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MELANOMA STAGING (TNM SYSTEM) AND PROGNOSTIC FACTORS

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Abstract

The process of figuring out how far a cancer has spread and where it is in the body is known as cancer staging. In addition to offering the most precise prognostic estimate, a comprehensive staging is essential since the tumor's stage affects a number of critical decisions, including therapy selection and follow-up tactics. The American Joint Committee on Cancer (AJCC) published the eighth version of the TNM classification in 2017, which serves as the foundation for the current melanoma staging system. There are five stages (0–IV) in both the clinical and pathological staging. The Breslow thickness, the pathological presence or absence of ulceration in the primary tumor, the number and presence of tumor-involved regional lymph nodes, the presence or absence of in-transit, satellite, and/or microsatellite metastases, and the presence of distant metastases are some of the factors that determine the stage of a melanoma. An appropriate medical workup in accordance with the stage and physical examination should be carried out after a melanoma diagnosis. In order to identify a possible recurrence or a second primary melanoma, ongoing patient monitoring is essential and should last a lifetime. Different follow-up plans have been proposed, but there is currently no widely accepted follow-up strategy program. With the rising usage of innovative current medicines (immunotherapies and targeted therapies), future prospective studies are required to assess various follow-up methods based on the chosen therapy.

Keywords: Melanoma, cutaneous melanoma, staging system, American Joint Committee on Cancer (AJCC), TNM classification

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Introduction

The process of staging involves figuring out where and how far a cancer has progressed throughout a person's body. Cancer stages range from 0 to IV, with stage IV cancer being associated with distant metastases. The well recognized TNM (Tumor, Node, Metastasis) staging technique is the most widely used method for staging solid tumors, including melanoma. Clinical and pathological staging are two categories of cancer staging. Although the criteria used to distinguish clinical and pathological phases may vary, they are often seen as complimentary to one another. Generally speaking, pathological staging is carried out by a pathologist and depends on the data from microscopic examination of the tumor after surgical resection, whereas clinical staging is based on all the information available prior to surgical excision of the tumor (e.g., by physical examination, blood tests, and imaging).

Only after the main tumor has been completely removed, a clinical examination of the skin and lymph nodes, and a radiologic evaluation for the identification of regional and distant metastases can the clinical stage of a melanoma be ascertained. In addition to the extensive excision and microstaging of the main tumor, pathological staging of a melanoma also takes into consideration data on regional lymph nodes following partial or total lymphadenectomy, if it is carried out. Because it offers the most precise prognostic prediction and enables the making of numerous critical decisions, including the choice of therapy and the follow-up plan, that are based on clinical tumor stage.

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stge IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any t, Tis	≥ N1	M0
Stage IV	Any T	Any N	M1

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The current staging system is based on the 8th edition of TNM classification for staging of melanoma issued by the AJCC in 2017 and is summarized in Tables 1–5 [1]. This relatively new system has been broadly accepted after its publication and is considered the cornerstone for classifying melanomas.

Melanoma staging system

Tables 1–5 provide a summary of the current staging approach, which is based on the 8th edition of the TNM classification for melanoma staging published by the AJCC in 2017.

Clinical staging (Table 1)

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1a/b, T2a	N1a, N2a	M0
Stage IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stage IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b,	T3a N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥ N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stage IIID	T4b	N3a/b/c	M0
Stage IV	Any T, Tis	Any N	M1

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Pathological staging (Table 2)

Category	Thickness	Ulceration
TX: Primary tumor cannot be assessed	N/A	N/A
T0: No evidence of primary tumor	N/A	N/A
Tis (in situ)	N/A	N/A
T1	≤1 mm	
T1a	<0.8 mm	Without ulceration
T1b	<0.8	With ulceration
	0.8–1.0 mm	With or without ulceration
T2	>1.0–2.0 mm	
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Definition of T (Table 3)

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Category	Number of Tumor-Involved Regional Lymph Node	Presence of In-transit, Satellite, and/or Microsatellite Metastases
NX: Patients in whom the regional nodes cannot be assessed	N/A	No
N0: No regional metastases detected	N/A	No
N1	1 tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved node	
N1a	1 clinically occult (ie, detected by SLN biopsy)	No
N1b	1 clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2 or 3 tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with 1 tumor-involved node	
N2a	2 or 3 clinically occult (ie, detected by SLN biopsy)	No
N2b	2 or 3, at least 1 of which was clinically detected	No
N2c	1 clinically occult or clinically detected	Yes
N3	4 or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with 2 or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	4 or more clinically occult (ie, detected by SLN biopsy)	No
N3b	4 or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	2 or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Definition of N (Table 4)

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Category	Anatomic Site	LDH level
M0: No evidence of distant metastasis	N/A	N/A
M1	Evidence of distant metastases	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Definition of M (T able 5)

There are five stages in both clinical and pathological staging, which are as follows:

Clinical Phase:

0: in situ illness

I and II: localized illness

Substages IA and IB make up stage I, whereas substages IIA, IIB, and IIC make up stage II. The Breslow thickness and the presence or absence of ulceration following the pathological evaluation of the main tumor are the decisive variables for staging and substaging (Tables 1 and 2). Notably, melanoma staging is no longer influenced by

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Clark's level of invasion and mitotic rate, which were formerly employed for sub-classification.

III: local illness

Metastases in regional lymph nodes, as well as "in transit metastases," "satellite metastases," and microsatellite metastases, are indicative of regional illness. Cutaneous or subcutaneous metastatic lesions up to two centimeters from the main tumor's edge are referred to as satellite metastases. Cutaneous or subcutaneous lesions situated between 2 cm from the main tumor and the regional nodal basin are referred to as in-transit metastases. Tumor nests greater than 0.05 mm in diameter in the reticular dermis, subcutis, or arteries underneath the original invasive tumor that are at least 0.3 mm away from it on the section where the Breslow measurement was made are known as microsatellite metastases.

Metastases in the lymph node basin that drains lymph from the area surrounding the tumor are referred to as regional lymph node metastases. After sentinel lymph node (SLN) biopsy (for clinically occult lymph node metastases) or therapeutic lymph node dissection (for clinically obvious regional lymph node illness), the involvement of regional lymph nodes is verified by pathological investigation. Clinical, radiologic, and/or diagnostic biopsies (clinical staging) can also identify regional lymph node involvement. As a result, there is just one stage group for clinical stage III. On the other hand, Breslow thickness, the pathological presence or absence of ulceration in the primary tumor, the number of tumor-involved regional lymph nodes, and the presence or absence of in-transit, satellite, and/or microsatellite metastases determine the A, B, C, and D stage groups for pathological stage III (Table 4).

IV: illness with distant metastases

This stage comprises nonregional lymph nodes, skin, soft tissue, and distant metastases to the lung, central nervous system (CNS), or other organs. For prognosis purposes, a sub-classification based on the number of organs implicated, which organs are involved, and serum levels of lactate dehydrogenase (LDH) is crucial, even if there is no further separation to substages (Table 5).

Staging workup

Histopathologic Examination

A biopsy should be carried out if a suspicious lesion is found. It is highly recommended to do an excisional biopsy with a thin margin (1-3 mm). The staging and subsequent treatment of primary melanoma are determined by the histological findings and clinical

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assessment. As a result, the Breslow thickness, ulceration status, dermal mitotic rate, margin status, presence or absence of microsatellitosis, and presence or absence of pure desmoplasia should all be included in the pathology report.

Physical examination

The physical inspection of the whole skin surface should get special attention in order to search for a second primary melanoma as well as satellites or in-transit metastases. Included should be a physical assessment of the local lymph node basin.

Imaging and Sentinel Lymph Node Biopsy

No additional imaging or laboratory testing is required for patients with melanoma in situ and clinical stage IA melanoma who have a normal physical examination and no other symptoms. Additionally, at baseline, they are not SLN biopsy candidates. Wide excision is the final step in the staging process [1].

At baseline, patients with clinical stage IB melanoma who have a normal physical examination and no other symptoms do not require further imaging or laboratory testing. In individuals with T1b melanoma, SLN biopsy should be taken into consideration. Numerous criteria, including age, lymphovascular invasion, mitotic rate, and comorbidities, influence the choice [1]. SLN biopsies should be performed on patients with T2a melanoma.

A SLN biopsy should be recommended for patients with clinical stage II melanoma who have a normal physical examination and no other symptoms, but they do not require further imaging or laboratory testing at baseline [1,4,5].

An ultrasound (US) should be investigated before an SLN biopsy in patients with melanoma of any stage if an unclear regional lymph node is found on clinical examination. Nevertheless, a negative nodal basin US should not be used in place of a biopsy of lymph nodes that are clinically questionable; instead, histology should be performed. Additionally, nodal basin US anomalies or suspicious lesions should be verified histopathologically.

Interestingly, it has been demonstrated that SLN biopsy has only prognostic (and not therapeutic) importance [9–13]. The importance of SLN biopsy as a staging method is highlighted by the fact that a positive biopsy would immediately advance a patient to stage III, particularly with the advent of adjuvant systemic treatment for stage III. Since a full lymph node dissection has minimal predictive value, little therapeutic effect, and is linked to surgical morbidity, it is no longer advised in cases of positive SLN biopsy

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[14–17]. However, in the absence of distant metastases, it is recommended for the treatment of lymph node metastases identified by imaging or clinical diagnosis.

Patients with pathological stage IIIA melanoma should be evaluated for baseline staging, and all patients with stage IIIB/C/D should undergo imaging [1]. Imaging methods include whole-body PET/CT with or without brain MRI with IV contrast, or chest/abdominal/pelvic CT with IV contrast. Additionally, if clinically necessary, a CT scan with intravenous contrast should be used to examine the neck area.

Lastly, individuals with stage IV melanoma require meticulous whole body imaging (CT or PET/CT, brain MRI). Additionally, it is important to measure plasma LDH [1].
Follow-Up
Following a diagnosis of melanoma, it is crucial to continue monitoring people who a re clear of the illness. The following are the follow-up's primary objectives: Early detection of recurrence (local or distant) and subsequent advice for adjuvant the rapy, if necessary. early identification of non melanoma skin cancer or a second primary melanoma.

Identification and management of adverse effects after receiving adjuvant systemic th erapy. A sufficient follow-up is crucial since early diagnosis of recurrence is linked to a greater survival probabi lity. The stage of melanoma at initial presentation affects the chance of recurrence. After extensive excision, patients with in situ melanoma had extremely little chance o f recurrence. However, there are certain outliers, including lentigo maligna type [18–20].
Patients who first arrive with melanoma at an early stage are often less likely to exper ience a recurrence than those who have more advanced stages.
As a result, the stage affects when relapses occur.
Individuals with advanced melanoma typically experience a faster recurrence than th ose with earlier stages [21–23].
However, the majority of relapses occur within two to three years after surgery, and th e majority occur within the first five years.
Furthermore, for melanoma stages, the chance of recurrence tends to decline over tim e; nonetheless, late recurrence (more than ten years after the first diagnosis) cannot be ruled out.

A second primary melanoma is most likely to occur in patients with a personal history of the disease. The information presented in the literature about the likelihood of getting a second primary melanoma is quite inconsistent. Between 2% and 20% of melanoma patients have been observed to acquire a second primary melanoma [23, 27–

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30]. The cumulative 5-year risk of developing a second primary melanoma was 8% in a group of individuals with melanoma who were prospectively tracked [30]. It is interesting to note that the risk seems to increase within the first year following the initial melanoma diagnosis, but it persists for at least five years and potentially longer [23, 27–30]. As a result, those with a history of melanoma should be regarded as having a lifelong higher risk of getting a new primary melanoma.

While there is no question about the necessity of a follow-up for patients with melanoma, surveillance guidelines differ greatly in terms of the techniques and frequency of visits and exams. Different follow-up plans have been presented, most of which are based on expert judgments, because there is currently insufficient information about the effectiveness of follow-up techniques. The melanoma stage and the existence or absence of other risk factors are taken into account in the recommended follow-up plans.

Due to the high chances of relapse, the first five years after the main tumor is removed are the most critical. Because of this, current guidelines recommend using more intensive follow-up techniques throughout this time. However, monitoring programs for melanoma patients should extend beyond five years, including at least one strongly advised yearly skin inspection throughout life, due to the lifetime increased risk of a second primary melanoma or a non-melanoma skin cancer, as well as the possibility of late recurrence [31].

Whole body skin examinations, physical examinations of the local lymph nodes, blood tests, and imaging tests such chest X-rays, ultrasounds, CT, PET/CT, and MRIs are among the modalities used to monitor melanoma patients. In order to detect local recurrences (scar, satellite/in-transit recurrence) and subsequent primary melanoma or other skin cancers, a clinical evaluation conducted by a dermatologist is required at any stage and includes a total body skin examination (with or without a total body clinical and dermoscopic digital documentation). Examining the local lymph nodes and assessing the patient's symptoms and/or indicators that would guide necessary imaging should also be part of the clinical assessment.

The most reliable way to identify nodal disease is through lymph node ultrasound, which is typically advised for patients with equivocal lymph nodes during physical examination, patients with AJCC T1b stage and above, patients who were offered SLN biopsy but did not have it done, and patients with positive SLN biopsy who did not undergo full lymph node dissection [32]. When monitoring asymptomatic patients in more advanced stages or when signs and symptoms may indicate distant metastases, other imaging modalities (CT, PET/CT, MRI, chest x-ray) should be taken into

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consideration [33]. Whenever feasible, histopathologic investigation should be used to confirm any suspected recurrence in a clinical setting.

Finally, while modest positive predictive values have been shown, regular blood tests (LDH, S100 protein) to identify recurrence is often not advised. The identification of molecular changes in melanoma patients' plasma and serum by the characterisation of circulating tumor cells and cell-free circulating tumor DNA is the subject of ongoing research on liquid biopsies [34, 35]. In the future, this might offer useful data on predictive results and evaluation of therapy response or resistance.

Follow-up guidelines for each stage of melanoma have been published by the National Comprehensive Cancer Network (NCCN), an association of 31 US cancer institutions [1]. They state that for stage 0 (in situ) melanoma, regular imaging is not advised. Regular imaging to check for silent recurrence or metastatic disease is not advised for patients in stages IA to IIA who show no signs of illness. For five years, clinical visits should be planned every six to twelve months; beyond that, they should be arranged yearly as clinically warranted. During these visits, the clinical examination should focus on the skin and local nodes. Scheduled visits should be carried out every three to six months for the first two years, every three to twelve months for the following three years, and yearly after that, as clinically recommended, with a focus on the skin and regional nodes, for patients in stages IIB to IV (without any indication of illness). Additionally, screening for asymptomatic recurrence in these phases may involve imaging (chest x-ray, CT, and/or PET/CT) every three to twelve months. In terms of the central nervous system (CNS), high-risk individuals with stage IIIC or higher melanoma should have a brain MRI every three years to check for asymptomatic brain metastases; those with previous brain metastases should have more regular monitoring. However, beyond three to five years, regular imaging is not advised. However, when clinically necessary, a suitable imaging test should be provided to assess particular symptoms in any situation and at any point throughout the follow-up period.

Lastly, imaging is advised to determine the severity of the illness if a recurrence takes place. Additionally, clinical assessment and/or imaging may be necessary during therapy to evaluate treatment response when active non-surgical treatment is started and full surgical resection of the recurrence is not practical.

The frequency of follow-up programs in Europe varies from two to four times a year for five to ten years, with higher-intensity tactics used during the initial years and in more advanced phases. Table 6 presents an example of the stage-based follow-up schedule exams suggested by the current European consensus-based multidisciplinary recommendations for melanoma.

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A tailored approach that considers the patient's risk factors—such as atypical mole syndrome, previous primary melanoma, recurrence risk, and family history of melanoma—is desirable regardless of the follow-up plan selected. Furthermore, a crucial part of the monitoring strategy must include patient education, which should include

a description of what to expect from follow-up tests and the importance of keeping the planned follow-ups.

- awareness that melanoma is often more common among family members.
- guidelines for doing regular self-examinations of the skin and peripheral lymph nodes.
- details on safe sun exposure techniques.

Conclusion

In conclusion, even though there is currently no widely used follow-up plan program to monitor patients with melanoma, the above-mentioned suggestions might act as a reference for doctors while further To improve the standardization of these follow-up procedures, prospective studies are needed.

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