

[ L I T E R A T U R E R E V I E W ]

# A Global Review of Melanoma Follow-up Guidelines

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## ABSTRACT

Early detection of a melanoma recurrence is a major concern for the clinician. However, the follow-up care of melanoma patients lacks a uniform approach. Different dermatological and oncological organizations have developed their own strategies of follow-up management that vary by specialty and methods of screening for recurrence. Some areas of controversy in the follow-up care of melanoma patients include providers of care, use of staging versus Breslow depth to determine follow-up, the role of imaging and laboratory tests, frequency and duration of physical exams, and psychological well-being. Studies have evaluated these aspects of follow-up management, but no consensus exists. However, it is essential for clinicians to collaborate between specialties for an effective, evidence-based approach to melanoma clinical follow-up care. (*J Clin Aesthet Dermatol.* 2013;6(9):18–26.)

Cutaneous malignant melanoma (MM) incidence has increased dramatically and is a major health concern for the dermatologist, oncologist, and surgeon. Despite its increasing incidence, MM follow-up care has remained an area of debate and challenge. To date, there have been few prospective randomized studies to substantiate any particular schedule for follow-up. Several dermatologic and oncologic organizations have developed their own guidelines for the follow-up care of melanoma patients. Encouraging more consensus among international organizations may reduce clinician frustration and the economic burden of melanoma on health care systems and improve patient outcomes. The objective of this article is to present current recommendations on the follow-up care of melanoma; highlight areas of overlap, distinction, and controversy; and support further collaboration among guideline societies.

## MELANOMA AS A CONTINUING HEALTH THREAT

In 2013, it is estimated that 76,690 persons in the United States will be diagnosed with MM with a median age of

diagnosis at 59 years.<sup>1,2</sup> A recent study performed by Linos et al<sup>3</sup> estimates that the incidence of melanoma has increased by 3.1 percent a year. However, melanoma incidence may be underestimated because many superficial and *in-situ* melanomas in outpatient settings are not reported.<sup>2</sup> In 2000, the lifetime risk of a person born in the United States developing melanoma was estimated at 1 in 41 and 1 in 61 for men and women, respectively.<sup>4</sup>

Incidence of melanoma is increasing in men more than any other malignancy. Among men ages 65 and older, the rates of melanoma have increased to more than 125 cases per 100,000 men.<sup>3</sup> Women also demonstrate a similar trend with melanoma increasing more than any other malignancy except lung cancer. Melanoma still remains the most common cancer death for women 25 to 30 years of age. Overall, melanoma is the fifth most common cancer for men and the seventh most common malignancy for women.<sup>1</sup> Deaths due to melanoma are estimated to be 9,480 for 2013. Mortality has been decreasing significantly for Caucasians younger than age 50 by 2.8 and 2.0 percent per year between 2005 and 2009 for men and women, respectively. However, in those older than 50 during the same time

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period, the death rate increased by 1.1 percent per year in men and remained stable in women.<sup>1</sup>

## MELANOMA STAGING

The stage at presentation of melanoma has a significant impact on the course of the disease. Most melanoma patients present with localized disease 82 to 85 percent of the time, followed by regional involvement 10 to 13 percent of the time, and distant metastatic disease 2 to 5 percent of the time.<sup>2</sup> The staging of melanoma holds prognostic value and dictates the recommendation in treatment. Staging is determined by the tumor, node, and metastasis (TMN) system developed by the American Joint Committee on Cancer (AJCC) (Table 1).<sup>5</sup> Criteria include microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy as well as a new emphasis on dermal mitotic index (measured in mm<sup>2</sup>) for T1 melanoma ( $\leq 1$  mm). Survival and recurrence rates for melanoma follow the pathologic stages set forth by the AJCC (Table 2)<sup>5</sup> and are used to guide follow-up recommendations.

## RECOMMENDATIONS FOR FOLLOW-UP CARE OF MELANOMA

Recommendations for follow-up care focus on duration and frequency of follow-up, history and physical examination, and the utilization of imaging and laboratory studies to detect recurrence or metastasis. These are summarized in Table 3.

**National Comprehensive Cancer Network (NCCN).** For all melanoma stages, the NCCN recommends at least annual skin examination for life and education regarding monthly self-skin exams. This is the only recommendation for Stage 0. The frequency of dermatologic surveillance is provided in a range and should be adjusted based on the patient's risk for disease recurrence as well as new primary melanoma based on mole phenotype and family history. Stages IA to IV patients should also be instructed to perform a self-lymph node exam in addition to regular self-skin exams. Patients with Stage IA to IIA disease should receive a history and

**TABLE 1. TNM staging categories for cutaneous melanoma**

CLASSIFICATION	THICKNESS (MM)	ULCERATION STATUS/MITOSSES
<b>T in situ</b>	NA	NA
T1	$\leq 1.0$	a. Without ulceration and mitosis $< 1/\text{mm}^2$ b. With ulceration or mitoses $\geq 1/\text{mm}^2$
T2	1.01–2.00	a. Without ulceration b. With ulceration
T3	2.01–4.00	a. Without ulceration b. With ulceration
T4	$> 4.00$	a. Without ulceration b. With ulceration
<b>N</b>	<b>Number of Metastatic Nodes</b>	<b>Nodal Metastatic Burden</b>
N0	0	NA
N1	1	a. Micrometastases <sup>1</sup> b. Macrometastases <sup>2</sup>
N2	2	a. Micrometastases <sup>1</sup> b. Macrometastases <sup>2</sup> c. In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes or matted nodes or in transit metastases/satellites with metastatic nodes	
<b>M</b>	<b>Site</b>	<b>Serum LDH</b>
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
M1c	Any distant metastases	Elevated

Abbreviations: NA=not applicable; LDH=lactate dehydrogenase  
<sup>1</sup>Micrometastases are diagnosed after sentinel lymph node biopsy.  
<sup>2</sup>Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Adapted from Balch CM, Gershenwald JE, Soong S, et al. Final version of 2009 AJCC Melanoma Staging Guidelines. *J Clin Oncol*. 2009;27(61):6199–6206.

physical exam with special attention to lymph nodes and skin every 3 to 12 months for five years and then annually as clinically indicated. Routine imaging is not recommended for stage IA to IIA disease. Patients with Stage IB to IV should have a history and physical with emphasis on nodes and skin every 3 to 6 months for two years, then every 3 to 12 months for three years, and then at least annually thereafter, with the specific recommendation for lifelong dermatologic surveillance. Five-year routine imaging considerations to monitor Stage IIB to IV melanoma for recurrent or metastatic disease include chest x-ray, computed tomography (CT), and/or positron emission tomography (PET) scans every 3 to 12 months and annual magnetic resonance imaging (MRI) scans of the brain. However, routine follow-up radiologic imaging is not recommended for Stage IA to IIA melanomas. Blood testing to detect recurrent disease is not recommended during follow-up for any stage of melanoma. However, serum lactate dehydrogenase (LDH) levels are considered valuable at the time of diagnosis in Stage IV melanoma for their prognostic value.<sup>2</sup>

#### **European Society for Medical Oncology (ESMO).**

The ESMO guidelines do not follow a staging system, but provide general recommendations for monitoring patients at risk for recurrent and new disease. In contrast to previous guidelines, there is no current consensus on the frequency of patient follow-up and use of imaging. Thin primary melanomas have a small risk of relapse, and routine imaging is not recommended for these patients. In high-risk patients (i.e., those with thick primary tumors or recent tumor resection), CT +/- PET scans are suggested for earlier detection of relapse. Should any laboratory tests be ordered, serum S100 is recognized as the most accurate marker in the blood for disease recurrence and is used to monitor disease progression. The ESMO also suggests patient education regarding sun avoidance and lifelong regular self-examinations of the skin and peripheral lymph nodes.<sup>6</sup>

**American Academy of Dermatology (AAD).** The 2010 AAD Guidelines/Outcomes Committee formed a task force to evaluate and give recommendations regarding the guidelines of care for primary cutaneous melanoma. The task force recommendations advise clinicians to evaluate the patient individually at least annually and possibly every 3 to 12 months based on several factors affecting the risk of recurrent and new primary melanoma. These modifying factors include tumor stage, history of multiple melanomas, presence of atypical nevi, family history of melanoma, patient anxiety, and the patient's ability to recognize signs and symptoms of a disease. Patients should also be educated on performing monthly self-skin and self-lymph node examinations.<sup>7</sup> Routine surveillance laboratory tests and imaging studies are not recommended in asymptomatic patients. Although imaging studies can be considered in patients with high risk for recurrence, they are not recommended after five years.

**British Association of Dermatologists (BAD).** The BAD follow-up recommendation for *in situ* melanomas is self-examination with no additional follow-up required. Stage IA melanomas should have a history and physical 2 to

4 times for 12 months. Stage IB to IIIA melanomas should receive a history and physical every three months for three years then every six months for two years. Stage IIIB to C and resected Stage IV melanomas should be evaluated every three months for three years, every six months for the next two years, and then annually for the next five years. CT surveillance may be considered in these patients if appropriate. Unresected stage IV melanoma should be seen according to clinical need. There are no specific guidelines given for the utilization of blood work as a part of follow-up practices.<sup>8</sup> Follow-up intervals should be tailored to a patient's individual stage and risk of recurrence.

**Swiss Melanoma Guidelines.** Swiss Melanoma Guidelines offer specific recommendations based on initial TNM staging and years following diagnosis to determine the interval of clinical examinations and imaging techniques. Stage I ( $\leq T1N0$ ) melanomas require a physical examination every six months for the first three years and yearly up to 10 years after the initial diagnosis. Physical examinations for Stage I ( $T2N0$ ) to IIB melanomas are advised every three months for the first three years, every six months for the next two years, and every 6 to 12 months for up to 10 years. For Stage IIC to III melanomas, physical examinations are suggested every three months for the first five years and then every six months afterwards for up to 10 years. S100 protein is a good marker for melanoma relapse and recommended in the first five years of follow-up every 6 to 12 months for Stage I ( $T2N0$ ) to IIB melanomas and every six months for Stage IIC to III melanomas. Similarly, locoregional lymph node sonography is recommended every 6 to 12 months for Stage I ( $T2N0$ ) to IIB melanomas and every six months for Stage IIC to III melanomas as well. Abdominal sonography and chest x-ray imaging studies are considered on an individual basis for patients with Stage I ( $T2N0$ ) to III melanomas for five years after the initial diagnosis. Whole body imaging by CT, MRI, PET, or PET-CT is recommended every 6 to 12 months in the first five years of follow-up in patients with Stage IIC to Stage III melanomas. In patients with Stage IV disease, all physical, laboratory, and imaging evaluations are evaluated on an individual basis.<sup>9</sup>

**German Cancer Society and German Dermatologic Society.** The German follow-up guidelines are based on stage and tumor thickness. Physical examination is advised for Stage I  $<1.0\text{mm}$  every six months for the first 1 to 5 years and then every 6 to 12 months for years 6 to 10. Stages I and II  $>1.0\text{mm}$  should receive a physical examination every three months for the first 1 to 5 years and then every 6 to 12 months for years 6 to 10. Stage III should have a physical exam every three months for years 1 to 5 and then every six months for years 6 to 10. No lymph node sonography is recommended for Stage I  $<1.0\text{mm}$ . It is suggested every six months for Stage I and II  $>1.0\text{mm}$  and every 3 to 6 months for Stage III during years 1 to 5. Serum S100 $\beta$  protein levels are only recommended every 3 to 6 months for 1 to 5 years for Stage I and II  $>1.0\text{mm}$  and Stage III. Imaging studies, including abdominal sonography and chest x-ray or CT, MRI,

**TABLE 2. Clinical and Pathological stage grouping for melanoma with comparison of 10-Year survival rates from 2002–2010**

STAGE	PATHOLOGIC STAGE GROUPING	10-YEAR SURVIVAL RATE	
		2002	2010
Stage 0	Tis N0 M0		
Stage IA	T1a N0 M0	88	94
Stage IB	T1b–T2a N0 M0	80	85
Stage IIA	T2b–T3a N0 M0	64	67
Stage IIB	T3b–4a N0 M0	52	56
Stage IIC	T4b N0 M0	32	40
Stage III	Stage IIIA T1–4a N1a/N2a M0	60	68
	Stage IIIB T1b–T4b N1a/N2a M0	42	44
	• T1a–T4a N1b/N2b M0	40	44
	• T1a–T4a/b N2c M0		52
	Stage IIIC T1–T4b N1b/2b M0	20	30
	• T1a–T4b N3 M0	18	26
	• Any T N3 M0		
Stage IV	Any T Any N M1	2.5–10	2.5–5

Abbreviations: *is=in situ*Adapted from Balch CM, Gershenwald JE, Soong S, Thompson JF, Atkins MB, Byrd DR, et al. Final Version of 2009 AJCC Melanoma Staging Guidelines. *J Clin Oncol*. 2009;27(61):6199-6206.

or PET scan are recommended for only Stage III at six-month intervals for years 1 to 5.<sup>10</sup>

**Guidelines for the Management of Melanoma in Australia and New Zealand (GMMANZ).** GMMANZ follow-up recommendations emphasize the importance of self-examinations in patients properly trained to detect recurrent disease. In conjunction with this cost-effective measure, patients with Stage I melanoma should receive a physical examination every six months for five years from a healthcare professional of their choice. Patients with Stage II, III disease should get a physical examination every 3 to 4 months for five years and yearly thereafter. Ultrasound is the one recommended imaging modality in patients with advanced disease, but only if performed by an experienced ultrasonographer. There are no specific recommendations for Stage IV disease. However, more frequent visits are recommended in patients with extensive disease, many atypical nevi, a family history of melanoma, and those with difficulty in performing self-evaluation. GMMANZ also emphasizes the importance of evaluating individual patient needs in developing a follow-up schedule.<sup>11</sup>

## CONTROVERSIAL ISSUES

The goal of any cancer follow-up regimen is to identify recurrence or metastasis early and initiate treatment in hopes of having a positive impact on the long-term outcome. Melanoma is no exception. Patients with a personal history of melanoma have a 4- to 8-percent lifetime risk of developing a secondary primary melanoma.<sup>2</sup> Societies are challenged to develop evidence-based follow-up guidelines that balance the medical needs of the patient with improved survival and economic costs to healthcare. Among them who should provide follow-up care and practice guidelines (i.e., based on staging, individual risk factors, or a combination thereof) vary from one organization to the next.

**Providers of follow-up care.** Melanoma follow-up care is carried out by physicians in primary care and by specialists in general surgery, dermatology, oncology, oncologic surgery, and plastic surgery. More recently, physician extenders, such as nurse practitioners and physician assistants, have also become involved in melanoma management. The provider of follow-up care is often dictated by melanoma stage, patient preference, and



TABLE 3. Summary of melanoma follow-up guidelines

	PROVIDER OR SPECIALTY	BASIS OF FOLLOW-UP GUIDELINES	FOLLOW-UP GUIDELINES			
			STAGE/ BRESLOW THICKNESS	H&P	IMAGING/ LABORATORY EVALUATION	COMMENTS
NCCN	Not discussed	Stage specific	Stage 0	H&P annually for life	None	<ul style="list-style-type: none"> <li>• Lifelong clinical exams</li> <li>• Routine blood tests not recommended</li> <li>• Frequency of H&amp;P given in ranges and should be adjusted based on risk factors</li> <li>• Self-skin exams should include self-lymph node exams</li> </ul>
			Stage IA–IIA	H&P every 3–12 months for 5 years and then annually as clinically indicated	Not recommended	
			Stage IIB–IV	H&P every 3–6 months for 2 years and then every 3–12 months for 3 years and then annually as clinically indicated	Consider CXR, CT+/-PET every 3–12 months and annual MRI of brain. No imaging in asymptomatic patients after 5 years	
ESMO	Not discussed	Risk	Low risk/ thin melanomas	No specific recommendations	Not recommended	<ul style="list-style-type: none"> <li>• Emphasis on patient education and lifelong regular self-exams</li> </ul>
			High risk	No specific recommendations	CT +/- PET recommended	
AAD	Not discussed	General recommendations	NA	H&P at least annually, possibly every 3–12 months	<ul style="list-style-type: none"> <li>• Not recommended in asymptomatic patients</li> <li>• Directed imaging and lab work not recommended after 5 years in high-risk patients</li> </ul>	<ul style="list-style-type: none"> <li>• Lifelong clinical exams</li> <li>• Follow-up should be based on individual risk factors</li> <li>• Not stage-specific recommendations</li> </ul>
BAD	Specialist skin cancer multidisciplinary teams	Stage specific	<i>in situ</i> Stage IA	Self-exam H&P 2–4 times for 12 months	No specific recommendations	No follow-up required for MIS
			Stage IB–IIIA	H&P every 3 months for 3 years then every 6 months for 2 years	No specific recommendations	—
			Stage IIIB–IV (resected)	H&P every 3 months for 3 years, every 6 months for the next 2 years and then annually for the next 5 years	Consider CT	—
			Stage IV (unresected)	Per patient need	No specific recommendations	Not discussed





TABLE 3 continued. Summary of melanoma follow-up guidelines

	PROVIDER OR SPECIALTY	BASIS OF FOLLOW-UP GUIDELINES	FOLLOW-UP GUIDELINES			
			STAGE/ BRESLOW THICKNESS	H&P	IMAGING/ LABORATORY EVALUATION	COMMENTS
German Cancer Society and German Dermatologic Society	Not discussed	Stage and Breslow thickness	Stage I <1mm	H&P every 6 months for years 1–5 then every 6–12 months for years 6–10	No imaging or blood work	<ul style="list-style-type: none"> <li>• Limit clinical exams to 10 years</li> <li>• Use of LNS, S100<math>\beta</math> levels emphasized</li> </ul>
			Stage I, II >1mm	H&P every 3 months for years 1–5 then every 6–12 months for years 6–10	LNS every 6 months for years 1–5	
			Stage III	H&P every 3 months for years 1–5 then every 6 months for years 6–10	S100 $\beta$ level every 3–6 months for years 1–5 No additional imaging studies LNS every 3–6 months for years 1–5	
			Stage IV	Not discussed	S100 $\beta$ level every 3–6 months for years 1–5 Abdominal sonography and CXR or CT, MRI, or PET every 6 months for years 1–5	
Swiss Guidelines	Not discussed	Stage specific	Stage I ( $\leq$ T1N0)	H&P every 6 months for years 1–3 then annually from years 6–10	None	<ul style="list-style-type: none"> <li>• Lifelong clinical surveillance is recommended</li> <li>• Use of LNS emphasized</li> <li>• Abdominal sonography and CXR on individual basis for Stage I (T2N0)–IV melanomas</li> </ul>
			Stage I (T2N0)–IIB	H&P every 3 months for years 1–3, every 6 months for years 4–5, then every 6–12 months for years 6–10	LNS and S100 every 6–12 months for years 1–5	
			Stage IIC–III	H&P every 3 months for years 1–5 then every 6 months for years 6–10	LNS and S100 every 6 months for years 1–5 CT, MRI, PET or PET-CT every 6–12 months for years 1–5	
			Stage IV	Individual	Individual	
Guidelines for Management of Melanoma in Australia and New Zealand	Patients themselves and/or preferred health professional	Stage specific	Stage I	H&P every 6 months for 5 years	<ul style="list-style-type: none"> <li>• Ultrasound may be used in conjunction with clinical examination only in patients with more advanced primary disease</li> <li>• No lab tests are recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Self examinations are essential and all patients should be properly educated on how to perform them</li> <li>• Individual patient's needs must be considered before appropriate follow-up is offered</li> </ul>
			Stage II, III	H&P every 3–4 months for 5 years then annually thereafter		
			Stage IV	Not discussed		

H&P=history and physical examination including review of systems, full skin examination, and lymph node examination; MIS=melanoma *in situ*; LNS=lymph node sonography; CXR=chest x-ray; DNS=dysplastic nevus syndrome



access to specialty care. In addition, the demands of an overburdened healthcare system and shortage of providers often necessitate melanoma patients following up with physician extenders. Follow-up may be multidisciplinary, with several physicians coordinating the patient's care.

There is some controversy over who should provide follow-up care. A study by McKenna et al<sup>12</sup> concluded that dermatologists should have a more integral role in managing melanoma because their patients have better survival when compared to general surgeons or plastic surgeons. Some argue that a thorough understanding of dermatologic disease is required for patient surveillance, while others maintain it is the surgeon's responsibility to follow the patient. Regardless, having a consensus on follow-up care might help decrease the discrepancies between specialists and health care professionals managing melanoma patients.

**Basis of follow-up care: Staging.** The NCCN, BAD, Swiss, German, and GMMANZ follow-up guidelines are based on melanoma staging. Unlike the other guidelines, the AAD and ESMO recommendations are neither stage specific or based on Breslow thickness. The guidelines offered by the AAD and GMMANZ present an integrated approach with follow-up care tailored to each patient's individual situation. In contrast to their previous recommendation, the ESMO questions the use of specific follow-up recommendations due to the large number of patients detecting their own melanoma recurrences from self-examination. In Australia and New Zealand, training patients to properly perform self-examinations is heavily emphasized. Which system has better survival outcomes has yet to be studied.

**Frequency and duration of the history and physical examination.** Since the majority of Stage I and II melanoma recurrences are locoregional, the physical examination remains the cornerstone of follow-up care, a critical aspect highlighted by all the recommendations of each society in this article. Basseres et al<sup>13</sup> reported that of 115 recurrences detected in 528 patients with Stage I melanoma, 87 percent were found on clinical exam. Weiss et al<sup>14</sup> reported that the physical exam detects metastasis 94 percent of the time and Wang et al<sup>15</sup> concluded physical exams uncover recurrences 50 percent of the time. Soft tissue metastases and remote nodal involvement can also be detected by a clinical exam, but visceral metastases are less likely to be identified by physical exam alone. In a review by Francken et al,<sup>16</sup> 62 percent of melanoma recurrences were detected by patients themselves. The "Check It Out" randomized trial additionally demonstrated that patient education improved thorough skin self-examination and earlier detection of melanoma.<sup>17</sup> These findings illustrate the importance of patient education and self-exams in follow-up care. Furthermore, patient self-exams and physician surveillance appear to be the most cost-effective methods of follow-up care.<sup>13,18,19</sup>

Despite the significance of a physical exam, no consensus exists regarding the optimal frequency and longitudinal duration of visits after a primary melanoma

diagnosis. The recommended duration varies from one year after the initial diagnosis of a primary melanoma to the patient's entire lifetime. The BAD recommends that physical exams for Stage IA melanomas should be limited to 12 months, five years for stage IB to IIIA, and 10 years for stage IIIB to IV. The BAD also states that *in situ* melanomas do not require follow-up care at all. The German guidelines limit clinical exams to 10 years for all stages. Regardless of stage or Breslow thickness, the NCCN, AAD, and Swiss Guidelines advise lifelong clinical exams. GMMANZ guidelines recommend follow-up for five years in patients with Stage I disease and annual evaluations for life in patients with Stage II or greater.

The frequency of follow-up intervals range from 3 to 12 months. Most melanoma recurrences occur within the first five years of diagnosis. Therefore, it would be logical to increase the frequency of surveillance during that period and decrease the intervals thereafter. Late recurrences have also been reported.<sup>20</sup> Difronzo et al<sup>21</sup> concluded that all patients diagnosed with cutaneous melanoma should undergo lifelong follow-up at biannual intervals to allow for earlier diagnosis and improved survival. However, no direct data support one interval schedule over another.<sup>22</sup>

Some recommending bodies, such as the NCCN, BAD, AAD, and GMMANZ, suggest using a patient's risk factors to determine the interval between exams. Risk factors include, but are not limited to, fair skin, history of atypical nevi, previous melanoma, family history of melanoma, staging, Breslow thickness, and the patient's ability to recognize signs and symptoms of disease.<sup>7</sup> These factors can assist in developing how often melanoma patients need to be seen and may account for how melanoma patients are followed differently.

**Imaging and blood work.** The use of imaging and blood work in the follow-up care of melanoma centers around two confounding issues. The first issue involves the sensitivity or specificity for detecting early metastasis or recurrence. The second issue is whether or not detection of metastasis confers improved survival. Ideally, imaging and blood tests should be highly specific and sensitive and increase overall survival.

The most extensively studied blood test in melanoma follow-up is serum S100 $\beta$ . Miliotis et al<sup>23</sup> reported that S-100 $\beta$  alone had a sensitivity and specificity of detecting recurrent melanoma of 43 and 94 percent, respectively. In addition, protein S100 $\beta$  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.<sup>24</sup> The results of a meta-analysis performed by Mocellin et al<sup>25</sup> suggested that S100 $\beta$  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 S100 $\beta$  in follow-up care. Serum S100 $\beta$  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. 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.

The primary imaging studies suggested by the various organizations include chest x-ray, CT scan, PET scans, lymph node and abdominal sonography, and MRI. Despite the fact that chest x-ray may detect metastasis in six percent of symptomatic patients,<sup>14</sup> Garbe et al<sup>26</sup> question the benefit of chest x-ray for screening in asymptomatic patients, a finding supported by other researchers.<sup>15,27</sup> Even with early identification of metastasis, the use of chest x-rays to detect asymptomatic pulmonary metastasis does not improve survival.<sup>27</sup> Routine CT,<sup>28</sup> MRI, or PET scanning in the absence of clinical symptoms, physical findings, or abnormal laboratory values has an extremely low yield for detecting metastasis. However, ultrasonography of the regional lymph nodes may improve survival rates.<sup>29,30</sup> Xing et al<sup>31</sup> recently reported that ultrasonography is the most accurate imaging modality for staging and surveillance in patients with Stage III and IV melanomas. The use of lymph node sonography is widely accepted abroad and recommended by the German, Swiss, and GMMANZ guidelines.

No consensus exists on the role of imaging or blood work in melanoma follow-up. In a survey of physicians following melanoma, Provost et al<sup>32</sup> showed that there was significant variability between physicians and the utilization of various imaging studies and lab work for follow-up care. The Swiss and German guidelines are very specific in recommending regular serologic and imaging examinations during follow-up care. In contrast, the ESMO and BAD do not offer specific guidelines for imaging and laboratory evaluation, but indicate their use in high-risk and stage IIIB to IV melanomas. The NCCN does recommend routine studies for stages IIB to IV and the AAD recommends directing imaging and lab work based on each individual patient. An obvious area of distinction exists between the Swiss and German guidelines, which both recommend lymph node sonography and S100 $\beta$  testing, two tests considered investigational in North America.

**Psychological impact.** Undeniably, melanoma has profound effects on patients both psychologically and emotionally. Follow-up care for melanoma may be adjusted to accommodate the psychological needs of the patient, a reality pointed out in the recommendations from the AAD.<sup>7</sup> Few studies have evaluated the psychological effects of follow-up care. Brandberg et al<sup>33</sup> found that regular follow-up may help patients cope with the idea of recurrence and offer opportunities for patient education. A melanoma diagnosis often creates a sense of despair and anxiety for patients and their loved ones. Many patients are consumed with the fear of a recurrence and demand certain tests or studies in hopes of earlier detection and better outcomes. This may go against the clinician's better judgment, but is often done to appease the patient.

**Future directions.** Although this article examines

guidelines from across the world, it is important to emphasize that despite the differences, all recommendations exist to improve patient survival. In fact, the guidelines are actually very similar philosophically. The TNM staging system is the standard by which guidelines are offered with room for flexibility based on a patient's individual risk factors. All guidelines seek to have patients evaluated by someone properly trained to detect recurrence or new primary disease. Other aspects of follow-up care (e.g., testing such as lymph node sonography) should be evaluated further and their role examined. A collaboration from all of the organizations would be beneficial to establish consistent guidelines for melanoma follow-up care.

## REFERENCES

1. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
2. NCCN Clinical Practice Guidelines in Oncology: Melanoma. 2013. [http://www.nccn.org/professionals/physician\\_gls/pdf/melanoma.pdf](http://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf). Accessed on January 23, 2013.
3. Linos E, Swetter SM, Cockburn MG, et al. Increasing burden of melanoma in the United States. *J Invest Dermatol*. 2009;129:1604–1606.
4. Desmond RA, Soong SJ. Epidemiology of malignant melanoma. *Surg Clin North Am*. 2003;83:1–29.
5. Balch CM, Gershenwald JE, Soong S, et al. Final version of 2009 AJCC Melanoma Staging Guidelines. *J Clin Oncol*. 2009;27:6199–6206.
6. Dummer R, Hauschild A, Guggenheim M, et al. Melanoma: ESMO Clinical Practice Guidelines of care for the diagnosis, treatment, and follow-up. *Ann Oncol*. 2010;21(Suppl 5):194–197.
7. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2011;65:1032–1047.
8. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised UK guidelines of care for the management of cutaneous melanoma 2010. *Br J Dermatol*. 2010;163:238–256.
9. Dummer R, Guggenheim M, Arnold AW, et al. Task Force Skin Cancer. Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. *Swiss Med Wkly*. 2011;141:w13320.
10. Garbe C, Hauschild A, Volkenandt M, et al. Evidence and interdisciplinary consensus-based German guidelines: diagnosis and surveillance of melanoma. *Melanoma Res*. 2007;17(6):393–399.
11. Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand. 2008. [www.nhmrc.gov.au/guidelines/publications/cp111](http://www.nhmrc.gov.au/guidelines/publications/cp111). Accessed June 6, 2013.
12. McKenna DB, Marioni JC, Lee RJ, et al. A comparison of dermatologists', surgeons' and general practitioners' surgical management of cutaneous melanoma. *Br J Dermatol*. 2004;151(3):636–644.
13. Basseres N, Grob JJ, Richard MA, et al. Cost-effectiveness of surveillance of Stage I melanoma: a retrospective appraisal based on a 10-year experience in a dermatology department in France. *Dermatol*. 1995;191:192–203.
14. Weiss M, Loprinzi CL, Creagan ET, et al. Utility of follow-up



- tests for detecting recurrent disease in patients with malignant melanomas. *JAMA*. 1995;274(21):1703–1705.
15. Wang TS, Johnson TM, Cascade PN, et al. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. *J Am Acad Dermatol*. 2004;51(3):399–405.
  16. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localized primary cutaneous melanoma. *Lancet Oncol*. 2005;6:608–621.
  17. Weinstock MA, Risica PM, Martin RA, et al. Melanoma early detection with thorough skin self-examination: the check it out randomized trial. *Am J Prev Med*. 2007;32(6):517–524.
  18. Hofmann U, Szedlak M, Rittgen W, et al. Primary staging and follow-up in melanoma patients: monocenter evaluation of methods, cost and patient survival. *Br J Cancer*. 200;87:151–157.
  19. Hengge UR, Wallerand A, Stutzki A, Kockel N. Cost-effectiveness of reduced follow-up in malignant melanoma. *J Dtsch Dermatol Ges*. 2007;5(10):898–907.
  20. Crowley NJ, Siegler HF. Late recurrence of malignant melanoma: analysis of 168 patients. *Ann Surg*. 1990; 212:173–177.
  21. DiFronzo LA, Wanek LA, Morton DL. Earlier diagnosis of second primary melanoma confirms the benefits of patient education and routine postoperative follow-up. *Cancer*. 2001;91(8):1520–1524.
  22. Kelly JW, Blois MS, Sagebiel RW. Frequency and duration of patient follow-up after treatment of a primary malignant melanoma. *J Am Acad Dermatol*. 1985;13 (5 Pt 1):756–760.
  23. Miliotis G, Cruse W, Puleo C, et al. The evaluation of new putative markers for melanoma (abstr). Presented at: Forty-Seventh Annual Cancer Symposium of the Society of Surgical Oncology; 1994:169.
  24. Garbe C, Leiter U, Ellwanger U, et al. Diagnostic value and prognostic significance of protein S-100beta, melanoma-inhibitory activity, and tyrosinase/MART-1 reverse transcription-polymerase chain reaction in the follow-up of high-risk melanoma patients. *Cancer*. 2003;97(7):1737–1745.
  25. Mocellin S, Zavagno G, Nitti D. The prognostic value of serum S100B in patients with cutaneous melanoma: a meta-analysis. *Int J Cancer*. 2008;123(10):2370–2376.
  26. Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. *J Clin Oncol*. 2003;21:520–529.
  27. Tsao H, Feldman M, Fullerton JE, et al. Early detection of asymptomatic pulmonary melanoma metastases by routine chest radiographs is not associated with improved survival. *Arch Dermatol*. 2004;140:67–70.
  28. Kuvshinoff BW, Kurtz C, Coit DG. Computed tomography in the evaluation of patients with stage III melanoma (abstr). Forty-Ninth Annual Cancer Symposium of the Society of Surgical Oncology; 1996: 29.
  29. Brountzos EN, Panagiotou IE, Bafaloukos DI, Kelekis DA. Ultrasonographic detection of regional lymph node metastases in patients with intermediate or thick malignant melanoma. *Oncol Rep*. 2003;10:505–510.
  30. Schmidt-Wendtner MH, Paerschke G, Baumert J, et al. Value of ultrasonography compared with physical examination for the detection of locoregional metastases in patients with cutaneous melanoma. *Melanoma Res*. 2003;13:183–188.
  31. Xing Y, Bronstein Y, Ross MI, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. *J Natl Cancer Inst*. 2011;103(2):129–142.
  32. Provost N, Marghoob AA, Koft AW, et al. Laboratory tests and imaging studies in patients with cutaneous malignant melanomas: a survey of experienced physicians. *J Am Acad Dermatol*. 1997;36(5Pt 1):711–720.
  33. Brandberg Y, Månsson-Brahme E, Ringborg U, Sjöden PO. Psychological reactions in patients with malignant melanoma. *Eur J Cancer*. 1995;31A(2):157–162. ●