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REVIEW ARTICLE

Follow-up of primary melanoma patients with high risk of recurrence: recommendations based on evidence and consensus

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Abstract

In spite of the good prognosis of patients with early-stage melanoma, there is a substantial proportion of them that develop local or distant relapses. With the introduction of targeted and immune therapies for advanced melanoma, including at the adjuvant setting, early detection of recurrent melanoma and/or second primary lesions is crucial to improve clinical outcomes. However, there is a lack of universal guidelines regarding both frequency of surveillance visits and diagnostic imaging and/or laboratory evaluations. In this article, a multidisciplinary expert panel recommends, after careful review of relevant data in the field, a consensus- and experience-based follow-up strategy for melanoma patients, taking into account prognostic factors and biomarkers and the high-risk periods and patterns of recurrence in each (sub) stage of the disease. Apart from the surveillance intensity, healthcare professionals should focus on patients' education to perform regular self-examinations of the skin and palpation of lymph nodes.

Keywords Melanoma · Risk of recurrence · Follow-up · Surveillance · Imaging · Prognostic factors

Introduction

Melanoma is a skin cancer with high impact due to its growing incidence, high mortality rate, and elevated costs of care in advanced stages. Clinical, dermatological, and histopathological presentation is heterogeneous, and several risk factors have been identified (skin type, exposure to sun radiation, number of nevi, age, gender, immune status, family history or former melanomas) [1]. During the last years, research efforts have been focused on shifting melanoma diagnosis toward earlier stages, preventing its occurrence, and developing breakthrough treatments. The introduction of new systemic therapies (immune checkpoint inhibitors and small-molecule-targeted drugs) has significantly improved patient prognosis and changed the landscape of advanced melanoma management [2]. These therapies are now indicated for unresectable stage III and stage IV melanoma [3, 4] and, in the adjuvant setting, for resectable stage III melanoma at high risk of recurrence [5–9].

Nearly 70% of primary melanomas are diagnosed before evidence of metastasis and are potentially curable by surgery only. In spite of the good prognosis, there is a substantial proportion of stage I–II melanoma patients that experience local and distant relapses within five years and even

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die [10–12]. Thus, early detection of recurrent melanoma, when it is amenable to be treated, is crucial to improve clinical outcomes. Due to the increased risk of second primary melanomas [13], detection of new lesions is another important issue in melanoma follow-up. However, there is a lack of universal guidelines regarding both frequency of surveillance visits and diagnostic imaging and/or laboratory evaluations [14]. In an effort to standardize the follow-up strategy for patients with different melanoma stages and understand which patient characteristics and disease-related factors could inform the optimal surveillance, a multidisciplinary expert panel performed an exhaustive literature review and provided consensus recommendations on the basis of the best available data and their own clinical experience.

Prognosis based on melanoma TNM staging: the need of additional prognostic factors

An accurate melanoma staging classification is crucial for initial patient assessment, treatment planning, and instructing surveillance strategies. The 8th edition of the American Joint Committee on Cancer (AJCC8) melanoma staging system introduced key changes regarding subcategorization of T and M, and pathologic stage grouping of stage I and III [15], resulting in stage shift from the previous edition (AJCC7) with better survival rates. Several studies applying the AJCC8 system to classify their patients have shown that outcomes in stage IIIA melanoma, in terms of recurrence-free survival (RFS) and melanoma-specific survival (MSS), are better than those in stages IIC and even IIB (Table 1) [16–18]. These findings highlight the limitations of the conventional TNM approach because nodal positivity itself is not necessarily associated with poorer outcomes, so additional prognostic factors should be considered.

Table 1 Melanoma-specific survival according to AJCC eighth edition [15]

AJCC8 Substage	5-year MSS, (%)	10-year MSS, (%)
IA	99	98
IB	97	94
IIA	94	88
IIB	87	82
IIC	82	75
IIIA	93	88
IIIB	83	77
IIIC	69	60
IIID	32	24

AJCC8, 8th edition of the American Joint Committee on Cancer

MSS melanoma-specific survival

The use of nomograms that include other pathological and demographic characteristics could facilitate a better stratification of recurrence or mortality risk in patients with early melanoma stages [19, 20]. For this purpose, it is necessary that the following elements of a primary lesion are included in the pathological report: Breslow thickness (mm), ulceration, dermal mitotic rate (per mm^2), peripheral and deep margin status, and microsatellitosis, which are considered essential factors [21]. Additional prognostic features that may be informative are macroscopic appearance (diameter), lymphovascular invasion, histologic subtype, tumor-infiltrating lymphocytes, neurotropism/perineural invasion, tumor regression, and Clark level [22]. In patients with stage IIB or higher melanoma, *BRAF* and *KIT* mutation status should be examined, as it also has prognostic impact [23, 24], apart from aiding to select the future therapy, if needed. The use of gene expression profiling for prognosis of early-stage melanomas is becoming more and more prevalent. This testing provides binary risk assessment and may be considered as an adjunctive tool to formulate individualized follow-up [25–28].

Role of sentinel lymph node biopsy and complete lymph node dissection beyond staging

The value of sentinel lymph node (SLN) biopsy as a key technique for accurate staging of the regional nodal basin is well established. It is indicated for patients with intermediate-thickness melanoma (1.1–4.0 mm; T2–T4) and patients with T1b melanoma ($\geq$0.8–1.0 mm thickness or $<$0.8 mm with other high-risk histologic features such us ulceration, high mitotic rate [$>2/mm^2$], and/or lymphovascular invasion) [29]. SLN biopsy should be considered for the latest in an individualized basis. Sentinel node positivity elevates melanomas from stages I–II to III, which obviously has prognostic and therapeutic implications [15, 30]. Apart from the staging utility, SLN biopsy is associated with lower regional node recurrence [31], possibly because the only important focus of metastatic melanoma is removed by the procedure [32]. However, the drawback of biopsy in terms of complications and sequelae and the possibility of using other less invasive strategies make this technique optional in some cases, such as in frail patients [33].

The findings of the phase III studies MSLT-2 and DeCOG-SLT [34, 35] regarding the therapeutic value of immediate completion lymph node dissection (CLND) after positive SLN biopsy were practice-changing, and immediate CLND is no longer routinely recommended for all patients with sentinel node positivity, given the lack of benefit in

terms of MMS (86% for CLND vs 86% for observation) or distant metastasis-free survival (75% for CNLD vs 77% for observation). In addition, the node intervention is associated with significant morbidity, for example lymphedema (24% for CNLD vs 6% for observation) [34]. However, the reduction of the number of CLNSs will lead to a loss of valuable prognostic information for treatment decisions. All the risks, benefits and alternatives of the procedure should be discussed with the patients before deciding whether or not to undergo CLND, and they should be offered similar clinical and ultrasound (US) follow-up of the regional lymph basins that was done in the MSLT-2 and DeCOG-SLT trials [34, 35]. The development of nomograms to predict the risk of non-sentinel node positivity may help clinicians to discuss with patients the opportunity of CLND [36–38]. Those patients with sentinel node macrometastasis (> 2 mm) or extracapsular extension will probably benefit from CLND.

Follow-up strategy according to recurrence risk and patterns

There is considerable variability in the post-surgery melanoma surveillance and international guidelines are usually flexible to accommodate a range of clinical practices [21, 39, 40]. An important issue to consider is the relapse pattern of each stage (or substage) and the associated risk factors. It has been shown that the median time to relapse in stage I–II and stage III patients is around 22 months and 13 months, respectively, being higher mitotic rate the main risk factor for poor RFS in both groups [41]. Most of the melanomas in node-positive patients (57.9%) developed distant metastases (predominantly, in lung, bone, liver, and brain), while locoregional relapses were more frequent (56.6%) in the stage I–II group [41]. Information about the most prevalent locations of relapse is important for targeting radiologic surveillance at specific body regions and to allocate selected patient groups for an efficient follow-up program. For example, Haydu et al. found that the cumulative incidence of brain metastasis at 5 years in patients with stage III melanoma ranged from 6.5% in IIIA substage to 29.4% in IIID substage [42], which may be useful for determining the pertinence or frequency of surveillance scans for brain lesions. Among patients with stage II melanoma, there are also differences in the risk and pattern of relapse by substage, as evidence demonstrated that stage IIC patients relapsed more frequently, earlier, and were more likely to relapse systemically (again the lung was the predominant site of systemic recurrence) [43]. Of note, relapses were mainly detected by the patients in all substages, followed by physician detection of local/in-transit and nodal relapses in asymptomatic patients, whereas programmed imaging detected 31% of systemic relapses in stage IIC patients [43]. These findings highlight the role of the patient in his/her own surveillance and the relevance of patients' education on self-examination [44].

Surveillance imaging during the follow-up

The role of imaging in the follow-up of patients with high-risk melanoma is increasingly relevant with the availability of effective targeted and immunotherapies, and it is particular important to detect the relapse as soon as possible to improve survival outcomes [45–47]. However, there is a lack of consensus regarding the optimal imaging modalities and schedules to best identify melanoma recurrences, but most of them, except the UK guidelines [48], recommend surveillance imaging from stage IIB (Table 2).

There is no doubt that cross-sectional imaging can aid in the early detection of systemic metastasis in melanoma patients [49–51], but an OS benefit was, until recently, not proven. A recent real-world investigation that included stage IIB–IIIC patients who underwent imaging surveillance compared the treatment and survival outcomes of patients with asymptomatic surveillance-detected recurrence (ASDR) versus symptomatic recurrence [52]. ASDR (45% of cases) relapse was associated with lower burden of disease at recurrence, better prognostic factors, higher rates and response to systemic treatment, and improved survival outcomes. Besides, scan interval also influenced the proportion of ASDRs: 57% for a 0–6-month interval; 34% for a 6–12-month interval; and 33% for intervals > 12 months [52]. Another retrospective study showed that whole-body imaging detected 50% of asymptomatic recurrences in stage IIC or higher resected melanoma patients [53]. Among stage II patients, routine imaging has demonstrated to be important in detecting recurrence in patients with distant metastasis and with substage IIC melanoma [54], whereas patients and physicians are more likely to diagnose locoregional disease and less likely to detect progressive systemic disease [43, 55].

Current follow-up imaging protocols are subject to a wide variation in relation to the timing of these studies and the clinical stages in which they should be performed (Table 2). Many published imaging protocols to detect recurrences in high-risk patients (stages IIB–IV) included at least three computed tomography (CT) or positron emission tomography (PET)/CT scans during the first 3 years of follow-up, normally two by year [56]. Even a more intensive CT surveillance schedule of every 3 months for the 1 year of follow-up has been suggested for patients with stage IIIB–IIIC melanoma [46].

Regarding detection of lesions in the brain, magnetic resonance imaging (MRI) seems to be more sensitive that PET/CT [57] and it is usually recommended during the follow-up of stage IIC or higher [21, 58, 59]. As stated above, patients

Table 2 Image-based surveillance strategies according to international melanoma guidelines

ESMO (2019) [40]	NCCN (2022) [39]	AAD (2019) [21]	NICE guideline NG14 (2015) [48]
Thin melanoma: not recommended High-risk melanoma (thick or previous metastases): US of LNs, CT or whole-body PET/PET-CT scans Encourage consultation of the respective national guidelines	Stages I–IIA: not recommended without symptoms Stages IIB–IV: consider surveillance imaging every 3–12 months for 2 years, then every 6–12 months for another 3 years Regional lymph node US in patients with a positive SLNB who did not undergo CLND should be considered (consistent with the MSLT-II and DeCOG trials)	Stages I–IIA: not recommended Stages IIB–IV: surveillance imaging for up to 3–5 years, based on risk of recurrence and new primary melanomas Forgoing SLNB when eligible, failed SLNB procedures, positive SLNB without CLND: surveillance US of nodal basin	Stages I–IIB, IIC with negative SLNB: not recommended Stage IIC without SLNB, Stage III: consider imaging in a clinical trial or every 6 months for 3 years (with policy and funding) Stage IV: offer personalized schedule

AAD American academy of dermatology, *CLND* completion lymph node dissection, *CT* computed tomography, *ESMO* European society for melanoma oncology, *LN* lymph node, MRI magnetic resonance imaging, *NCCN* national comprehensive cancer network, *NICE* national institute for health and care excellence, *PET* positron emission tomography, *US* ultrasonography, *SLNB* sentinel lymph node biopsy

with SLN micrometastasis should receive frequent nodal US evaluation by an experienced radiologist when they are not treated with CLND, ideally every 3–4 months during the first 2 years, every 6 months during years 3 through 5, and then annually, based on MSLT-II and DeCOG-SLT trials [34, 35]; the elevated prevalence of regional nodal recurrences makes also nodal US a key element of the surveillance of stage II melanomas [60].

Despite the clinical advantage of intensive follow-up imaging surveillance, the cost of large numbers of imaging tests, and the relatively low diagnostic performance of certain imaging techniques should be taken into account. In this setting, Podlipnik, et al. evaluated the cost-effectiveness of different imaging protocols for follow-up of stage IIB, IIC and III malignant melanoma. These authors concluded that CT is cost-effective in the first 3 years in stage IIB melanoma and in the first 4 years of follow-up in stage IIC–III melanoma and that brain MRI is cost-effective in the 1 year in stage IIC–III melanoma [61].

Potential biomarkers to support melanoma surveillance

Several biomarkers have been examined for their clinical utility in melanoma, but few have been validated or approved for clinical use. Levels of serum lactate dehydrogenase (LDH), a marker of tumor burden and progression, are traditionally determined among patients with advanced disease, as elevated LDH levels are an independent predictor of poor survival [62], and it is included in the TNM classification [15]. A valid approach for patients with stage II and III melanoma may be to test LDH every 3–6 months during the first 2 years, and every 6–12 months until 5 years. Serum S100B protein is also seen as a measure of tumor burden and it has been investigated for its potential to select stage III patients for CLND [36] and to detect disease relapse during follow-up of stage IIB-III patients using the dynamic changes of S100B levels [63]. However, there are no prospective studies validating its implementation in clinical practice.

Imaging biomarkers represent an attractive non-invasive alternative to predict long-term outcomes in patients with melanoma. PET-based metabolic parameters, such as SUV max and total lesion glycolysis, were significantly higher in patients with recurrence versus without recurrence and non-survivors versus survivors [64–66]. Moreover, a negative PET 18 months after surgery seems to be highly predictive (80–84%) of subsequent non-recurrence in stage III melanoma, which may provide reassurance for patient and clinicians [67]. Finally, Reinert et al. evidenced an association of PET parameters with serologic tumor markers (LDH and S-100 protein) and inflammatory markers (C-reactive protein and alkaline phosphatase) in melanoma patients and

demonstrated their role as independent imaging predictors for overall survival [68].

With the improvements in genomic and molecular methods, liquid biopsy, a blood-based analysis of tumor-specific biomarkers, has been proposed as a valuable tool to identify early cancer progression [69]. Particularly, circulating tumor DNA (ctDNA) is emerging as a prognostic marker of relapse in stage II/III melanoma, as it can reveal occult metastatic disease that is not evident on radiological imaging [70]. There is also evidence that ctDNA concentration in advanced disease is significantly associated with solid tumor burden as determined by imaging, suggesting that it may provide a blood-based means to monitor tumor burden more frequently than imaging [71]. Moreover, increasing ctDNA levels could detect disease progression significantly earlier than do routine radiologic scans [72]. Once the methods to determine ctDNA are standardized, its implementation for the routine follow-up of melanoma patients as part of personalized medicine will broadly establish.

Outpatient follow-up and detection of second primary melanomas

Dermatologists and primary care physicians have an essential role in the multidisciplinary follow-up care for melanoma patients after primary lesion excision. Clinical recommendations after melanoma diagnosis and treatment should focus on patient education to increase compliance with sun protection and to perform self-examinations of the skin and lymph nodes for recurrence detection [73]. Moreover, it is well known that patients with melanoma have an increased risk of having other melanomas and non-melanoma skin cancers [74, 75], highlighting the importance of rigorous controls and adherence to regular full skin body examination. In this regard, digital dermoscopy is currently an effective tool for screening and diagnosing melanoma when employed by experienced users, decreasing the number of unnecessary excisions and enabling the detection of thinner melanomas compared to naked eye examination [76–78].

Risk factors for future primary melanomas include presence of atypical nevi, a family history of melanoma, a history of previous melanoma or non-melanoma skin cancer, sun exposure, and fair skin and hair pigmentation [1]. Familial melanoma should be suspected in individuals with a younger than usual age of diagnosis (< 54 years at diagnosis), personal or family history of melanoma and/or pancreatic cancer, or multiple dysplastic nevi [79]. The criteria for offering a genetic testing in Spain (a geographical area with low incidence of melanoma) are the following: at least, two primary melanomas in an individual; or two cases of melanoma among first- or second-degree relatives; or one case of melanoma and one case of pancreatic cancer in first- or second-degree relatives [80]. Genetic testing should include the germline mutations in high-penetrance melanoma predisposition genes, *CDKN2A* (cyclin-dependent kinase 2A) and *CDK4* (cyclin-dependent kinase 4) [81]. Other genetic predisposition syndromes associated with increased risk of melanoma are breast–ovarian cancer predisposition syndrome (*BRCA* genes), Li-Fraumeni syndrome (*TP53*), xeroderma pigmentosum (*XP* genes), and Cowden syndrome (*PTEN*) [82].

Recommendations and conclusions

Although there is no robust evidence that clearly defines the clinical follow-up of these patients,, based on available guidelines, the evidence discussed in the previous sections, and their own clinical experience, the expert panel's recommendations for melanoma patients' follow-up (Table 3) consider:

(1) The suitability of intensifying follow-up in the 1 years.
(2) The need to adapt it to the patient's risk (substage, pathological and molecular characteristics, etc.).
(3) The possible use of more sensitive imaging techniques, such as PET, which, given the clinical benefit of early detection of asymptomatic tumor relapse, could be cost-effective in the first years of follow-up.
(4) The use of imaging techniques in specific organs, such as brain MRI or ultrasound, in the follow-up of certain clinical stages based on the higher risk of relapse at that level.

This is currently the protocol used in our regional practice. We consider that the varying survival outcomes among stage II melanoma patients, currently not eligible for adjuvant treatment, should focused the attention on this population, with more exhaustive imaging-based surveillance (lymph node US and body CT scan) for those with thicker tumors [83]. Head MRI is recommended at baseline and every 6 months for 3 years in patients with stage IIC or higher, as it has been shown to be a frequent site of relapse [42, 43]. Given that the greatest benefits shown in the metastatic setting with targeted therapy and immunotherapy, both in response and survival rates, are associated with lower tumor burden, it is reasonable to think that the sooner the recurrence is detected, the tumor burden will also be lower, and therefore, the chances of obtaining a survival benefit will be greater. Detecting recurrence at a time of lower tumor burden, when patients are asymptomatic, may lead to improved clinical outcomes with effective systemic therapies. Additionally, the identification of individuals at high risk for developing second primary

Table 3 Recommended follow-up strategy for melanoma patients by substage

Assessment	Stage 0	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage IIC	Stage IIIA	Stages IIIB–D	Stage IV
Anamnesis and PE	Anually	Every 6 months for 3years; every 12 months afterwards			Every 3 months for 3 years; every 6 months for years 4 and 5; every 12 months afterwards				Individualize[a]
Laboratory test + LDH	–	–	Every 6 months for 3 years; every 12 months afterwards		Every 3 months for 3 years; every 6 months for years 4 and 5; every 12 months afterwards				Every 3 m
Lymph node US	–	–	Every 3–6 months for 2 years; every 6 months for years 3–5[b]						Individualize[a]
CT TAP (± neck)	–	–	–	–	Baseline post-operatively; follow-up every 6 months for 3 years	Every 3 months for 1y; every 3–6 months for years 2 and 3; every 12 months for years 4 and 5			Individualize[a]
CNS MRI	–	–	–	–	–	Baseline and every 6 months for 3 years or clinical suspicion			If clinical suspicion
PET/CT	–	–	–	–	–	Baseline postoperatively (if available and preferable including contrast-enhanced CT)[c]			
					Solving doubts/Uncertain findings during the follow-up				
Self-examination	Importance of patient education to perform self-examinations of the skin and lymph nodes								
Genetic testing	In case of suspected familial melanoma								

CNS central nervous system, *CT* computed tomography, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *US* ultrasonography, *SLN* sentinel lymph node, *TAP* thorax, abdomen and pelvis

[a]According to tumor board or trial protocol

[b]In stage IIB/C patients not undergoing SLN biopsy and in stage IIIA patients without lymphadenectomy, the frequency of US evaluation should be every 3 months during the first 2 years

[c]In case of PET is not available, baseline evaluation should be done with contrast-enhanced CT

melanomas is essential to tailor surveillance intensity, and patients should be aware of the importance of regular self-examination [84]. The provided recommendations are intended to assist health care professionals in their decisions about the frequency and type of assessments to be performed during the follow-up of early-stage melanoma patients with high risk of recurrence. These recommendations could serve as a basis for future prospective observational studies and even be updated if new scientific evidence emerges.

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Declarations

Conflict of interest Begoña Campos Balea has received honoraria as consultant or advisory boards from Roche, Sanofi, and Boehringer. She has received speaking honoraria from Roche, Pierre-Fabre, Novartis, Bristol-Myers-Squibb, Astra-Zeneca, MSD, and Sanofi. Ovidio Fernández-Calvo has received honoraria as consultant or advisory boards from Astellas Pharma, Roche, Pfizer, Bristol-Myers-Squibb, Sanofi, EUSA Pharma and Sanofi. He has received speaking honoraria from Pierre-Fabre, Novartis, Bristol-Myers-Squibb, Ipsen, Roche, Astellas Pharma, Bayer, and Janssen. Roberto García-Figueiras and Carlos Neira declares no conflicts of interest. Carmen Peña Penabad has received speaking honoraria from Roche, Novartis, Bristol-Myers-Squibb, Sanofi and LeoPharma. Carmela Rodríguez-López has received honoraria as consultant or advisory boards from Novartis. She has received speaking honoraria from Pierre-Fabre, Novartis, Bristol-Myers-Squibb, Roche, MSD, and Ipsen. Rocio Vilchez Simo has received honoraria as consultant or advisory boards from Novartis. She has received speaking honoraria from Novartis, Sanofi, Eisai, Roche and Pfyzer. María Quindós-Varela reports honoraria and advisory/consultancy from AstraZeneca, GSK, MerckSharp and Dohme, Novartis, PharmaMar, Roche, Bristol-Myers-Squibb, and Pierre Fabre. She has received Travel/Accommodation/Expenses from AstraZeneca, Pharmamar, Roche, GSK, Novartis Merck Sharp and Dohme and speakers

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