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Melanoma Staging and Sentinel Lymph Node Biopsy

Ana-Maria Forsea

Department of Oncological Dermatology and Allergology, Elias University Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author:
Ana-Maria Forsea, MD, PhD
Stefan cel Mare 44,
Bl 33A, Ap. 52, Sector 2,
Bucharest, Romania
aforsea@yahoo.com

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SUMMARY Tumor staging of melanoma is a crucial step for estimating patient prognosis, deciding on therapy approach, and efficient collection, analysis, comparison and communication of scientific data across borders and research groups. Recently, the Melanoma Staging Committee of the American Joint Committee on Cancer (AJCC) has proposed a revision of the widely used melanoma staging system, using an evidence-based approach, to reflect the improved understanding of this disease. Important adjustments were made related to the role of mitotic rate as a prognostic factor, definition of N category and classification of all microscopic nodal metastases, regardless of the extent of tumor burden, and specifically including micrometastases detected by immunohistochemistry as stage III. These revisions are to be implemented by early 2010 and are likely to be adopted and incorporated in international guidelines. Within the updated AJCC staging system, sentinel lymph node biopsy (SLNB) remains a standard-of-care diagnostic procedure, widely accepted as an important prognostic tool. According to current recommendations, SLNB is routinely offered as a staging procedure in patients with tumors more than 1 mm in thickness. Beyond its prognostic value, the therapeutic benefit of this procedure in improving overall survival yet remains to be proven. This article reviews and discusses the new aspects and challenges of the current staging recommendations for melanoma.

KEY WORDS: melanoma, staging, sentinel lymph node, prognosis

INTRODUCTION

Melanoma staging is a crucial step of melanoma diagnosis and management, as it allows the stratification of prognostic classes of patients and a better-informed treatment decision. At the same time, it is necessary for standardized and efficient collection, analysis and communication of scientific data across borders and research centers, which is indispensable for better understanding of the behavior and characteristics of a tumor that so far defies all human efforts to destroy it.

Melanoma staging systems as a method of patient stratification in prognostic classes are continuously being revised and refined, as new insights into molecular and genetic pathways of tumorigenesis on the one hand, and new statistical data from ever larger multicenter studies on the other hand become available.

Until 2009, melanoma staging worldwide has relied on the last version of melanoma staging system proposed by the American Joint Committee on Cancer (AJCC) in the 6th edition of the Cancer Staging Manual, published in 2001 (1). This system was based on the TNM tumor classification and it was built on an evidence-based

approach using the statistical data obtained from an international, collaborative database of 17,600 melanoma patients.

Implemented in 2002, it was adopted by the International Union against Cancer (IUCC) and has gained wide acceptance worldwide. It was also endorsed by the most prominent European organizations, such as European Dermatology Forum (EDF), European Association of Dermato-Oncology (EADO), European Society of Medical Oncology (ESMO) and European Organization for Research and Treatment of Cancer (EORTC), being consequently included in the latest versions of interdisciplinary consensus guidelines on melanoma management (2,3).

At the end of 2009, the 7th edition of AJCC Cancer Staging Manual was published, proposing a new, revised version of melanoma staging system (4). The new version is meant to be implemented in the US starting from January 2010 and it is likely to become, as the previous one, the accepted melanoma staging system worldwide.

This article aims to offer a succinct overview of the new elements that the 2010 AJCC recommendations bring to the melanoma staging system, with more detailed discussion of the current opinions and debates on the topic of the sentinel lymph node biopsy.

THE 2010 AJCC MELANOMA STAGING SYSTEM

The new revision of the melanoma staging system proposed by AJCC relies on the multivariate analysis of the expanded and updated AJCC Melanoma Staging Database, which contained prospective data on 38,918 melanoma patients, gathered during 2008 from 17 major medical centers, free-standing cancer centers, or cancer cooperative groups at the international level (4). The database included 30,946 patients with stages I, II, and III melanoma and 7,972 patients with stage IV melanoma. This was the largest international cooperative database of melanoma patients to date, allowing the evidence-based revision and clarification of TNM classification and stage grouping criteria.

The new TNM classification (Table 1) and stage grouping (Table 2) proposed by the 2010 AJCC recommendations and their changes from the previous version are discussed below.

T classification

For the primary tumor classification of the new 2010 AJCC staging system, tumor thickness (Breslow index) and tumor ulceration remain the main determinants of T categories stratification. Melanoma thickness continues to be the primary determinant of T staging, with the same thickness thresholds (1, 2 and 4 mm), while ulceration remains the secondary determinant of T and N staging.

The major change that 2010 AJCC version brings to T classification is the introduction of the primary tumor mitotic rate (defined as number of mitoses/mm^2) for categorizing T1 melanoma. Thus, the mitotic rate ≥1/mm^2 replaces the Clark level of invasion for defining T1b melanomas, and Clark invasion level is no longer recommended to be used for melanoma staging.

This change was imposed by the analysis of the AJCC melanoma staging database, which showed that in 10,233 patients with clinically localized melanoma, mitotic rate was the second most powerful predictor of survival after tumor thickness and the increased mitotic rate was associated with lower survival rates in patients with thin melanomas (4). In this analysis, the 10-year survival rate of non-ulcerated T1 melanomas decreased from 95% for tumors with a mitotic rate of less than 1/mm^2 to 88% for tumors with a mitotic rate of at least 1/mm^2 (*P*_.0001) (4). Therefore, the current recommendation is to include the assessment of mitotic rate in the histopathologic diagnosis of all primary melanomas.

The prognostic significance of T classification has been preserved, with 10-year survival rate decreasing from 95% for T1a melanomas to 85% for T1b, 80% for T2 patients (1.01 to 2.00 mm), 63% in T3 patients (2.01 to 4.00 mm), 50% in T4 patients (>4 mm), and 40% in patients with T4b (>4 mm, ulcerated) melanomas.

N classification

For the analysis of lymph node status (N classification), the 2010 AJCC staging system maintains the number of nodal metastases as the primary determinant, and the metastatic volume (microscopic *vs*. macroscopic metastases) as the second determinant of N staging. Both clinical and pathological staging continue to be required for the assessment of lymph node status, as large variability in outcome has been observed between the two staging systems (5). Pathological staging continues to rely on the technique of sentinel lymph node biopsy (SLNB), which the new 2010 AJCC version recommends further as a standard staging tool for melanoma stages Ib and II. Satellite metastases remain included in N category, merged with in-transit lesions.

Table 1. TNM classification of melanoma, AJCC 2010[4]

Classification		
T	Thickness (mm)	Ulceration
Tis	NA	NA
T1	≤1.00	a: Without ulceration, mitosis <1/mm^2 b: With ulceration or mitoses ≥1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	No. of metastatic nodes	Nodal metastatic burden
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In-transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in-transit metastases/ satellites with metastatic nodes	
*Micrometastases are diagnosed after sentinel lymph node biopsy. †Macrometastases defined as clinically detectable nodal metastases confirmed pathologically.		
M	Site	Serum LDH
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Elevated

The changes of AJCC 2010 staging system in N classification refer to the definitions of node metastases.

First, in the new staging system, microscopic nodal metastases (detected following SLNB) can be defined by either hematoxylin and eosin or immunohistochemical (IHC) staining, while previously only hematoxylin-eosin stain was accepted for formal diagnosis of metastases. IHC alone can be accepted if it includes at least one melanoma associated marker (e.g., HMB-45, Melan-A, MART-1) and the cells have malignant morphological features that can be detected in the IHC stained tissue.

RT-PCR evaluation of nodal status is still under debate and not yet accepted as a method of detecting nodal metastases for staging purposes.

The second change is that in the new system there is no lower threshold of tumor burden required for the definition of nodal metastases. While previously only tumor aggregates greater than 0.2 mm could be defined as nodal metastases (1), in the new staging system isolated tumor cells or tumor deposits of any size meeting the criteria for histologic or immunohistochemical detection of melanoma should be scored as N+, with the consecutive prognostic implications.

The prognostic significance of N classification is maintained, with the 5-year survival of node-positive patients decreasing from 70% for patients with T1-4N1aM0 melanomas to 39% for patients with T1-4N3M0 melanomas. Patients with intralymphatic (in-transit/satellites) metastases without

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Table 2. Anatomic Stage Grouping for Melanoma, AJCC 2010[4]

Clinical staging				Pathological staging			
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0	IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0	IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0	IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	AnyT	N>0	M0	III A	T 1-4a T1-4a	N1a N2a	M0 M0
				IIIB	T1-4b T1-4b T 1-4a T 1-4a T 1-4a	N1a N2a N1b N2b N2c	M0 M0 M0 M0 M0
				IIIC	T1-4b T1-4b T1-4b Any T	N1b N2b N2c N3	M0 M0 M0 M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

nodal metastases (N2c) have 5- and 10-year survival rates of 69% and 52%, respectively (Fig. 1C), while those with combined intralymphatic metastases and nodal metastases (N3) have survival rates of 46% and 33%, respectively (4).

M classification

The M classification in the AJCC 2010 system remains unchanged from the previous version. The site of distant metastases and elevated serum lactate dehydrogenase (LDH) continue to be the two dominant components in defining the M category.

The differences in prognosis between distant cutaneous or node metastases, lung metastases and other visceral metastases justify the distinction of three M classes (M1a, b, c). Among 7,972 stage IV patients, one-year survival rates decreased from 62% for M1a to 53% for M1b, and to 33% for M1c melanomas. Elevated serum LDH, irrespective of the site of distant metastases, corresponds to the worst prognostic class, M1c. Stage IV patients in the 2008 AJCC Melanoma Staging Database had an 1-year overall survival rate of 32% if they also had elevated serum LDH, compared to 65% when serum LDH was normal at the time of staging (4).

The new staging system also clarifies the approach to metastases of occult primary tumor. Melanoma metastases without known primary tumor, arising in lymph nodes, skin or subcutaneous tissue, in the absence of other distant metastases, should be regarded as regional disease and consequently assigned to stage III of the tumor rather than to stage IV.

Melanoma stage groupings

Anatomic stage groupings for cutaneous melanoma of AJCC 2010 staging system (Table 2) remains fundamentally the same as in the previous version, however, taking into account the changed definitions of TNM classification highlighted above.

Thus, for stages I and II, primary tumor thickness and primary tumor ulceration remain the main determinants, while mitotic rate with the threshold of 1/mm^2 replaces Clark level of invasion for the definition of T1b melanoma. From the point of view of prognosis, the 10-year survival rate ranges from 93% for stage IA to 39% for stage IIC melanomas.

For patients with stage III melanomas, the most predictive independent factors for survival remain

the number of tumor-bearing nodes, tumor burden at the time of staging (i.e. microscopic *vs.* macroscopic), the presence or absence of primary tumor ulceration, and thickness of the primary melanoma. Five-year survival within substages of stage III ranged from 78% for patients in stage IIIA to 59% in stage IIIB and 40% for patients with stage IIIC melanoma (4).

Stage IV does not have any substages. Although some differences in 1- and 2-year survival rates have been noticed between M1a, 1b and M1c categories, the prognosis of patients with distant metastases remains overall very poor, so that no further stage grouping is recommended for stage IV.

SENTINEL LYMPH NODE BIOPSY

Sentinel lymph node biopsy (SLNB) has been confirmed over the last decade as a minimally invasive, highly valuable prognostic tool for melanoma. Since the presence or absence of melanoma cells in lymph nodes draining the primary tumor site is the strongest predictor of both overall survival and risk of recurrence (4,6), SLNB has taken an important role in melanoma staging and it is recommended by both 2002 and 2010 AJCC melanoma staging systems for standard evaluation of node status in patients with high risk localized primary tumor.

However, the precise value and position of SLNB within the management of melanoma remains a subject of intense international debate, since conflicting opinions exist on the prognostic and therapeutic benefits of this procedure. The main issues of the SLNB controversy relate to the true prognostic value of this method in selected patient subgroups, its therapeutic benefits, its true impact on patient quality of life and of management decisions and, most of all, if it should or not be considered a 'standard of care'for melanoma patients.

Prognostic value of SLNB

Substantial information from clinical trials sustain that sentinel lymph node status is currently the most important predictor of disease-free and overall survival for patients with melanoma of intermediate thickness (1-4 mm Breslow) (6-8). Therefore, SLNB is the most sensitive and specific staging tool available today. Recently, this was confirmed by the MSLT-1 trial (9), to date the largest prospective, multicenter study, which analyzed the consequences of sentinel-node biopsy *versus* nodal observation alone in 1269 melanoma patients, gathering survival data over 5 years. This trial showed that SLN status is the most statistically significant predictor of survival for clinically localized (stage I/II) intermediate thickness melanoma (1-4 mm), with a potential to provide more accurate information for a given patient than demographic (gender) or histopathologic factors of the primary tumor (Breslow depth or ulceration). The 5-year disease-free survival for patients with positive SLN status was 72.3%, compared to 90.2% in those with negative SLN status.

Much more controversy exists regarding the prognostic benefit of SLNB in thin (less than 1 mm) and respectively thick (over 4 mm) melanomas.

For melanoma less than 1 mm, a recent meta-analysis of 3651 patients with melanoma ≤1 mm, enrolled in 34 studies (10) showed that the rate of SLNB specimen positivity in thin melanomas was 5.6%, well below the 10% rate necessary to justify the procedure as determined by the International Sentinel Node Society (ISNS) (11). Other studies (12-16) found similar positivity rates of SLNB ranging from 2% to 4.9% in thin melanomas. Only few reports found a SLNB positivity around the 10% threshold in melanomas less than 1 mm, but over 0.75 mm and ulcerated or with mitotic rate ≥1/mm^2 (10,14).

More important, the same meta-analysis by Warycha *et al*. (10) demonstrated an equal number of melanoma-related deaths in the SNB-positive and SNB-negative groups, which casted serious doubt on the prognostic use of this SLNB in patients with melanomas <1 mm.

The results are even more conflicting for thick melanomas over 4 mm. In some studies, SNB status was found to be a strong independent predictor of survival in melanomas over 4 mm (17-19). One of these latter studies, by Gutzmer *et al*. (19), analyzing 152 patients with thick melanomas, estimated recently that the 5-year overall survival rate was 37.5±8.1% after positive SLNB, in comparison to 67.6±6 6.7% after negative SLNB.

On the contrary, other authors hold SNB status irrelevant for prognosis in thick melanomas (20,21). This opinion is also supported by the argument that patients with thick (>4 mm) melanomas have anyway a high risk of occult distant disease at the time of initial presentation and therefore treatment of regional lymph nodes is not justified given their poor overall prognosis (6,22).

Therapeutic value of SLNB

To date, there is no firm evidence that performing SLNB, followed by early complete removal of

lymph nodes in SLN-positive patients improves overall survival from melanoma, compared to observation and delayed dissection of clinically manifest nodal metastases. Several previous small non-randomized trials provided conflicting results, with limited statistical significance. The most important clinical trial so far addressing this issue was the First Multicenter Lymphadenectomy Trial (MSLT-1), a multicenter, randomized study involving 1347 patients with stage I/II melanoma, randomized to undergo SLNB, with immediate complete lymph node dissection if SNB was positive, or to be kept on observation alone and undergo complete lymph node dissection only if nodal metastases became clinically manifest during the follow-up. The results of the third interim analysis of the 5-year follow-up data of this trial were published in 2006 (9), and did not show any statistically significant difference in overall survival between the two groups of patients.

Beyond this negative conclusion, the MSLT-1 study authors have also reported further secondary end-point results that were strongly contested by the scientific world. Thus, they have reported that patients who underwent SLNB had an improved 5-year disease-free survival compared to those in the observation group. This interpretation of data was disputed (23), based on the argument that disease usually recurs first in lymph nodes, and the apparent survival benefit was due to the fact that SLNB+ patients had their nodes already removed.

Another conclusion of the MSLT-1 study that was highly argued and criticized was an overall survival benefit of SLNB positive patients who underwent immediate complete lymph node dissection (CLND) in comparison to patients from the observation group who underwent delayed CLND only when nodal metastases became clinically manifest. This benefit was widely contested as being the result of underpowered design of the trial and inappropriate subset analysis by the authors (23-25). Moreover, contrary results have been published, like the study by Wong *et al*. (26), which found that patients with melanoma and positive SLNB had similar survival irrespective of whether CLND was performed immediately or delayed until clinically palpable nodes developed.

In these circumstances, definitive evidence is missing that immediate CLND in patients found to be SLN+ brings any overall survival benefit in comparison with observation and delayed CLND. These doubts are sustained by the fact that only 15%-20% of SLNB positive patients are found with further involved nodes on completion of immediate CLND (27,28). This could mean that in the rest of 80% of patients, immediate CLND is actually not necessary and to date no factor has been identified that could accurately predict the involvement of other lymph nodes in SLNB+ patients (29,30). Second, it is not clear that all detected microscopic metastases would eventually progress to clinically relevant disease (31). Therefore, further studies are necessary to clarify if immediate CLND should be further recommended to all SLN+ patients, as currently recommended. To this aim, a decisive body of evidence is expected from the ongoing MSLT-II study, organized by the same multicenter team as MSLT-I. This major trial began accrual in 2005, will include at least 4500 melanoma patients and will determine if for SLNB positive patients, immediate CLND is associated with higher overall survival than observation (32).

Beyond these controversial points related to the therapeutic value and survival benefit of SLNB, numerous trials over the last years have produced sufficient firm evidence to clarify several other important issues. Thus, it was shown that SLNB after wide local excision of primary melanoma did not increase the frequency of local or in-transit recurrences (9,33-35). At the same time, MSLT-1 and other large studies demonstrated that SLNB followed by immediate CLND in SNB+ patients was associated with lower postoperative complication rate (24% *vs*. 41%) and better control of nodal disease (less tumor burden) than delayed therapeutic lymph node dissection for clinically manifest nodal disease (36,37). Delayed CLND of clinically manifest metastatic nodes was associated with an increased number of involved nodes, higher percentage of extranodal tumor extension (37), as well as with higher surgical failure rates (31,38), and higher surgical complication rate and postoperative morbidity (37,39).

Indications and selection of patients for SLNB

AJCC Melanoma Staging Committee currently recommends that SLNB be performed 'in patients for whom the information will be useful for planning subsequent treatments and follow-up regimens'(4), and that this procedure should be required as entry criterion for all melanoma patients in stage Ib or II, before entry into therapeutic trials. Specifically, SLNB is recommended for all T2, T3 and T4 melanomas, without clinically involved nodes and selectively in T1b melanomas.

Many authors suggest that these recommendations should be taken with caution, beyond the

proven prognostic role of SLNB in intermediate thick melanomas.

Thus, the assumed psychological benefit for patients who gain through SLNB more information on their prognosis and could subsequently make better informed decisions and planning is sustained by only very limited evidence (40,41). These small, statistically limited studies suggested only a small and transient psychological benefit for patients after performing SLNB, and highlighted in change an important percentage of patients who actually preferred a higher risk of recurrences to any toxic or invasive procedure. Moreover, beyond the statistical prognosis classes, the individual prognosis of each patient depends on by far more factors than SLN status, while in selected patient groups, such as elderly patients or thick melanoma patients, the prognostic information added by SLNB is very limited (42). As such, the positive impact that performing SLNB may have on patient quality of life and 'peace of mind'remains to be determined.

The utility of SLNB for planning consequent adjuvant treatment is also arguable, as it depends on the existence of effective adjuvant treatment. As far as beyond interferon in selected patient subgroups, no other treatment has yet been proven to be effective for melanoma in adjuvant setting (43-45), this use of SLNB should be advocated with caution.

The recommendation to include SLN status as entry criterion for any further adjuvant therapeutic trials has also raised criticism (23,46). SLN status is currently one of the prognostic factors for melanoma. As the understanding of melanoma biology and evolution advances and studies at the molecular and genetic level bring more insight in the mechanisms of melanoma metastasis or therapy resistance, new refined criteria are expected to emerge, based on primary tumor analysis, that would allow for a more accurate stratification of patients in prognostic classes and better design of therapeutic trials, fitting closer to melanoma behavior. These criteria would put in question the justification of systematic performing SLNB to qualify for an investigational study.

Sentinel lymph node biopsy as a standard of care?

The current international recommendation (11) to offer SLNB as a standard of care to melanoma patients, based on the staging guidelines of AJCC, remains a subject of intense debate.

SLNB has proven benefits, as it is a powerful prognostic tool for stages I and II melanomas, especially in tumors of intermediate thickness (1-4 mm), and is required for melanoma recording and reporting by the current melanoma staging system. It is a minimally invasive procedure, with low morbidity and allows for better control of locoregional disease.

At the same time, its prognostic value is controversial in certain subsets of patients and information on melanoma lymphangiogenesis, intralymphatic spread and behavior of intralymphatic tumoral deposits is still greatly needed in order to clarify the predictive value of sentinel node metastases. SLNB has no proven therapeutic benefit, while immediate CLND, which is systematically performed in SLN+ patients, significantly increases the costs and morbidity of the procedure, is not therapeutically justified in ~80% of patients and it has not yet been definitely proven to bring a survival benefit compared to delayed CLND of clinically manifest node metastases. SLNB is an expensive procedure in that it requires a skilled team and should be performed only in experienced centers, with appropriate interdisciplinary facilities (47). It has been shown that it is not cost-effective for thin melanomas <1.2 mm in terms of costs *per* life-saved (48), and its psychological benefit has not yet been confirmed based on evidence.

Based on these arguments, numerous experts suggest that instead of promoting SLNB as a standard of care in melanoma patients, this procedure should be proposed to patients on the basis of individual evaluation of each case, thorough discussion of indications, benefits and risks with the patients, and of providing the most accurate information available to the patients, in support of their own decision-making.

CONCLUSIONS

The new AJCC Melanoma Staging System is being implemented since the beginning of this year. These recommendations are the result of a wide multinational cooperation and based on the multivariate analysis of the largest set of clinical data on melanoma available so far. International reactions and positions to it are yet expected, but it is very likely that the new staging version, like the previous one, will be incorporated in the international consensus guidelines worldwide.

The main changes to melanoma staging proposed by the 2010 AJCC guidelines are the introduction of mitotic rate >1/mm^2 in the definition of T1b melanoma, replacing in this regard the Clark level of invasion; acceptance of immunohistochemistry

alone as a method of formal diagnosis of lymph node metastases; and elimination of the lower threshold of tumor volume required for the definition of nodal metastases. The new version of staging system has also clarified the definitions of primary tumor ulceration, mitotic rate, microsatellites as well as the staging definition of metastatic melanoma from unknown primary tumor.

In the revised staging system, SLNB continues to be required as a staging instrument, necessary for the identification of occult nodal metastases and for the N classification; it is recommended for all high-risk melanoma patients with localized tumors, specifically to those in clinical stages IB and II, and as entry criterion for all patients who will be enrolled in therapeutic trials. Beyond the prognostic value, the role of SLNB in the management of melanoma remains controversial. Conclusive information regarding the value of SLNB in patient stratification for adjuvant therapy and the benefit of immediate *versus* delayed CLND in SLN positive patients are expected from the current major ongoing trials like the Sunbelt Melanoma Trial (49) and MSLT-II (32). Their results are expected to bring decisive arguments in the debate on the definition of SLNB as a standard of care in melanoma patients.

AJCC melanoma staging system is an important tool for statistical evaluation of the prognosis, and for standardized, comparable gathering, analysis and communication of clinical melanoma data from medical practice and clinical trials. However, to estimate the prognostic and survival chances of individual patients, additional factors beyond the current staging system criteria should be taken in account. These comprise clinicopathologic and phenotypic factors like age, sex, tumor location (50), while other potential prognostic markers have emerged from recent studies on melanoma molecular and genetic characteristics (51). Presently, several attempts have been made to integrate these additional factors in the mathematical models of prognosis prediction for individual patients, based on which internet-based tools of prognostic calculators have been developed (52,53). These may better assist individual patients in planning and personalized treatment decision, while being under constant improvement as new information on melanoma behavior and course become available.

The 2010 AJCC Melanoma Staging System represents an improved staging tool, based on consistent clinical data available to date. It is one step further on the way on which our deeper understanding of the stage-specific prognostic factors and the expansion of molecular-based profiling studies of melanoma will eventually provide more refined and precise instruments of individualized prognosis assessment and treatment decision in melanoma patients.

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