Management of cutaneous melanoma: comparison of the leading international guidelines updated to the 8th American Joint Committee on Cancer staging system and workup proposal by the Italian Society of Dermatology

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The melanoma care landscape is changing fast in the last years. As a result of new insights in melanoma biology, prognosis and therapeutic options, both the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) Classification of Skin Tumors underwent substantial changes in 2018. Consequently, all the leading guidelines on melanoma management have been updated. Most of the recommendations derive from systematic reviews, while others are based on expert opinion, due to the lack of high-level evidence in some aspects of melanoma management. We provide a revision of all the available guidelines that have been updated to the 8th version of the AJCC classification system. Comparison is not provided for topics on which there is agreement on the standard of care.

Finally, we present a workup proposal summarizing all the recommendations suitable to the Italian context, based on expert opinion.

Clinical presentation

The clinical characteristics of cutaneous melanoma largely depend on body location and it is subclassified as following:

• superficial spreading melanoma. The most frequent clinical subtype, usually presenting on trunk and extremities as a light-to-dark brown or black flat macule. With time, development of a palpable elevated or papular component, appearance of multiple colors, shape and border irregularity may occur;[1]

• lentigo maligna and lentigo maligna melanoma. It occurs on chronically sun-damaged skin, most commonly on face, as a long-standing tan macule slowly expanding peripherally. Change in color (light brown, dark brown, and black areas) and regression (whitish areas within the lesion) may occur when lentigo maligna (*in-situ* melanoma) becomes invasive (lentigo maligna melanoma);[1]

• acral melanoma (or acral lentiginous melanoma). It develops much more frequently on the soles compared to the palms, presenting as a pigmented flat lesion with variable shades of brown or black color.[1] Subungual melanoma (nail melanoma) usually originates from melanocytes of the nail matrix. Clinically it presents with a brown to black pigmented band that extends from the proximal nail fold to the distal end of the nail plate;

• nodular melanoma. Usually presents as blue to black, but also pink to red, fast-growing nodule which may be ulcerated or bleeding. Nodular melanoma arises as a *de novo* vertical growth phase tumor without the pre-existing horizontal growth phase, being associated to a poorer prognosis.[1]

Weigh up the issue: melanoma statistics in Italy

Incidence

In 2018 in Italy, an estimated 13.700 patients have been diagnosed with melanoma, 7200 men and 6500 women (4% of all cancers in both sexes).[2] Melanoma is the second cancer in men and the third in women younger than 50 years (9% and 7% of all tumors, respectively). In the age groups 50-69 years and 70+ it represents respectively the 3% and 2% of all cancers in both sexes.

The incidence of melanoma continues to increase dramatically, at an overall rate of 43% from 2010 to 2017 and at an annual rate of 3.4% for men and 2.0% for women in 2018.[2] Noteworthy, the incidence is higher in the central-northern regions while in the south the incidence is 45% lower in men and 42% lower in women.[2] The lifetime risk of developing cutaneous melanoma is 1 in 58 for men and 1 in 77 for women. In young men the risk is lower while in women the risk is steady in all age groups.

Mortality

In 2018 in Italy there were 1.943 deaths from melanoma (1.136 men e 807 women) that represent 1% of cancer-related deaths in both sexes. Mortality is slightly higher in the younger age groups. The lifetime risk of death from melanoma is 1 in 281 for men and 1 in 534 for women. As opposed to incidence, the trend of mortality from melanoma is stable, but standardized rates are still higher in the northern regions in both men and women (+26% and +9%, respectively).[2]

Survival

Based on 2018 AIRTUM data, the relative 5-year melanoma specific survival (survival in the absence of other causes of death, which is calculated using survival life tables) was 87%, meaning that 13 out of 100 patients diagnosed with melanoma will die of the disease in the next 5 years after diagnosis.[2] The 5-year survival has increased in the last fifteen years (76.5% in the period of incidence 1990-1994) especially in men (+14%) partially due to overdiagnosis and to a broader diffusion of early-diagnosis tools (self-examination and opportunistic screenings). The 5-year survival is reported to be different among age groups, being 94% in patients aged 15 to 44 years *versus* 73% in the elderly (75+ years). Also, different geographic areas show different survival rates, with higher values in the central-northern regions with respect to the south. Italian survival statistics are similar to those in Northern Europe (88%) but are lower than those in US (93%) and Australia (90%).[2]

Risk factors

The risk of onset of cutaneous melanoma is linked to genetic, phenotypic, and environmental factors, as well as to combinations of these (Table I). The risk of superficial spreading melanoma and nodular melanoma has been reported to increase with intermittent intense sun exposure to high-intensity sunlight (*e.g.*, sunbathing or holidaying in a place with strong sunlight).[3] The risk of these melanoma

TABLE I.—*Melanoma risk factors.*

Genetic factors
• Personal or family history of melanoma
• Genetic syndromes (melanoma-subordinate syndrome): Li-Fraumeni syndrome; Cowden syndrome; xeroderma pigmentosum
• Genetic syndromes (melanoma-dominant syndrome): familial atypical mole and malignant melanoma syndrome (FAMM); CDKN2A, CDK4, BAP1, POT1 mutations
Phenotypic factors
• Phototype I-II
• High total nevi count and presence of atypical nevi
• Presence of giant congenital nevus
Environmental factors
• Sun exposure (intermittent intense sun exposure to high-intensity sunlight, sunburns)
• Artificial UV sources (tanning beds)
• Immune suppression
• Previous radiation therapy

variants is more than doubled in people with a history of sunburn, compared with people who have never been sunburned and the increased risk of melanoma is irrelevant of whether sunburn occurred in childhood or adulthood.[4] In contrast, chronic sun exposure (*e.g.*, being in an outdoor occupation) — for which a relationship with the risk of non-melanoma skin cancers and the risk of lentigo maligna melanoma have been well-established — has not been reported to increase risk of superficial spreading melanoma and nodular melanoma, unless it is associated to histological and other clinical features of severe chronic photodamage.[5] In fact, a chronic moderate and suberythemogenic exposure might even protect from developing melanoma in melanocompetent subjects because of a protective effect of tan, adaptive increase of the stratum corneum and other photoprotective cellular mechanisms.[6] Artificial UVA in tanning booth has been found to increase significantly the lifetime risk of melanoma because UVA as well as UVB radiations induces mutagenic DNA photoproducts and other cell damages with a carcinogenic potential and artificial tanning is not photo-protective against further sun exposure.[7]

People with fair complexion, blue gray or green eyes, red or blond hair, and lots of freckles are at higher risk of developing melanoma as compared to people with other skin types. In particular melanoma risk is almost double for all people with skin phototype II and is 35% higher for people with skin phototype III, always compared with the melanoma risk for those people having skin phototype IV.[8]

Among phenotypic factors, the total number of nevi is a very useful predictor for melanoma; it is considered the most commonly associated risk factor for melanoma and it can easily be documented in all Caucasian populations. Individuals with a large number (50-100) of common nevi exhibit a melanoma risk that is nearly 7 times higher than those with very few (less than 15) moles.[8] Melanoma risk increases by around 2% for every additional common mole, while individuals with atypical nevi have a 4-10 times higher risk of melanoma when compared to those who do not have atypical nevi.[8]

Melanoma is also observed at higher-than-expected rates in other hereditary cancer syndromes as xeroderma pigmentosum, Cowden syndrome, and Li Fraumeni syndrome even if it is less frequent than other cancer types (melanoma-subordinate syndrome).[9]

With regards to iatrogenic exogenous factors, radiotherapy for a previous cancer increases the risk for melanoma and the risk is 2.4 times higher in organ transplant recipients compared with that in the general population.[8]

Familial melanoma

A small proportion of melanomas (approximately 5-12%) occurs in patients with a family history of melanoma. About 45% of familial melanomas have been attributed to inheritance of a mutation in a highly penetrant predisposition gene while the remaining 55% is likely due to the inheritance of lower-penetrance predisposition genes and/or shared environmental exposures.[10]

Among highly penetrant predisposition genes the most common is the *CDKN2A* gene, which is involved in approximately 20-40% of large, high-risk families. Families that carry a germline mutation in *CDKN2A* have an increased risk for different cancer types like melanoma, pancreatic cancer, and neurological tumors. Individuals in these families frequently, but not always, have a large number of atypical moles. A substantially increased number of atypical moles in the setting of CDKN2A mutation has been termed familial atypical mole and malignant melanoma syndrome (FAMMM). Other high-penetrant predisposition genes include CDK4, BAP1, POT1 (melanoma-dominant syndrome).[11]

According to the "rule of twos or threes"[12], in areas with lower melanoma incidence (rate <10 per 100,000), such as Italy, genetic counseling for CDKN2A mutation should be considered for individuals or families with a history of two or more melanomas (or melanoma and pancreatic cancer combinations). While in US only invasive melanomas are taken into account, it has been determined that in situ melanomas can be included in the "rule of two" criteria applied to the Italian population.[13] The melanoma gene panel for screening hereditary predisposition should include CDKN2A, CDK4 and BAP1. It is recommended to add also POT1 and MITF. Testing other genes is only for research purposes.

Melanoma care pathway

Following a specific cancer care pathway provides a consistent, safe, high-quality and evidence-based care for patients with cancer. The optimal steps in the journey of a patient suffering from cutaneous melanoma according to the Italian Society of Dermatology (SIDeMaST) are outlined in Figure 1, 2, 3, 4, 5, 6.

A preliminary stage is the screening supplied first by general practitioners (primary care) and then by dermatologists working in the territorial health care (secondary care). Physicians of the primary and secondary care should refer to the tertiary care only patients with suspicious lesions or patients already diagnosed with melanoma (Figure 1). Invest-

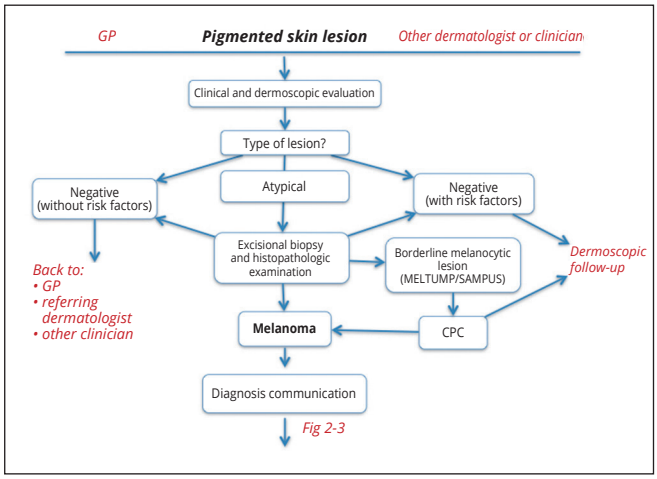

Figure 1.—Preliminary workup in case of a suspicious pigmented cutaneous lesion.
GP: general practitioner; CPC: clinical pathological correlation.

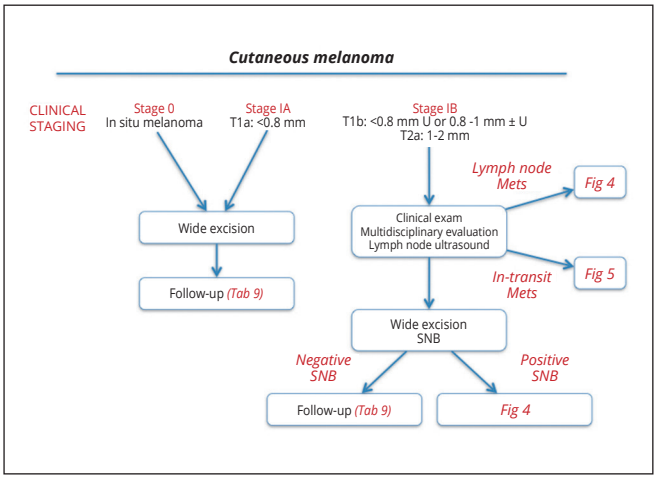

Figure 2.—Workup according to clinical staging (Stages 0-I).
SNB: sentinel node biopsy.

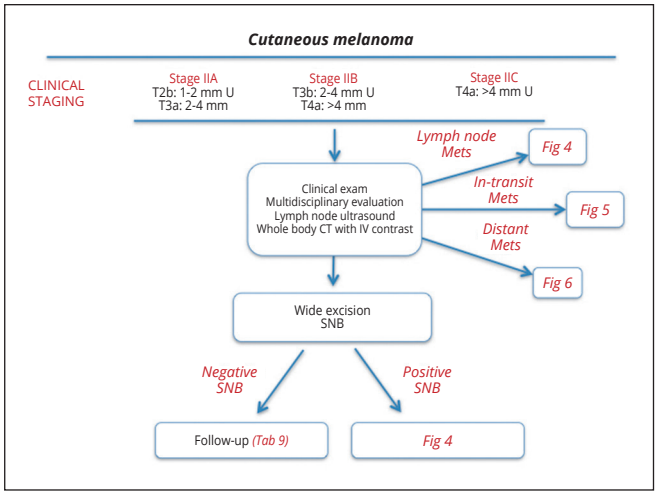

Figure 3.—Workup according to clinical staging (Stage II).
CT: computed tomography; IV: intravenous; SNB: sentinel node biopsy.

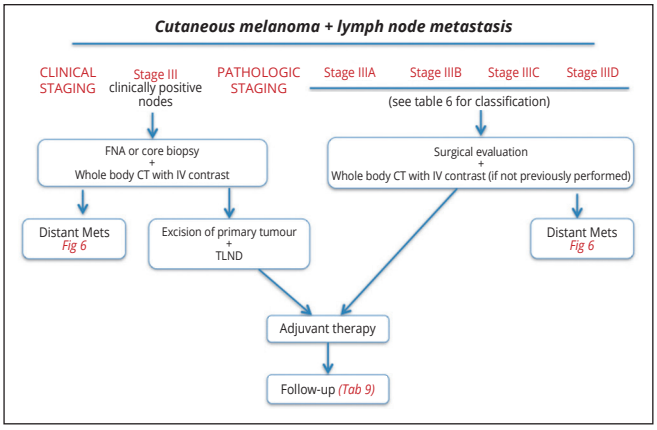

Figure 4.—Workup in case of lymph node metastasis clinically detected (Stage III with no sub-classifications) or pathologically detected after performing SNB (Stages IIIA-D). In patients with borderline resectable lymphadenopathy or high risk of recurrence after surgery consider clinical trial or adjuvant treatment.
FNA: fine needle aspiration; CT: computed tomography; IV. intravenous.

ing into educational programs and promoting connection between clinicians in the territorial health care and referral centers is crucial to allow melanoma early-detection as well as to avoid long waiting lists in the tertiary care centers.

In tertiary care settings there should be an integrated team approach in which all the specialists involved in the management of melanoma (dermatologist, oncologist, surgeons, radiotherapist, radiologist, pathologist, geneticists and molecular biologist) take into considerations all relevant treatment options and collaboratively develop an individual treatment and care plan for each patient.

Diagnosis: total body skin examination, dermoscopy and reflectance confocal microscopy

Total body skin examination (TBSE) is a recommended method to facilitate early detection of melanoma. The 20-nevi on the arms rule has been proved to be an accurate, simple and practical method for the identification of high-risk patients deserving TBSE.[14]

Dermoscopy improves the sensitivity and specificity of clinicians for melanoma diagnosis; it allows the detection of clinically inconspicuous melanomas (earlier stages) and

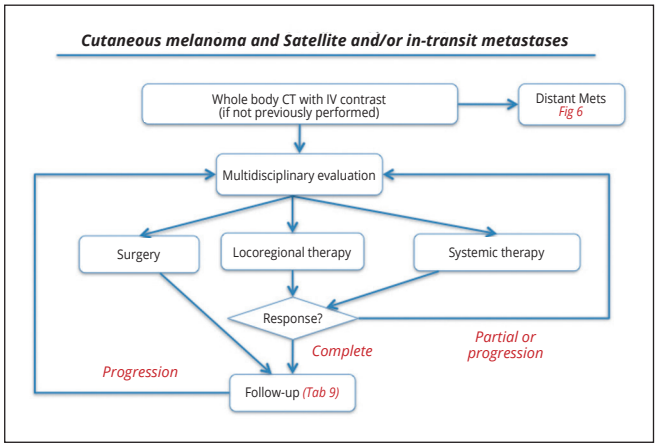

Figure 5.—Workup in case of satellite and/or in-transit recurrence.
CT: computed tomography; IV: intravenous.

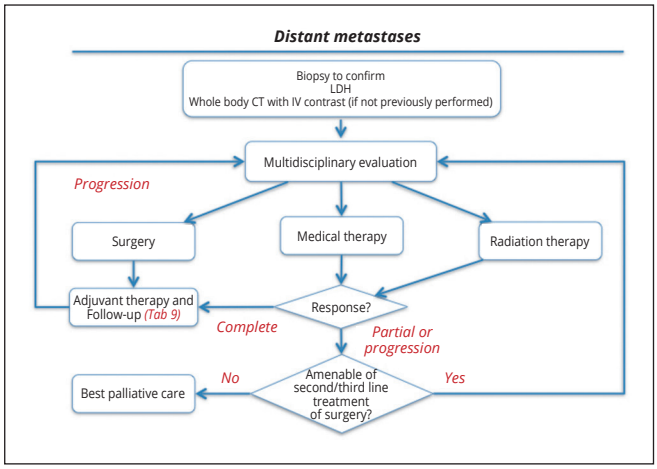

Figure 6.—Workup in case of distant metastases.
CT: computed tomography; IV: intravenous; LDH: lactate dehydrogenase.

enables the recognition of benign lesions that might look clinically worrisome, reducing therefore, the number of unnecessary excisions.[15] Dermoscopy should be always used to perform TBSE in secondary care settings.

Total body photography (TBP) and sequential digital dermatoscopic imaging (SDDI) are two helpful tools for the diagnosis of melanoma in patients with multiple nevi and atypical mole syndrome with or without a previous history of melanoma.[16, 17] TBP describes the use of clinical photography to provide a photographic record of patients' entire skin surface. SDDI is performed in two settings: short-term dermoscopy monitoring (over a period of 3 months) for suspicious melanocytic lesions without evidence of melanoma, and long-term monitoring for surveillance (usually at intervals of 6-12 months). Long-term monitoring is generally used in the surveillance of high-risk patients, usually with multiple atypical nevi. In contrast, short-term monitoring of individual suspicious nevi can be used in any patient setting. Several authors have advocated that a multimodal approach with the combination of TBP and SDDI provides optimal surveillance in high risk patients and may assist with early melanoma diagnosis.[18] However, the definition of criteria for selection of patients deserving of total body imaging and/or sequential digital dermatoscopic imaging is essential to avoid false positive findings in low-risk patients and long waiting lists in tertiary care centers.[19]

In tertiary care settings reflectance confocal microscopy is a second-level examination tool for dermoscopically difficult-to-diagnose lesions. It is also useful in the case of facial lesions for which a biopsy is not always accepted by the patients and sufficient for the pathologist to make a conclusive diagnosis.[20]

Noninvasive diagnostic tools for melanoma diagnosis

Total Body Skin Examination and Dermoscopy are the mainstay of melanoma diagnosis. Total Body Photography, Sequential Digital Dermatoscopic Imaging, and confocal microscopy are additional tools in case of difficult to diagnose lesions.

Diagnosis: excision and pathology report of the primary tumor

Any suspicious cutaneous lesion should be excised with 1- to 3-mm clinically negative margins (Figure 1). Prebiopsy photographs are an important aid to clinical/pathologic correlation. Surgical excision should be performed along underlying lymphatic channels in the extremities and considering the possibility of a subsequent wide-excision. Wider margins or flaps should be avoided.

Incisional biopsy for diagnostic purpose can be performed in large lesions or lesions located on anatomic areas such as nails, palm/soles, genitalia and head/neck region; it should include the thickest portion of the lesion; there is no evidence that incision of a primary melanoma affects survival or prognosis.[21, 22]

Shave biopsy should be avoided as it may impair the correct evaluation of Breslow thickness, but it is possible that lesions with low clinical suspicion undergo this procedure.

TABLE II.—*Definitions of the most relevant parameters of the pathology report.*

Criterion	Definition	Value
Histotype (WHO, 2018)	• Low-CSD melanoma (superficial spreading melanoma; low-CSD nodular melanoma) • Melanoma in chronically sun-exposed skin (lentigo maligna melanoma; desmoplastic melanoma; high-CSD nodular melanoma); • Melanoma arising in sun-shielded sites or without known etiological associations with UV radiation exposure (malignant Spitz tumor [Spitz melanoma]; acral melanoma; mucosal melanoma; melanoma arising in congenital nevus; melanoma arising in blue nevus; uveal melanoma)	Correlation among clinical, histopathological, and genetical features
Breslow thickness	Tumor thickness, measured from the granular layer of epidermis (or, if ulcerated, the base of the ulcer) to the deepest point of tumor invasion (both the leading edge of a single mass or an isolated group of cells deep to the main mass). Measurements are recorded to the nearest 0.1 mm. Microsatellites should not be included.	Staging criterion
Ulceration	Tumor-induced full-thickness epidermal defect above dermal melanoma growth, with reactive tissue changes (fibrin, neutrophils) and atrophy or hypertrophy of the surrounding epidermis, with no history of trauma.	Staging criterion
Mitotic rate	'Hot spot' method: microscopic assessment at 400x magnification, starting from the field with the greatest number of mitoses and then covering an area of 1 square mm, usually corresponding to four 400x fields.	Prognostic factor (-)
Regression	Replacement of a portion of dermal tumor tissue by fibrosis with newly formed vessels and a variable amount of lymphocytes and melanophages. To be reported as 'focal' (regression of a portion of the dermal component), 'partial' (regression of the entire dermal component) or 'complete' (regression of the whole tumor). The percentage of the tumor involved by regression may be specified if up to 75% or more than 75% of the horizontal breadth of the tumor	Prognostic factor (controversial)
Microsatellitosis	Microscopic cutaneous and/or subcutaneous metastasis adjacent/deep to and completely discontinuous from a primary melanoma with unaffected stroma occupying the space between - identified on pathological examination of the primary tumor site. There is no minimal threshold or distance from the advancing edge of the tumor for defining microsatellites; however, the intervening tissue should be not scar-like or inflamed, because these features might indicate focal regression. The histologic report of microsatellites should be delivered only after examination of multiple tissue sections, in order to rule out a simply discontinuous tumor growth.	Staging criterion
Lymphovascular and perineural invasion	Presence of intravascular tumor deposits that cannot be attributed to "artifacts" (cells intimately admixed with blood cells, focally adherent to the vessel wall) - Presence of cancer cells along nerves and/or within the neuronal sheath.	Prognostic factor (-)
Status of the surgical margins	Microscopically measured distances between tumor and ink-labelled lateral or deep margins	Indication to further surgery

(-): negative prognostic factor.

The pathology report must include the primary histologic subtype, Breslow thickness, ulceration, mitotic rate, lymphovascular and perineural invasion (if presents), microsatellitosis and lateral and deep surgical margins. If present, regression should be reported even if its role is still debated, and it does not influence the final stage. Detailed data on pathology criteria are listed in Table II.

Although the primary histologic subtype was not considered an independent prognostic factor and has not been included in the AJCC classification system, the WHO 2018 classification has proposed a correlation among the 'classical' histological subtypes of melanoma, the pathogenetic role of sun exposure, and the genetic background (with the respective [actionable] mutations) of the tumor.

Biopsy of the primary melanoma

Initial excisional biopsy with 1- to 3-mm negative margins is recommended. Incisional biopsy can be performed in case of large or special-site lesions.

Clinical staging

The AJCC staging system is the most used worldwide.[23] In the 8th edition, the clinical stage is defined by information derived from the excision of the primary tumor (Breslow thickness and ulceration), from clinical/radiological assessment for regional and distant metastasis, as well as biopsies performed to assess for regional and distant metastases, as appropriate.[24]

TABLE III.—*Comparison of baseline imaging workup according to stage among the international guidelines updated to the updated to the 8th AJCC staging system and SIDeMaST proposal.*

	National Comprehensive Cancer Network (NCCN)	Cancer Council Australia	AIOM	SIDeMaST
Stage 0	Imaging not recommended	Imaging not recommended	Imaging not recommended	Imaging not recommended
Stage I	Ia: Imaging not recommended Ib: *Consider* NBU prior to SNB for melanoma patient with an equivocal physical exam	Imaging not recommended	Ia: *Consider* NBU for melanoma patient with an equivocal physical exam Ib: NBU prior to SNB - Abdomen ultrasound	Ia: *Consider* NBU Ib: NBU prior to SNB
Stage II	*Consider* NBU prior to SNB for melanoma patient with an equivocal physical exam CT or PET/CT not recommended	Imaging not recommended	IIa: NBU prior to SNB - Abdomen ultrasound IIb: NBU prior to SNB - Abdomen ultrasound - chest CT IIc: CT or PET/CT	NBU prior to SNB CT or PET/CT
Stage III	IIIa (with positive SNB): *Consider* imaging (CT or PET/CT) IIIb/c (with positive SNB): CT or PET/CT recommended III (with satellite or in transit mets or with clinically positive nodes): CT or PET/CT recommended. *Consider* brain MRI for asymptomatic stage IIIc patients	III (with positive SNB): Ultrasound may be used for identification of the extent of in-transit and nodal disease, and also used to diagnose liver metastases. Consider NOT performing CT or PET/CT III (with clinically positive nodes): CT or PET/CT recommended	CT or PET/CT	NBU prior to SNB CT or PET/CT *Consider* Brain MRI
Stage IV	CT or CT/PET + brain MRI Serum LDH level	Whole body PET/CT recommended (superior diagnostic accuracy over CT) Serum LDH level	CT or PET/CT Serum LDH level	CT or CT/PET Serum LDH level

Unless otherwise specified CT refers to brain, lung and abdomen (whole body) CT with intravenous contrast and PET/CT to whole body FDG combined PET/CT. NBU: nodal basin ultrasound; CT: computed tomography; PET/TC: positron emission tomography combined with computed tomography; SNB: sentinel node biopsy; LDH: lactate dehydrogenase.

According to the clinical stage, guidelines define different diagnostic and therapeutic pathways for melanoma patients. Information derived from the subsequent workup (wide excision, pathological data about SNB ±CLND and imaging) contributes to build up the pathological stage. The guidelines vary from one Country to another due to the absence of high-quality trials on baseline staging procedures and, presumably, even due to differences in health care reimbursement systems.

Our proposal is outlined in Figure 2, 3, 4, 5, 6. The differences with the main guidelines (currently updated to the 8th AJCC staging system), namely National Comprehensive Cancer Network,[25] Cancer Council Australia,[26] and the Italian Association of Medical Oncologists[27] guidelines, are summarized in Table III.

With regards to loco-regional metastases, in both stages I and II, neither NCCN nor the Australia Cancer Council guidelines[28] advice to perform nodal basin ultrasound prior to sentinel node biopsy (SNB). NCCN guidelines advice to consider it only for a patient with an equivocal physical exam. Nevertheless it has been demonstrated that nodal basin ultrasound allows detecting clinically negative nodes that already show signs of neoplastic invasion,[29] thus achieving better sensitivity and specificity than clinical examination alone.[30, 31] It is likely that regional nodal ultrasound for melanoma detection is less commonly used in some countries (US and Australia), as it requires specific radiologic expertise and understanding of established lymph node criteria.[32] Moreover, high-resolution ultrasound showed better value than PET/CT in preoperative identification of positive nodes.[33]

Regional nodal ultrasound may be considered in stage Ia patients. SIDeMaST advice to perform routine regional nodal ultrasound from stage IB onwards at first diagnosis, as detection of clinically occult lymph node metastases may switch surgical treatment to upfront therapeutic lymph node dissection.

In order to preliminary detect distant metastases, nei-

ther the NCCN nor the Australian guidelines suggest whole body CT or PET/CT for stage I and II patients, while AIOM guidelines suggest abdomen ultrasound even in stage IB patients. NCCN guidelines advice to perform whole body CT or PET/CT prior to SNB in case of palpable disease, satellite or in-transit metastases (clinical stage III) and in stage IIIB/C patients diagnosed after a positive SNB (pathological stage III). In pathological stage IIIA patients, NCCN guidelines state that whole body CT or PET/CT can be "considered".[25] The Australian Cancer Council suggests to perform whole body CT or PET/CT in clinical stage III patients and to "consider to not perform" it in pathological stage III patients.[34] However, these recommendations are categorized as grade C. AIOM expert panel recommends performing chest CT plus abdomen and nodal basin ultrasound in stage IIA patients, and whole-body CT or PET/CT from stage IIB onwards.[27] Indeed, it has been demonstrated that initial CT let to identify clinically occult melanoma metastases in 8.1% of patients affected by melanoma of the head and neck, thus leading to a change in practice.[35] Moreover, analyses from the first oncologic PET/CT registry in Germany showed that the use of PET/CT imaging in melanoma resulted in a 46% change of clinical management.[36] SIDeMaST suggests performing brain, lung and abdomen CT with contrast (henceforth referred as whole-body CT) from stage IIa onwards.

In stage IV, whole-body imaging is recommended, as well as testing of serum LDH level, as elevated level is associated to worse survival and it may predict response to therapy. Australia Cancer Council recommends whole body PET/CT for its superior diagnostic accuracy over CT while brain MRI is widely preferred to diagnose and monitor brain metastases.

With regards to laboratory tests, the most extensively studied blood test in melanoma staging and follow-up is serum S100β. Miliotis *et al.*[37] reported that S-100β alone had a sensitivity and specificity of detecting recurrent melanoma of 43 and 94 percent, respectively.[37] In addition, protein S100β and melanoma-inhibitory activity (MIA) demonstrated a higher sensitivity, specificity, and diagnostic accuracy in the diagnosis of newly occurring metastasis than alkaline phosphatase (AP), LDH, and tyrosinase reverse transcriptase-polymerase chain reaction (RT-PCR) diagnostics.[38] The results of a meta-analysis performed by Mocellin *et al*.[39] suggested that S100β may play a role in follow-up care of patients with Stage I to III disease but should not be implemented routinely as a prognostic biomarker for management of all patients with melanoma. Only the German, ESMO, and Swiss guidelines recommend using S100β in follow-up care. Serum S100β is not employed routinely in the United States given its prognostic value is limited to advanced/disseminated melanoma and lack of superiority over serum LDH. Given conflicting data, S100β is not recommended by SIDeMaST as a routine test in staging and follow-up of melanoma patients.

Interestingly, the use of LDH was not specifically recommended by any of the organizations presented in this article except by the NCCN and AAD for its use in the initial workup of Stage IV melanoma patients. SIDeMaST recommends the LDH dosage in stage IV melanoma and stage III melanoma patients who are amenable of adjuvant therapy and encourages it from stage IIc onwards.

Wide excision

Surgical treatment of the primary tumor is completed by wide margins excision aimed to minimize the risk of local recurrence. The purpose of a wide excision is to remove local micrometastases and otherwise phenotypically normal tissue that might be harboring genotypically abnormal cells located in either the surrounding skin or superficial lymphatics. In stages 0 and IA wide excision is performed alone while from stage IB onwards it is associated to SNB. Excision recommendations are based on measured clinical margins taken at time of surgery and not on histologic margins, as measured by the pathologist.

Radial margins recommended according to T category are listed in Table IV. However, this topic is still much debated. Data from the long-term follow-up of the "UK excision margin trial" suggests that excision margin of 1 cm is associated with worse disease-specific survival in cutaneous melanomas with Breslow thickness greater than 2 mm on the trunk and limbs.[40] In contrast, a long-term retrospective study did not demonstrate any differences in recurrence rate, local metastases, or overall survival between 1- and 2-cm margins in melanomas thicker than 2 mm. A critical interpretation of the data, however, suggests that this subgroup of patients with worse prognosis in case of a narrower excision is small and that most patients could be safely managed without creating 4-6 cm wide excision

TABLE IV.—*Radial margins recommended according to Breslow thickness.*

In situ	0.5-1.0 cm
<1 mm	1.0 cm
>1-2mm	1.0-2.0 cm
>2-4 mm	2.0 cm
> 4 mm	2.0 cm

defects.[41] It is likely that these patients suffer from aggressive melanomas presenting with micrometastasis already at the time of diagnosis.

Sentinel node biopsy

Sentinel node biopsy (SNB) is a minimally invasive surgical procedure aimed to detect nodal metastases in patients with clinically occult disease. The role of SNB in melanoma has been extensively debated over the last years. SNB technique evolved from the observation that most primary cutaneous melanomas spread initially through the intradermal lymphatics to the regional nodes and then move to distant sites. According to the "incubator hypothesis", the primary melanoma sends immunosuppressive factors to the sentinel node; these signals foster a nodal microenvironment that favors the growth of tumor cells, which subsequently spread to non-sentinel nodes and then to distant sites.[42] This sequential model of melanoma metastasis has not been universally accepted and has been lately disproved by the results of two multicenter selective lymphadenectomy trials (MSLT-I and MSLT-II). Currently sentinel node is considered an "indicator" of disease as its status illustrates metastatic potential, but removal cannot prevent further spread. This concept is reaffirmed by a recent systematic review by the American Society of Clinical Oncology (ASCO) and the Society of Surgical Oncology (SSO)[43] aimed to update the guideline for SLN biopsy in melanoma. Twelve articles were selected; most studies were retrospective; there was one prospective but nonrandomized study, while only the MSLT-I had a randomized controlled study design. Results from the MSLT-I showed that SNB does not impact survival but is associated with a benefit in terms of rate of recurrence within the primary tumor region.[44] The joint ASCO-SSO guideline panel recommend SNB biopsy as a staging procedure that can help identify patients with intermediate thickness melanoma who may benefit from adjuvant therapy. The prognostic significance of SNB has been established and incorporated into the 8th AJCC staging system. SNB is recommended for patients with primary melanoma greater than 1 mm in thickness and it has to be considered for T1b patients (0.8 to 1.0 mm Breslow thickness or <0.8 mm Breslow thickness with ulceration) after discussing with the patient the benefits and risks associated with the procedure. Anyway, overall rates of SLN positivity in this subset of patients is still relatively low (<5-12%) (AJCC).

According to NCCN guidelines decision not to perform SNB may be based on significant patient comorbidities, patient preference, or other factors, in which case follow-up with regional basin ultrasound may be considered. With regard to patient age, although SNB may have less prognostic value and may be technically more difficult in older individuals, there is currently no consensus for an upper age cut-off to recommend against this procedure.[32]

SNB should be performed in a center with expertise in the procedure, including nuclear medicine, surgery and pathology to optimize the accuracy of the test.

It is recommended that the pathology protocol for the examination of the sentinel node should follow the updated European Organisation for Research and Treatment of Cancer (EORTC) protocol.[45] Although the differential criteria between nodal nevus and nodal metastatic melanoma are well established,[46] it is accepted that some cases may remain 'histopathologically undefined'; for practical purposes, such cases should be managed as being node-negative.

Complication rates for SNB vary from 6-14% and are significantly lower than for completion or therapeutic lymphadenectomy.[47] Complications predominantly consist of seroma and wound infections; these are usually mild, manageable and of limited duration. Complication rates are inversely correlated with procedure volume.[47]

The AJCC Melanoma Expert Panel and the International Melanoma Pathology Study Group are working to standardize histologic measurements of SLN tumor burden and other factors that may affect survival.

Melanoma staging

- Regional lymph node ultrasound and sentinel node biopsy from stage Ib onwards.
- Whole body computed tomography from stage IIa onwards.
- LDH dosage from stage III (adjuvant setting) onwards.
- Sentinel node biopsy is recommended for patients with primary melanoma from stage T1b onwards.

Completion lymph node dissection

Routine elective completion lymph node dissection (CLND) has traditionally been recommended and performed following a positive SNB because approximately 8% to 20% of patients will harbor non-sentinel nodal metastases. Lately, the therapeutic role of CLND has been questioned, not only in melanoma but also in other cancers, including breast cancer.[48]

Results from the MSLT-II[49] trial and the DeCOG-SLT[50] trial showed that in melanoma patients early CLND improved disease-free survival (DFS), but did not increase distant metastases free survival (DMFS), melanoma-specific survival (MSS) and overall survival (OS). In addition, it is associated with a high incidence of lymphedema.

Immediate CLND in stage IIIA melanoma does not provide significant additional information (up-stage) beyond the information given by sentinel node tumor burden (stratification of the sentinel node positivity according to the Rotterdam criteria for the maximum diameter of the largest metastasis expressed as an absolute number).[51] Also, among a retrospective cohort of SN-positive patients, CLND led to upstaging the N-category in 19% of the patients, resulting in a change in AJCC stage in only 5-6% of cases. Thus, only few patients would actually have a meaningful change in staging following CLND.[52] Moreover it has been demonstrated that the predictive ability of a model incorporating ulceration and SN tumor burden category (less or more than 1.0 mm) was similar to a model based on the CLND result.[53] Overall, these data question both the therapeutic and the prognostic value of CLND.

On the other hand, supporters of CLND underlined that a bias of MLST-II trial may be the dilution of a therapeutic effect, since approximately three quarters of the population did not have melanoma cells in non-sentinel nodes and the median tumor burden in the sentinel node was 0.6 mm.

As a consequence, all guidelines currently differentiate the workup in low and high-risk patients (see below for the definition of low and high-risk patients, Table V). CLND, considering the associated morbidity, can no longer be recommended for patients with low-risk micrometastatic disease. For higher risk patients, CLND may be considered after a thorough discussion with patients about the potential risks and benefits of CLND if the patient cannot easily undergo follow-up observations.[43] Careful observation performed in the MSLT-II trial was performed using lymph node ultrasound every 4 months for 2 years, then every 6 months for 3 years, then annually.

Profiles of low and high-risk patients have not been clearly identified. High-risk features can be defined on the basis of the exclusion criteria of the MSLT-II trial, such as extracapsular spread/extension in the SN, concomitant microsatellitosis of the primary tumor, more than three involved nodes, more than two involved nodal basins, and immunosuppression of the patient.[49] A high-risk feature is also the presence of a sentinel node burden >1 mm because this subgroup of patients was less represented in both MSLT-II and DeCOG-SLT trials and, thus, results may not be generalizable to patients with more than low-risk micrometastatic disease in the nodal basin. However, it should be underlined that also in the third of the patient subpopulation that had a SLN burden >1 mm, statistical analysis did not demonstrate any improvement in survival. In the meanwhile, waiting for additional data on the future of CLND, two nomograms have been designed in order to predict the non-sentinel node status in melanoma patients with a positive SNB. The nomograms combine information from the primitive tumor as Breslow thickness, ulceration,[53] and anatomic site,[54] and from the positive sentinel node to calculate the risk of a patient of harboring other positive nodes in the same basin. The two nomograms, as well as exclusion criteria of MLST-II trial (Table V) may orient in the decision to performing or not CLND.

Complete lymph node dissection is recommended for stage III patients with clinically evident nodal metastases due to its therapeutic role. Lastly, the therapeutic consequence of omitting CLND will depend on which eligibility criteria for adjuvant treatment will be set up, a topic that is still being defined.

TABLE V.—*Definition of low and high-risk disease after positive SNB according to MSLT-II and DeCOG-SLT trials.*

Low risk micrometastatic disease	
• Sentinel node burden <1.01 mm (66% of patients in both trials)	No differences between CLND arm and observation arm in: • Distant metastases free survival • OS / MSS • Relapse free survival Above 30% of patients in CLND arm→ lymphedema (grade ¾)
High risk disease	
• Sentinel node burden >1.01 mm* • Extracapsular spread/extension • Concomitant microsatellitosis of the primary tumor • More than three involved nodes • More than two involved nodal basins • Immunosuppression of the patient	Relatively small numbers of patients with higher SLN burden in both trials However, even in this subgroup no differences in survival Worse adverse events (as lymphedema) if CLND performed with clinically palpable nodes

Lymph node dissection

• Completion lymph node dissection is no longer recommended in patients with positive sentinel node biopsy.

• Lymph node dissection is recommended for stage III patients with clinically evident nodal metastases due to its therapeutic role.

In-transit and satellite metastases

In transit metastases are cutaneous or subcutaneous recurrences located more than 2 cm from the primary tumor, but not beyond the regional nodal basin. Satellite lesions are cutaneous or subcutaneous lesions within 2 cm from the primary tumor.

Various treatment options exist according to the presentation that can range from a single or a few lesions to several and/or bulky lesions. Surgical resection is the curative approach, but treatment can be difficult when the interval between new lesions is short, when numerous and bulky metastases are present and multiple treatment modalities have already been performed with only partial results.

Recently, in a systematic review undertaken to identify evidence on effective treatments for satellite and in-transit metastatic melanoma, no high-level evidence was identified on which to base recommendations.[26]

For limited disease NCCN guidelines report the following therapeutic options: intralesional injection of talimogene leherparepvec (T-VEC), INF, IL-2 and BCG, or topical imiquimod in case of superficial dermal lesion. However, the use of these therapies is mainly based on expert opinion and some of them are off-label. T-VEC is an injectable modified herpes virus genetically engineered to selectively replicate in tumor cells, and to produce granulocyte-macrophage colony-stimulating factor which enhances antigen presentation by tissue-resident macrophages. The combination of the virus and cytokine production induce T-cell recognition of virally-infected tumor cells and to promulgate a broader immune response to tumor antigens. T-VEC must be administered directly into tumors but responses were observed in adjacent uninjected lesions, and occasionally at distant metastases.[55] This new emerging technique is likely to replace the older intralesional treatments. Radiation therapy, with definitive or palliative intent, may be considered in case of unresectable satellite and in-transit disease, or residual local, satellite or in-transit disease after prior treatment.[25] AIOM guidelines recommend also the use of electrochemotherapy, while in Australia topical diphenylcyclopropenone is suggested due to its easy administration and limited toxicity, but this drug is not currently available in Italy.

Regional disease may be treated both with isolated limb infusion and isolated limb perfusion with melphalan. Isolated limb infusion, despite its slightly reduced effectiveness, is associated to less frequent and less severe toxicity and reduced resource utilization compared to isolated limb perfusion.[56]

For patients with extensive, progressive and/or recurrent disease systemic therapy may be appropriate.

Molecular assessments

Cutaneous melanomas can be divided into four genomic subtypes based on the pattern of the most prevalent significantly mutated genes: mutant BRAF, mutant RAS, mutant NF1, and Triple-WT (wild-type). About 50% of patients with melanoma carry mutations in the *BRAF* gene that lead to constant activation of a signaling pathway that fuels tumor growth.[57]

The assessment of BRAF gene status is now standard practice in patients diagnosed with metastatic melanoma or unresectable stage III disease, with its presence predicting a clinical response to treatment with BRAF inhibitors. The gold standard in determining BRAF status is currently by DNA-based methods. Routine genetic testing of stage 0, I, and II patients is not recommended outside of a clinical trial; whereas determining the BRAF status is recommended in stage III patients due to the proven efficacy of BRAF inhibitors in the adjuvant setting.[58]

Although more than 30 mutations of the BRAF gene associated with human cancers have been identified, in the context of current clinical melanoma practice, only molecular analysis of BRAF V600 mutation is essential to guide treatment decision-making. V600E mutation is by far the most common, comprising 74-86% of all BRAF mutations. The prevalence of V600K mutations among the BRAF-V600-mutant population can range from 10% up to 30%.[55]

The most recently obtained tumor biopsy should be used for analysis; preferably a direct biopsy from a site of stage IV disease or prior stage III disease. Use of a primary melanoma for analysis is not recommended, especially if there is a long-time interval between the primary and the diagnosis of stage IV melanoma. However, it can be used if samples from metastasis are not available.

Detection of BRAF gene mutations in tumor DNA from peripheral blood samples has a high false-negative rate and is not recommended for routine use.

Activating mutations of the NRAS oncogene are found in 15%-20% of melanomas and the NRAS-mutant subset of melanoma is more aggressive and associated with poorer outcomes, compared to non-NRAS-mutant melanoma. Despite promising preclinical data, current therapies for NRAS-mutant melanoma remain limited and the ideal treatment for NRAS-mutant melanoma remains unknown.[59] NRAS and c-KIT status should be determined for research purpose or in the context of clinical trials. C-KIT status may be tested in case of acral melanoma in case of failure of first choice systemic therapy (anti-PD 1 or ipilimumab), and in case of BRAF-negative mucosal melanoma.

Molecular assessment

Molecular assessment of BRAF status is recommended in stage III and stage IV melanoma patients.

Pathological staging and prognostic curves

Pathological staging includes all clinical staging information, plus any additional staging information derived from the wide excision specimen of the primary tumor, the pathological information about the clinically node-negative regional lymph nodes after SNB, with or without CLND, or the therapeutic lymph node dissection for clinically evident regional lymph node disease.[24] The latter information allows allocating the disease in one of the subgroups of the stage III (Table VI).[24] Classification based solely on SNB without CLND is designated as "(sn)".

The 8th AJCC staging system provided prognostic curves of melanoma patients stratified by pathological stage (Figure 7).[24] Melanoma specific survival (MSS) rates were overall improved compared with patients who had similar stages of melanoma in the seventh edition analyses, although changes in stage III classification rendered a direct comparison difficult. For instance, in the 7th classification, melanoma included in stage IIIA ranged from thin melanoma (<1.0 mm) with one micrometastatic node to melanomas with a Breslow thickness >4 mm not ulcerated with up to 3 micrometastatic nodes, making the subcategory and relative prognostic rates too heterogeneous.[60] The new subgroups of the 8th AJCC classification probably will better fit to the real-life practice than the previous edition, particularly in the case of the revised stage IIIA.

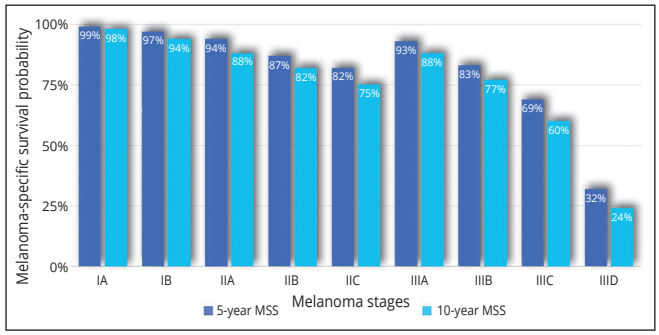

Figure 7.—Melanoma-Specific Survival probability according to stage sub-groups for patients with stage I, II and III melanoma from the Eighth Edition International Melanoma Database. Modified from Gershenwald *et al.*[24]

Noteworthy, a prognostic hierarchy between the stage II and III seems to be partially lacking as the MSS rates for patients with stage IIC disease are lower than those with both stage IIIA and IIIB disease.[61] This confirms that Breslow thickness and ulceration (T) are the most important indicators of the biologic behavior of melanoma, while nodal involvement (N) should be stratified for tumor load. In future, this discrepancy should be taken into account for its implication in the adjuvant setting.

Adjuvant therapy

From 2011 onwards, breakthroughs in new therapies have changed clinical outcomes of melanoma but, de-

TABLE VI.—*Melanoma stage III subgroups according to the AJCC classification system 8th Edition.*

N Category		T Category								
		T0 Occult primary tumor	T1a <0.8	T1b <0.8 U *or* 0.8-1.0	T2a >1.0-2.0	T2b >1.0-2.0 U	T3a >2.0-4.0	T3b >2.0-4.0 U	T4a >4.0	T4b >4.0 U
N1a	1 node c.o.	N/A	A	A	A	B	B	C	C	C
N1b	1 node c.d	B	B	B	B	B	B	C	C	C
N1c	only S/T mets	B	B	B	B	B	B	C	C	C
N2a	2/3 node c.o.	N/A	A	A	A	B	B	C	C	C
N2b	2/3 node, at least 1 c.d.	C	B	B	B	B	B	C	C	C
N2c	S/T mets + 1 node*	C	C	C	C	C	C	C	C	C
N3a	≥4 node c.o.	N/A	C	C	C	C	C	C	C	D
N3b	≥4 node, at least 1 c.d. or matted nodes	C	C	C	C	C	C	C	C	D
N3c	S/T mets + ≥2 node* or matted nodes	C	C	C	C	C	C	C	C	D

T category is expressed in mm.
U: ulceration; c.o.: clinically occult (diagnosed after sentinel node biopsy); c.d.: clinically detected (by palpation or imaging); S/T mets: satellite and/or in-transit metastases. *In N2c and N3c subcategories involved nodes may be either clinically occult or clinically detected.
Modified from Gershenwald *et al.*[24]

spite the efforts, melanoma mortality trend seems to remain stable.[62]

The answer to this contradiction may be connected to a well-known observation: long-survival patients affected by metastatic melanoma are those that started the therapy with low tumor load and tumor burden. In contrast, the most aggressive melanomas that impact on mortality are those that literally break out with fast-growing multiple metastases and do not leave time to set up a treatment that will change this course. These are the cases in which adjuvant therapy may hopefully change the course of the disease.

The concept of adjuvant therapy for melanoma is based on the hypothesis that these therapies may have an effect on residual — after primary tumor resection or after dissection of regional lymph node metastases — micro metastatic disease that is the source for future relapse. The goal of adjuvant therapy is to reduce the rate of recurrence and to increase the overall survival.

The first drug tested for adjuvant therapy in melanoma was interferon alpha (INF-α). Recently, several meta-analyses,[63-65] bringing together all the available data from randomized trials of adjuvant INF-α *versus* no INF-α, tried to point out the role of INF-α and its effectiveness. Data on the efficacy of INF-α at both high dose and low dose regimens (High dose regimen: 20 million IU/m^2/day intravenously for five consecutive days every week for 4-week induction phase, followed by 10 million IU/m^2/day every other day three times each week for an additional 48 weeks. Low dose regimen: 3 million IU/m^2/day subcutaneously three times per week for 2 years) resulted unsatisfying with a little gain in overall survival (OS) only in the subset of ulcerated primary melanomas. However, in many countries INF-α is still the only approved option for high-risk patients.[66] AIOM guidelines recommend considering low-dose INF-α in stage IIB patients and low-dose or high-dose INF-α in stage IIC-III patients, according to patient characteristics and expertise of the caring clinicians.[27] Given the significant toxicity, routine follow-up is preferred to INF-α by the Australian guidelines for stage II and III patients, while NCCN expert panel definitively excluded INF-α from the list of adjuvant treatments.

Both target and immunotherapy, whose efficacy is well known in advanced melanoma (see below), showed promising results in the adjuvant setting. Ipilimumab, the first immunotherapy tested in the adjuvant setting, led to significant improvement in RFS[67] but as much significant toxicities (up to drug-related deaths in five patients), which have been considered not acceptable for a treatment to be offered to a patient with no evidence of disease (NED).[68] The BRIM8 study tested vemurafenib alone *versus* placebo in patients with surgically resected stage IIC or stage IIIA-C *BRAF*-mutated melanoma. Vemurafenib did not improve the primary endpoint of distant metastases free survival in stage IIIC melanoma patients but appeared to be effective and well tolerated in patients with resected stage IIC-IIIB *BRAF* mutated melanoma.[69]

In COMBI-AD trial dabrafenib plus trametinib in stage III patients had significantly reduced the risk of disease recurrence or death by 53% compared to placebo, and improved both OS and DMFS.[70] Same results in DMFS in stage IIIB, C and D patients were obtained by nivolumab, which resulted to be superior to ipilimumab, even due to the lower rate of grade 3/4 treatment-related adverse events.[71, 72] Also pembrolizumab administrated for or up to 1 year resulted in significantly longer RFS than placebo in resected stage III melanoma patients.[73] Noteworthy, in this trial patients who relapsed in the placebo group could cross over to the pembrolizumab arm, thus future results will show the real gain between patients undergoing adjuvant treatment and those starting systemic treatment at recurrence.

Given these results, all the guidelines agree that newer systemic therapy will be the first choice for melanoma adjuvant treatment. However, this change may have an important impact on costs and reimbursement from national health systems. A big issue in the approval of adjuvant therapy for melanoma will probably be the selection of the target population due to the discrepancy between the trials in terms of inclusion criteria, and to the recent change of stage classification. Only the ongoing trial testing nivolumab plus ipilimumab has been designed according to the 8th AJCC classification system (Table VII). In patients with very-low-risk stage IIIA disease (non-ulcerated primary, SLN metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit.

The recommendation by SIDeMaST is in line with the other guidelines.

Adjuvant therapy

Target and immunotherapy for adjuvant treatment of stage III melanoma patients is currently available in selected Italian centers. This option should be offered to stage III patients.

TABLE VII.—*Adjuvant treatment in melanoma: target population according to study design.*

Agent(s)	Trial	Stage IIC	Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID	Stage IV NED	PD-L1 status	Only BRAF-mutated
Old staging (7th AJCC edition)									
Vemurafenib	BRIM8	✓	✓	✓	✓	n/a			✓
Dabrafenib + Trametinib	COMBI-AD		✓	✓	✓	n/a			✓
Nivolumab	Checkmate-238			✓	✓	n/a	✓	✓	
Pembrolizumab	Keynote-054		✓	✓	✓	n/a		✓	
New staging (8th AJCC edition)									
Nivolumab + Ipilimimab	Checkmate-915			✓	✓	✓	✓	✓	

Stage IIID did not exist at the time of 7th AJCC edition but this subgroup of patients was comprised in stage IIIC. Thus, all the treatments are indicated in stage III independently from sub-groups.

n/a: not applicable.

TABLE VIII.—*Systemic therapy for unresectable stage III and stage IV melanoma (advanced disease) and stage III and resected stage IV (adjuvant setting).*

Agent	Mechanism	AIFA-approved indication (advanced disease)	R*	AIFA-approved indication (adjuvant setting)	R*
Target therapy					
Vemurafenib	BRAF inhibitor	As monotherapy and in combination with cobimetinib for *BRAF^{V600}*-mutant melanoma	✓		
Cobimetinib	MEK inhibitor	In combination with vemurafenib for *BRAF ^{V600}*-mutant melanoma	✓		
Dabrafenib	BRAF inhibitor	As monotherapy and in combination with trametinib for *BRAF ^{V600}*-mutant melanoma	✓	In combination with trametinib for resected stage III *BRAF ^{V600}*-mutant melanoma	✓
Trametinib	MEK inhibitor	As monotherapy and in combination with dabrafenib for *BRAF ^{V600}*-mutant melanoma	✓		
Immunotherapy					
Ipilimumab	Anti-CTLA-4 antibody	As monotherapy (from 12 years)	✓		
		In combination with nivolumab	✗		
Nivolumab	Anti-PD-1 antibody	As monotherapy	✓	As monotherapy in resected stage III and stage IV patients	✓
		In combination with ipilimumab	✗		
Pembrolizumab	Anti-PD-1 antibody	As monotherapy	✓	As monotherapy is resected stage III	✓
Oncolytic viral therapy					
Talimogenelaharparepvec	Modified oncolytic herpes virus	Local treatment of unresectable melanoma with locoregional or distant metastases (stages IIIB, IIIC and IVM1a)	✗		

R*: Reimbursed by the National Health Care System; ✓: yes; ✗: no.

Systemic therapy for advanced melanoma (stage IV)

Under the AJCC Staging Manual 8th Edition, stage IV melanoma is subdivided into four groups according to site of the metastases and LDH level (AJCC).

Systemic therapeutic option for advanced melanoma may be divided into target-therapy and immunotherapy (Table VII, VIII). Development of immune checkpoint inhibitors has been among the most important breakthroughs in cancer treatment in the 21st century. Yet, this new class of therapeutic agents has challenged the oncology community to redefine fundamental aspects of melanoma treatment including prognostication, disease monitoring and management of toxicity.

The first of such agent tested was ipilimumab, a monoclonal antibody (mAb) against cytotoxic T- lymphocyte-associated protein 4 (CTLA-4). The interaction with CTLA-4 prevents binding of the costimulatory ligands to cluster of differentiation 28 (CD28), the major costimulatory receptor on the T cell necessary for a robust T cell response. Despite concerns about uncontrollable autoim-

munity resulting from systemic CTLA-4 blockade, ipilimumab, improved OS in patients with metastatic melanoma, being approved in 2011 for first-line treatment of advanced melanoma in the United States and Europe.[74, 75] Notably, after the recent progress in the immunotherapy field and the introduction of anti PD-1 agents, weighed by less adverse events, ipilimumab became a second line option for metastatic or unresectable disease.

Programmed cell death-1 (PD-1) is an immune-inhibitory receptor that belongs to the CD28/CTLA4 receptor family. PD-1 binds two known ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which are widely expressed, in a variety of tissues. Once PD-1 binds to PD-L1, it negatively regulates T cell functions. Nivolumab is an IgG inhibiting antibody that targets PD-1. Pembrolizumab is a humanized monoclonal antibody (IgG4/kappa isotype) that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Both drugs have demonstrated significant benefits in RFS and OS and a favorable safety profile in the treatment of metastatic melanoma that are superior to ipilimumab, as monotherapy and in combination with ipilimumab.[76, 77]

In patients with metastatic melanoma, the BRAF-MEK inhibitors, vemurafenib-cobimetinib (Genentech-Roche) and dabrafenib-trametinib (Novartis), and received regulatory approval after demonstrating significant improvements in RFS and OS in this patient population.[78, 79]

Results from long follow-up of the registration trials demonstrated that both target and immune-therapy can result in long-term benefit, especially in patients with good prognostic features at baseline (low tumor burden, low LDH level, no brain metastases). In contrast, patients with brain, multifocal and rapidly progressing disease are largely incapable of achieving long-lasting remissions from either molecularly targeted treatments or novel immunotherapies. Indeed, the presence of brain metastases is associated with the worst prognosis even due to their resistance to current available systemic therapy.

The mainstays of treatment of brain metastases are systemic therapies in association with local treatment modalities such as neurosurgical resection, stereotactic radiosurgery (SRS), stereotactic ablative radiotherapy (SABR), or whole brain radiotherapy (WBRT). The best candidates for neurosurgical resection of brain metastases are patients with a very limited number of superficial metastases in non-eloquent areas of the brain and adequate condition to undergo surgery. Patients suitable for SRS may have up to ten metastases with a total cumulative volume ≤15 mL.

Follow-up

No randomized trials are available on follow-up schedule in melanoma patients. A recent systematic review failed to find high quality evidence on this topic[80] and all the available guidelines are based on level III-IV evidence and expert opinion.

The different approaches of the leading international and national guidelines are listed in Table IX.

Self-examination is warranted as an effective tool to detect melanoma recurrence and new primary melanomas if the patient is aware of signs and symptoms.[81] In Australia, patients themselves detect up to 75% of recurrences, while in other countries this can be as low as 20%, probably due to a lower awareness of the disease.[80] However, it is obvious that the ability of individual patients to detect recurrence varies. Some can identify recurrences that are not discernible to doctors, while others can be unaware of a large tumor mass. The existence of these latter patients explains the need of a routine follow-up.

The mainstays of follow-up in melanoma patients includes: 1) history and physical examination of lymph nodes (H&P), aimed to detect loco-regional or symptomatic distant metastases; and 2) TBSE, aimed to detect satellite and in-transit metastases as well a subsequent primary melanoma or other non-melanoma skin cancer. Indeed, history of melanoma is associated with a lifelong higher risk of a second melanoma and, indirectly, even with the development of basal cell carcinoma and squamous cell carcinoma. Although skin and nodes examination should be performed together at each control that a patient undergo, in some guidelines they are separately scheduled and timed (Table IX). This dissociation is likely due to the separate care role of dermatologist and oncologist in the management of melanoma patients in some countries. However, the ideal approach to melanoma patients should be providing an integrated visit in which TBSE and H&P are jointly performed by a dermatologist experienced in dermoscopy. Patients with high-risk melanoma should be evaluated by a multidisciplinary team for discussion of surveillance imaging and adjuvant therapy. This strategy would save patient's stress and costs of a double check-up. In stage IV melanoma patients treated with target or immune therapy, TBSE is also aimed to manage cutaneous adverse events.

Most local, satellite/in-transit, and regional nodal recurrences are identified by clinical examination of the skin and lymph nodes. It has been demonstrated that nodal basin ultrasound is superior to palpation for detection of lymph node metastases[21] and even superior to CT scan or

TABLE IX.—*Comparison of follow-up in asymptomatic patients according to stage among the main international guidelines and SIDeMaST proposal.*

	National Comprehensive Cancer Network (NCCN)	Cancer Council Australia	AIOM	SIDeMaST
Stage 0	TBSE annually for life Imaging not recommended	Self-examination + H&P (timing not reported) Imaging not recommended	TBSE + H&P annually (or every 6 months if multiple nevi or multiple melanoma) Imaging not recommended	TBSE + H&P annually (or every 6 months if multiple nevi or multiple melanoma) Imaging not recommended
Stage I	TBSE + H&P every 6-12 months for 5 years, then annually for 5 years Imaging not recommended	TBSE + H&P annually for 10 years Imaging not recommended	TBSE 6-12 months interval IA: H&P 6 months interval for 5 years then annually NBU (optional) 6 months interval for 5 years IB: see stage IIA	TBSE + H&P 6 months interval for 5 years then annually NBU 6-12 months interval for 5 years
Stage II	IIA: TBSE + H&P every 6-12 months for 5 years, then annually for 5 years Routine imaging not recommended IIB/C: TBSE + H&P every 3-6 months for 2 years, every 3-12 months for 3 years then, annually for 5 years Consider chest/abdominal/pelvic CT or whole body FDG PET/CT every 3-12 months for 3-5 years	IIA: TBSE + H&P every 6 months for 2 years, then annually for 8 years Routine imaging not recommended IIB: TBSE + H&P every 4 months for 2 years, every 6 months during year 3, then annually for 5 years. Routine imaging not recommended IIC: TBSE + H&P every 4 months for 2 years, every 6 months during year 3, then annually for 5 years. CT or PET/CT every 3-12 months for the first three years (optional)	TBSE 6-12 months interval IIA: H&P 3-6 months interval for 2 years then 6 months interval for 3 years, then annually for 5 years NBU 6 months interval and abdomen ultrasound every year for 5 years IIB: H&P 3 months interval for 2 years then 6 months interval for 3 years, then annually for 5 years NBU and scar area ultrasound 3 months interval Abdomen ultrasound 6 months interval Chest CT every year for 5 years IIC: see stage III	IIA/IIB: TBSE + H&P 4 months interval for 5 years (3 visits per year) then 6 months interval for 5 years NBU + abdomen ultrasound twice per year (visit 1 and visit 3) for 5 years then annually for 5 more years Scar area US (optional) CT or PET/CT 12 months interval (visit 2) for 5 years IIC: see stage III
Stage III	IIIA/B: see stage IIB/C IIIC/D: TBSE + H&P every 3-6 months for 2 years, every 3-12 months for 3 years then, annually for 5 years Consider chest/abdominal/pelvic CT or whole body FDG PET/CT + Brain MRI every 3-12 months for 3-5 years	TBSE + H&P every 3 months for 2 years, every 6 months during year 3, then annually for 5 years. CT or PET/CT every 3-12 months for the first three years	TBSE 6-12 months interval H&P 3 months interval for 2 years then 6 months interval for 3 years, then annually for 5 years CT or PET/CT 6-12 months interval for 3 years then annually NBU + scar area ultrasound 3 months interval for 5 years Abdomen ultrasound optional	TBSE + H&P 3 months interval (4 visits per year) for 5 years then 6 months interval for 5 years NBU + abdomen ultrasound 6 months interval (visit 1 and visit 3) for 5 years then annually for 5 more years Scar area US (optional) CT or PET/CT 6 months interval (visit 2 and visit 4) for 3 years then annually for 5 more years

Unless otherwise specified CT refers to whole body CT with intravenous contrast and PET/CT to whole body FDG combined PET/CT.
TBSE: total body skin examination with dermoscopic evaluation of cutaneous lesion; H&P: history and physical exam with palpation of nodal basins: melanoma surgical scar and surrounding area; NBU: nodal basin ultrasound; CT: computed tomography; PET/TC: positron emission tomography combined with computed tomography; SNB: sentinel node biopsy; LDH: lactate dehydrogenase.

PET/CT.[82] Clinical-based and ultrasound-based follow-up of lymph nodes have been compared in stage IB-IIA and the results showed that detection of lymph node metastases using ultrasound did not increase survival[83] and there was no significant difference in median time to detection of the first recurrence between the two groups. However, in that study there was no mention on the lymph node tumor burden at the time of detection, as well as on the subsequent therapy that the patients underwent in both the clinical-based and ultrasound-based follow-up. In the period of the study the new treatment options for unresectable stage III and IV patients were still not available and, thus, the result is not applicable to the current practice.

In our estimation, nodal basin ultrasound should be encouraged in the current setting, as immunotherapy is more effective with low tumor burden.[84] Moreover, if not performing CLND will be the future trend, the use of surveillance nodal basin ultrasound may be necessary in stage

III patients. Thus, we suggest performing regional lymph node ultrasound to follow patients who have excised an invasive melanoma with stage-related time intervals. The current standard method to confirm the presence of suspected nodal metastases for lymphadenopathy is fine needle aspiration, even if core biopsy showed higher sensitivity and specificity.[80]

Despite the fact that more than 50% of patients progressing to metastatic advanced disease had a previous low-risk thin melanoma,[85] NCCN and Australian Cancer Council guidelines recommend against investigation for distant metastases in early stage melanoma patients (stages I-IIA), unless clinically indicated (presence of signs and/or symptoms of disease recurrence).

A 10-year prospective analysis of stage IIB, IIC, and III melanoma patients assessed the detection rates of imaging with CT of the chest/abdomen/pelvis and brain MRI every 6 months for 5 years after diagnosis, followed by annual chest radiography until year 10. Imaging detected 56.7% of recurrences (mainly visceral), as compared with 41.5% of recurrences initially detected by patient or provider examination. Most clinically detected recurrences were cutaneous.[86] This difference is considered relevant by AIOM expert panel that recommend performing chest TC together with abdomen ultrasound in stage IIB patients, and whole-body CT or PET/CT from stage IIC onwards. NCCN guidelines recommend considering imaging for asymptomatic patients with stages IIB and higher for the first 3-5 years after diagnosis, however timing is not well defined (3-12 months) and the decision is delegated case by case to clinicians. The Australian Cancer Council guidelines suggest CT or PET/CT only for stage IIC and III; major objections include the potential risk of false positives (and related patient's anxiety), the risk of radiation-related side effects (including thyroid cancer and cataracts) and, above all, the absence of high-quality data on survival improvement. However, as new therapies for advanced melanoma continue to evolve, it is possible that systemic treatments may be more effective in patients with earlier, low-volume metastasis, and surveillance imaging recommendations may change as a result.

SIDeMaST suggest performing whole body CT from stage II onwards.

Surveillance for stage IV melanoma depends on the purpose of follow up: in case of active treatment, follow up is aimed at determining treatment efficacy; in patients who are not undergoing active therapy, either due to disease volume too limited to be considered for active therapy or those undergoing supportive care, follow up should be scheduled on an individual basis at the discretion of the patient and the treating doctor. Some guidelines state recommendations for follow-up of stage IV NED patients (Table IX).

An appropriate patient counseling on follow-up is needed, as some patients may prefer more frequent follow-up for reassurance, while others may prefer less frequent follow-up because of the anxiety provided by the follow-up visits, or the time and expense associated with attendance for follow-up.

Follow-up

- Regional lymph node ultrasound from stage I onwards.
- Whole body CT scan from stage II onwards (Table IX).

Conclusions

The management of melanoma is changing fast, over a relatively short period of time. Neo-adjuvant therapy, new combinations of systemic therapies, different dosing and sequential strategies, and new drugs are perspectives of a near future. The detection of new bio-markers and the development and diffusion of liquid biopsy will improve both diagnosis and monitoring of treatment response. Lastly, new insights in the genetic and immune landscape of melanoma will drive to more effective and patient-tailored treatments. And perhaps, finally, the melanoma mortality rates will be lowered.

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