day 1 and dacarbazine 200 mg/m² i.v. on days 1–5 (the treatment was repeated every 4 weeks); Muphoran = fotemustine 100 mg/m² i.v. weekly for 3 consecutive cycles (induction phase) followed by a 5-week rest period, then cycles of triweekly fotemustine 100 mg/m² as maintenance phase; CVD = vinblastine 1.6 mg/m²/day for 5 days, dacarbazine 800 mg/m² i.v. on day 1, and cisplatin 20 mg/m²/day for 4 days starting on day 2 of chemotherapy (the courses of chemotherapy were repeated at 3-week intervals).

patients. In our study, metastatic volume was calculated from radiologic imaging obtained from CT scans, where each metastasis was considered either as a spherical formation, the diameter of which was the average of the minimum diameter and maximum diameter of the observed lesion, or as a tri-axial ellipsoid, the volume of which was calculated considering the semiprincipal axes of length a, b, c. The great improvement of imaging technology, further bettered over the study period, has allowed an accurate evaluation of even the smallest le-

sions, leaving little or no doubts about their metastatic nature.

Upon the whole, our measurements allowed to establish a cut-off metastatic volume of 15 cm³ over which the prognosis of the affected patients was significantly worse, regardless of the absolute number of metastases or of their location. In other words, the presence of either a single metastasis with a mean diameter (maximum diameter + minimum diameter divided by 2) of around 3 cm (smaller than a golf ball), or of 30 metastases with a mean

Fig. 3. Survival curves of 239 patients with metastatic melanomas at distant sites subgrouped by metastatic volume evaluated by Cox proportional-hazard regression.

Table 2. Impact of variables statistically significant in univariate analysis on survival time analysed with a Cox proportional-hazard regression

	p value	95% CI	Exp(b)
Site of metastases	0.5730	−0.4926 to 0.2717	0.8954
LDH serum level	0.7910	−0.4306 to 0.3276	0.9498
Melanoma stage (AJCC 2009)	0.3030	−0.1980 to 0.6414	1.2482
Number of affected organs	0.0016	0.1668 to 0.7044	1.5458
Number of metastases	0.3772	−0.5628 to 0.2120	0.8391
Metastatic volume	0.0001	0.6386 to 1.4737	2.8753

CI = Confidence interval; Exp(b) = instantaneous relative risk.

Table 3. Impact of metastatic volume (MV) on median survival in patients clustered in 3 groups in accordance with the 2009 AJCC staging system

Characteristic	Patients, n	Median survival, months	2-year survival, %	log-rank p
M1a				
MV ≤15 cm ³	24	20.4	49.7	0.0702
MV >15 cm ³	17	16.3	31.2	
M1b				
MV ≤15 cm ³	23	32.5	58.0	0.0224
MV >15 cm ³	18	16.5	31.5	
M1c				
MV ≤15 cm ³	28	15.1	63.8	<0.0001
MV >15 cm ³	129	6.5	9.3	

diameter of 1 cm distributed across any body part suffice to assess the patient as belonging to the worse-prognosis subgroup. According to our calculations, this proves particularly pertinent to patients in group M1c [2]. As shown in table 3, measurements of metastatic volume in this subgroup of patients identify in a highly significant manner ($p < 0.0001$) those having a poorer prognosis (2-year survival rate: 63.8% for those with metastatic volume ≤ 15 cm³ vs. 9.3% for those with metastatic volume > 15 cm³). Metastatic volume measurements in M1a and M1b group patients apparently had a lower statistical reliability, probably due to the limited number of cases considered. However, also in these groups, patients with a metastatic volume greater than 15 cm³ consistently had a lower chance of 2-year survival. Notably, metastatic volume emerges as the most significant variable ($p = 0.0001$) in distinguishing patients with better or worse prognoses also in multivariate analysis (fig. 3).

The role of metastatic volume in determining survival remains to be understood. Of course, a large metastatic volume may mean more advanced cancer, therefore shorter life expectancy. However, in the present case this explanation is not very likely, since our results identify a rather low cut-off metastatic volume as predictor of impaired survival. A possibility to be considered is that cancer cells produce molecules that may affect the response of the organism to the disease. Indeed, many tumours are known to secrete both RNA and proteins that may act either locally or systemically. For instance, we have shown in the past that metastatic melanoma cells degrade insulin-like growth factor binding protein-3, a circulating and tissue protein with marked antitumoural properties, and that stage IV melanoma patients undergo a marked loss of serum insulin-like growth factor binding protein-3 [23]. Thus, a cancer may reach a threshold volume over which the concentration of cancer-produced molecules becomes capable of exerting systemic effects on the organism.

Obviously, the present results need to be confirmed and refined in larger cohorts of patients. Nevertheless, our data suggest that metastatic volume is a parameter that may merit to be considered in the development of new, or the refinement of former, staging systems, all the more since it can be easily determined at the time of a stage IV melanoma diagnosis.

The median survival of 15.46 months for stage IV melanoma patients observed throughout our data series is consistent with previous studies. Since the pertinent literature extends as far back as 20 years [4], the evident lack of progress in the treatment of stage IV melanoma is disheartening. A number of clinical trials assessing the ef-

fectiveness of new therapies in stage IV melanoma patients is currently under way [24]. It is crucial that groups of patients with similar survival probability are included in these trials. Including metastatic volume among the parameters adopted to estimate survival may be useful to identify a more effective treatment for patients. Currently, for instance, ipilimumab and BRAF (B-Raf enzyme) inhibitors represent a new hope in the treatment of metastatic melanoma. However, BRAF inhibitors have high response rates but low durability, while ipilimumab has low but durable response rates. Currently, interest has turned to combining both agents to achieve more durable responses in BRAF-mutant melanoma patients. The use of BRAF inhibitors to debulk and sensitize a patient's tumour to immunotherapies is an exciting prospect [25]. Melanoma patients with a higher metastatic volume might benefit receiving a BRAF inhibitor as a first-line therapy, as many experts suggest in patients with symptomatic, rapidly growing disease, or with high serum

LDH concentrations. These patients are less likely to benefit from immunotherapy and can achieve rapid improvement in symptoms with a selective BRAF inhibitor. Instead, in patients with BRAF-mutant melanoma who have asymptomatic disease, a normal LDH concentration, and a small metastatic volume, immunotherapy with ipilimumab could be considered as first line, followed by BRAF inhibitors if patients show signs of disease progression.

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Disclosure Statement

None declared.

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