Imaging and Laboratory Workup for Melanoma

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KEYWORDS

• Melanoma • Metastasis • CT • MRI • PET • Ultrasound • LDH • S100B

KEY POINTS

- Imaging and laboratory work have no role in the workup of early-stage melanoma nor in routine surveillance.
- Computed tomography (CT) and MRI play roles in melanoma workup; however, they have site-specific limitations.
- Fused PET/CT and PET/MRI improve the diagnostic accuracy compared with PET alone in the detection of metastatic disease.
- Single-photon emission tomography/CT improves the nodal detection rates compared with planar lymphoscintigraphy in sentinel lymph node workup.
- Lactate dehydrogenase represents a reliable serum biomarker in late-stage melanoma. S100B continues to be studied and may represent a helpful marker in intermediate to late-stage disease.

INTRODUCTION

Skin cancer represents by far the most common cancer in the world, and among those, melanoma represents about 1% of all skin cancers. However, melanoma accounts for most deaths related to skin cancer.[1] Approximately 80% to 85% of patients diagnosed with melanoma without evidence of metastasis survive at least 5 years, indicating that about 15% to 20% of patients without clinical signs of metastasis die from progression of disease and occult metastasis within 5 years, thus representing a significant rate of mortality from this type of cancer. Therefore, a thorough and comprehensive workup is always warranted to rule out metastatic disease.[2] Patients with early-stage melanoma have favorable outcomes following complete surgical resection. However, about 50% to 80% of patients with locoregional disease and almost all patients with distant metastasis experience recurrence after primary treatment.[3] Hence, management of patients with advanced metastatic disease has been a challenge. The most common sites of metastasis in decreasing frequency are skin, lymph nodes, lungs, liver, brain, bone, and gastrointestinal tract.[4] Physical examination remains the mainstay of the initial evaluation, particularly in localized disease, and in evaluation of local and regional lymph nodes, although it is relatively insensitive and has limited use for detection of metastasis in visceral sites. Unlike squamous cell carcinoma of the head and neck where imaging is used for both assessment of local disease and regional involvement, imaging and laboratory studies in melanoma are used primarily to assist in detection of locoregional and distant metastatic disease once the diagnosis of melanoma has been made. This

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article focuses on the advanced imaging techniques and laboratory evaluations that can be used in the workup and staging of melanoma of the head and neck.

IMAGING

The use of imaging studies in the diagnostic workup of both cutaneous and mucosal melanoma of the head and neck is crucial to obtain the appropriate staging. Imaging can be used to assess the extent of disease at the initial presentation, detect and evaluate recurrence, and monitor disease progression, regression, and response to treatment. In routine workup, a variety of imaging modalities can be used, such as plain films, computed tomography (CT), ultrasound (US), fluorodeoxyglucose (FDG) -PET, MRI, or a combination of these.

Historically, plain chest radiographs have been used to evaluate potential involvement of the lungs, as this is the most common visceral site of metastasis, and because of the ease of obtaining this study.[5] A retrospective study conducted by Terhune and colleagues[6] showed chest radiographs are not beneficial, especially in stage I and II melanoma, and in asymptomatic patients. Chest radiographs yield true positive rates of about 0.1% and, in fact, have in other studies yielded false positive and inconclusive rates as high as 8% to 15%.[7] When melanoma spreads to the lungs, it often will appear as multiple subcentimeter foci,[8,9] and as such, because the resolution of plain films is limited to lesions that measure at least 1 cm or greater,[10] they do not possess the level of sensitivity necessary to detect small metastatic foci. As such, the Clinical Practice Guidelines in Melanoma released by the National Comprehensive Cancer Network no longer state the recommendation of plain chest films in a standard head and neck melanoma workup. In patients with pulmonary symptoms or higher-stage disease, however, plain chest films may play a role in the initial workup.

CT of the chest, on the other hand, has shown that it is superior to plain chest films in detection of pulmonary metastasis, in particular in high-risk individuals, and has been shown to be about 20% higher than plain films.[11] A study by Silverman and colleagues[12] looked at 70 symptomatic patients with Clark level III, IV, and V melanoma using CT imaging, and metastatic disease was detected in lymph nodes in 24%, 33%, and 75% of patients with Clark level III, IV, and V melanoma, respectively, as well as hepatic and splenic metastasis in 25% of patients with Clark level V disease. However, the routine use of CT scanning in low-risk individuals, such as those with stage I and II disease, has not been recommended because of low detection rates and high rate of false positives, which have been shown to be up to 17%.[13] In a study by Buzaid in 1995,[14] 89 symptomatic patients with clinical evidence of lymphatic metastasis all had normal chest films, and chest CT images revealed a true positive rate of 6.7% and a false positive rate of 22%, with only detection of 1 patient (1.1%) via CT scan where the plain film was negative. Abdominal and pelvic CTs in this study revealed only 5.6% true positives. If CT scans are used, an image taken after intravenous contrast has been administered increases the sensitivity significantly, as metastatic melanoma is hypervascular, and thus, lesions appear hyperdense on early-phase contrast-enhanced CT.[15] Multiple-phase imaging consists of several sets of CT images obtained at different times following contrast injection to increase the detection of metastatic melanoma, ideally with 2 image sets, 1 set before contrast injection and the second set during the portal venous phase (60 seconds following the start of contrast injection).[16] Despite this, the use of CT scans of the head, neck, chest, abdomen, and pelvis in detection of metastatic melanoma has demonstrated poorly reliable results and thus is not routinely recommended in both localized lesions and tumors with evidence of locoregional lymphatic spread.[17]

The use of MRI in the workup of patients with melanoma has been well established, in particular, the use of whole-body MRI techniques with diffusion-weighted imaging (DWI). The lack of ionizing radiation and whole-body coverage make it an attractive option in evaluation of metastatic disease. DWI reflects the movement of water molecules in the tissues owing to their random thermal motion, and restriction of water diffusion is inversely associated with the integrity of cell membranes and tissue cellularity.[18] This provides functional information and is used for the detection of pathologic condition, in particular, processes such as acute cerebral infarction and malignant tumors.[19] The imaging characteristics of metastatic melanoma are distinct; with the presence of melanin and propensity for hemorrhage, they result in T1-weighted signal hyperintensity and T2-weighted signal intensity loss.[20] In a comparison of whole-body MRI with DWI and CT scanning in detection of metastatic melanoma, Mosav and colleagues[21] found that CT scans performed better than MRI scans in the detection of thoracic metastasis (lungs, mediastinal lymph nodes), likely because of the cardiac and respiratory motion artifact (**Fig. 1**). However, in the detection of abdominal and bone metastasis, MRI performed

considerably better than CT. Cerebral metastatic involvement in cases of advanced melanoma carries with it a significantly higher mortality, with patients that have melanoma brain metastases having a median overall survival of about 4 to 6 months, or less than 2 months if leptomeningeal involvement is present[22]; thus, accurate detection of brain involvement is crucial. Melanoma represents the third most common cause of brain masses with an unknown primary[23] and should always be considered in these cases. Recommendations currently for stage IIIc and higher melanomas involve imaging of the brain in the form of an MRI with and without gadolinium contrast at the outset of diagnosis, because of the higher risk of brain involvement, with MRI being the preferred method for evaluation of the brain.[24] Tyler and colleagues[25] demonstrated that the incidence of brain metastasis at the time of diagnosis is very low at about 0.2% (46 out of 19,066 patients), although this number has been shown in the literature to be as high as 5%,[26] and the risk of brain involvement increases as time goes on and thus must be assessed, especially in high-risk patients.

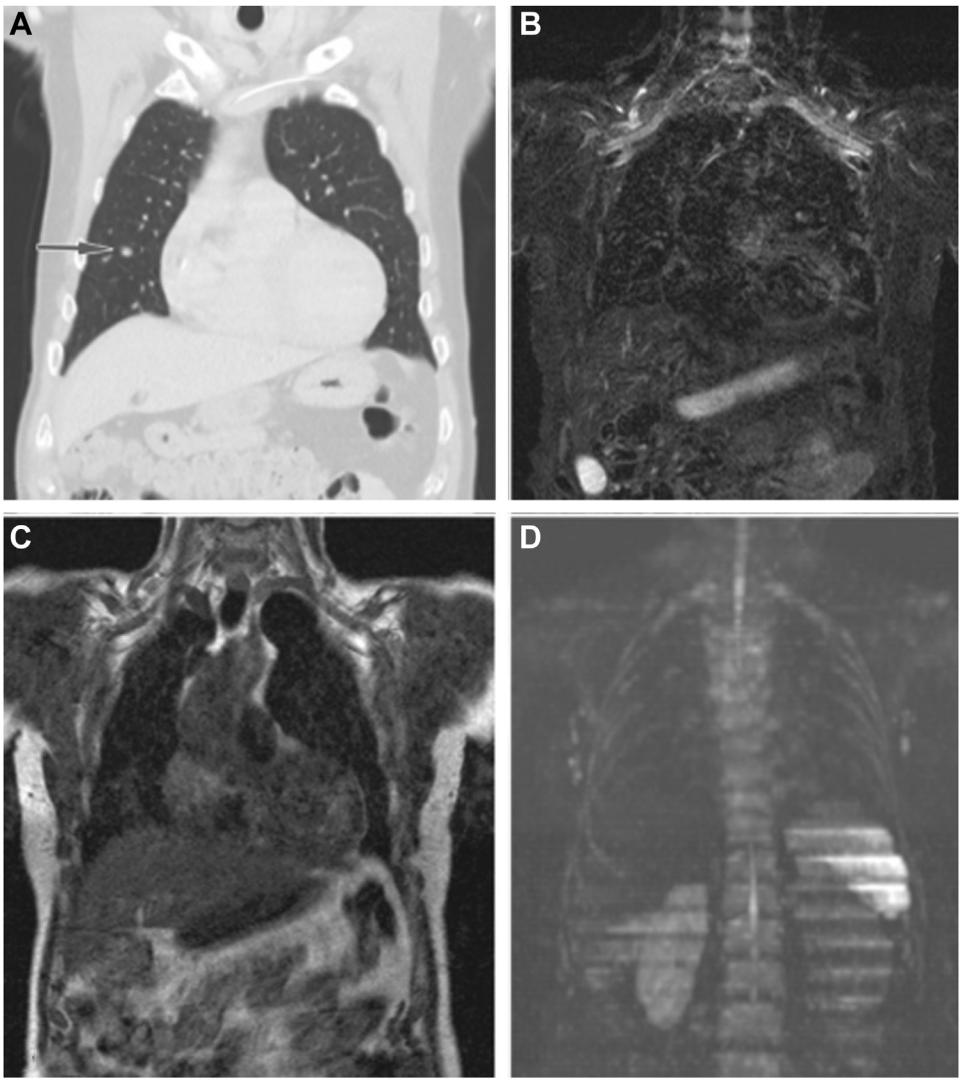

Fig. 1. A patient with evidence of multiple malignant melanoma metastases. CT image (*A*) shows lesion in the right lung measuring 7 mm in diameter. The lesion was not detectable on short tau inversion recovery and T1-weighted imaging (*B*, *C*), nor could it be detected on coronal maximum intensity projection DWI image (*D*). (*From* Mosavi F, Ullenhag G, Ahlström H. Whole-body MRI including diffusion-weighted imaging compared to CT for staging of malignant melanoma. Ups J Med Sci. 2013 May;118(2):91-7.)

Vital cell signaling pathways can explain the aggressive nature of the tumor biology in melanoma. About 90% of melanomas involves activating oncogene mutations in the MAPK pathway. The MAPK pathway plays a significant role in coordinating the differentiation and proliferation of melanocytes. About 50% of patients with melanoma demonstrates mutations in BRAF-V600; about 20% shows NRAS mutation; 14% shows NF1 gene mutation, and 3% to 5% of patients harbor activating KIT mutation.[27–29] These mutations lead to overexpression of GLUT1 receptors, which forms the basis of imaging with FDG-PET. This imaging modality has been shown to have a role in initial diagnosis and workup in the assessment and staging of melanoma, demonstrating the increased tissue metabolism and uptake of the 18F-FDG radiotracer in metastatic lesions. Metabolic parameters in FDG-PET imaging, such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), are used as prognosticators. SUVmax is a semiquantitative parameter that represents pixels with the highest glucose uptake. MTV is a distal volumetric assessment of FDG uptake within the lesion, whereas TLG is obtained by multiplying the mean SUV across the lesion with MTV. A retrospective review conducted by Son and colleagues[30] showed that in 41 biopsy-proven cases of cutaneous melanoma, the SUVmax and TLG in staging FDG-PET were higher in patients who presented with recurrence and in nonsurvivors. This imaging modality has been shown to be particularly useful in more advanced stage III and higher melanomas, where its role has been demonstrated to influence the management of 22% to 49% of stage III and IV cases.[31] In contrast, the use of FDG-PET in staging of early cases of melanoma has not been recommended because of the lack of sensitivity in detection of lesions.[32] Wagner and colleagues[33] conducted a prospective study involving 70 patients with melanoma greater than 1 mm thickness and 4 patients with locally recurrent melanoma, and FDG-PET and sentinel lymph node biopsy (SLNB) were performed. PET/CT demonstrated a specificity of 100%; however, it had poor sensitivity. They also concluded that FDG-PET could not reliably detect metastasis in lymph nodes smaller than 80 mm^3. PET/CT may not be useful in the initial staging of skin melanoma without clinical evidence of local or distant metastasis.[34–38] The diagnostic sensitivity of FDG-PET has been shown to be approximately 90% for metastatic lesions that are greater than 78 mm^3 in volume (>5.3 mm in diameter),[39,40] and thus, PET alone is unable to accurately detect micrometastasis. A study conducted by McIvor et al[41] did however demonstrate a 17% detection rate of occult metastasis by PET alone in a group of 322 patients with stage I or II disease, with 43% of those having distant metastasis with or without nodal disease. Thus, the use of PET scanning alone has shown limited value in detection of metastatic disease in melanoma, in particular, in its early stages. The fusion of PET imaging with other modalities, such as CT or MRI, has demonstrated an improved performance in detection of distant disease in the patient with melanoma, and continues to show promise, as it combines anatomic as well as physiologic information of the tissues that increases the effectiveness in detecting metastatic disease.[42] In a study by Krug and colleagues,[43] comparing the use of PET alone versus PET/CT in stage III and higher disease, the combination of PET/CT performed better with increased detection of metastatic disease, with sensitivity and specificity of up to 83% and 85%, respectively. Furthermore, it has also been demonstrated that PET/CT imaging demonstrates an overall improved detection of metastatic disease as compared with whole-body MRI, except for brain involvement, where MRI has the highest level of sensitivity in detection of suspicious lesions.[44] In the latter study, a site-specific analysis showed that whole-body MRI was more sensitive for tumor detection in the central nervous system, liver, as well as the bone marrow, whereas PET/CT was superior for detection of lymph node metastases and involvement of all other organs (**Fig. 2**). The diagnostic role of PET/CT has not been substantially evaluated in early stages of malignant melanoma (stage I and II), and considering the relatively high rate of PET/CT false positives and low rate of nodal disease (less than 15%) as well as distant metastasis (less than 5%) at the time of primary diagnosis in these cases,[45,46] PET/CT does not yet represent a standard of care in these cases, as SLNB is the preferred method of initial staging in these early cases.[47] Nevertheless, some studies have demonstrated a high diagnostic accuracy for PET/CT in the detection of metastasis in patients with high-risk melanoma with stage I or II disease, with sensitivities of 91% and 98%.[48,49] The use of PET/MRI has also gained favor in some institutions, given its improved soft tissue imaging capability as compared with CT. In a direct comparison of PET/CT and PET/MRI done in patients with melanoma by Berzaczy and colleagues,[50] the sensitivity of PET/CT was 89.1%, whereas for PET/MRI was 92.7% with specificities equal at 100% for both; however, these results were not found to be statistically significant. Site-specific analysis revealed that although PET/MRI may be more

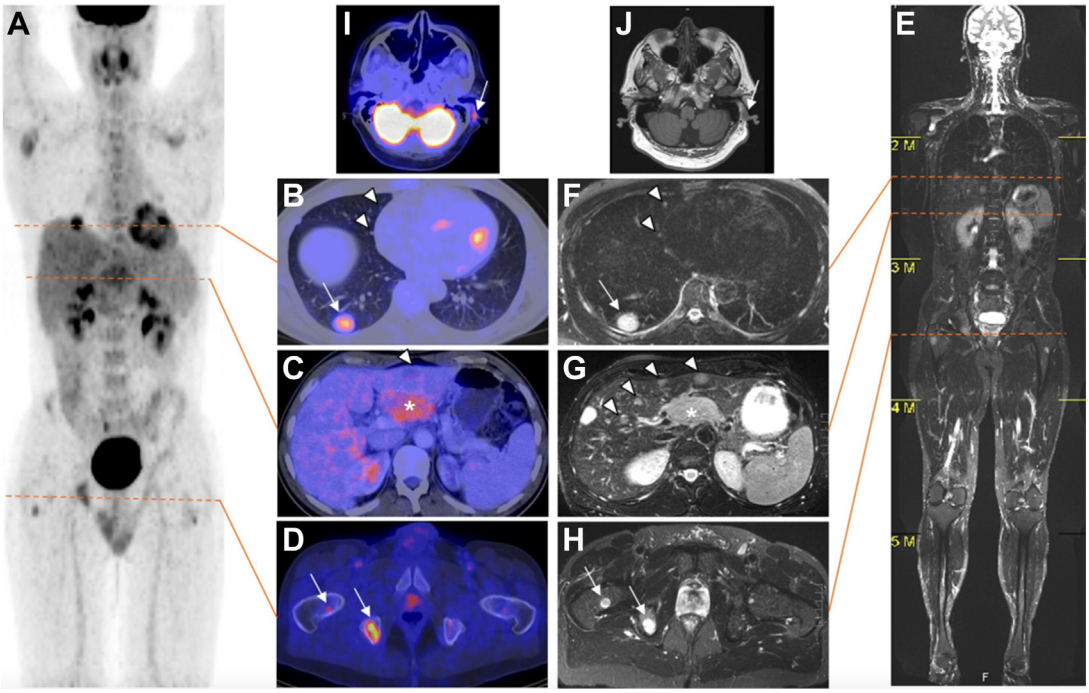

Fig. 2. PET/CT (*A–D*) and whole-body MRI (*E–H*) of patient with metastatic malignant melanoma. CT and MRI detected more lung metastasis than PET/CT (*B* and *F, arrows*), and MRI found more liver lesions than PET/CT (*C* and *G, arrows*). Bone metastasis was equally detected (*D* and *H, arrows*). Nodal metastasis behind the left ear (*I* and *J, arrows*) was detected solely by PET/CT. (*From* Pfannenberg C, Aschoff P, Schanz S, Eschmann SM, Plathow C, Eigentler TK, Garbe C, Brechtel K, Vonthein R, Bares R, Claussen CD, Schlemmer HP. Prospective comparison of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma. Eur J Cancer. 2007 Feb;43(3):557-64; with permission.)

sensitive for melanoma metastasis in some tissues, such as bone, brain, and liver, it does not do as well as PET/CT for evaluation of lung and lymph node metastases (**Fig. 3**).[51] Given this, it may be extrapolated that PET/MRI may be more useful in higher-stage (stage III or above) melanoma, because it appears to be more sensitive in sites where detection of tumor may result in changes in therapeutic modalities (ie, radiation therapy for brain and bone metastasis). Despite the promising results seen with fused imaging modalities, they have been shown to continually be inferior to SLNB and thus cannot replace the latter as the preferred method of diagnosis and staging.[52]

The most important prognostic factor in early-stage melanoma is metastasis to local and regional lymph nodes, and thus, identification of involved nodes is crucial in the workup process.[53] Nuclear imaging finds utility in staging and prognostication, evaluation of recurrence, and response assessment to personalized, targeted therapy. The use of SLNB has been well established in the literature as a reliable method to determine lymphatic spread and is recommended to be used starting in stage IB tumors.[54,55] This procedure was first introduced in 1953 and then was made popular in a large international study entitled the Multicenter Selective Lymphadenectomy Trial, which notably showed that patients with positive sentinel nodes (SNs) who proceeded to have completion lymph node dissection had double the disease-specific survival and triple the disease-free survival.[56] Lymphoscintigraphy represents an inexpensive, relatively noninvasive, and sensitive imaging technique (approximately 95%)[57] for identification of nodal drainage patterns and guidance for SLNB procedures, delivering a low dose of radiation to the patient in the process. It is performed in patients with intermediate-risk primary lesions (1.0–4.0 mm lesion thickness) and clinically nonpalpable regional lymph nodes (cN0 disease) and helps in localization and biopsy of sentinel lymph nodes (SLN) that drain the primary tumor. It is well known that metastasis to locoregional lymph nodes is an essential predictor of recurrence in melanoma,[36] and as such, biopsy-proven metastasis to an SLN would prompt

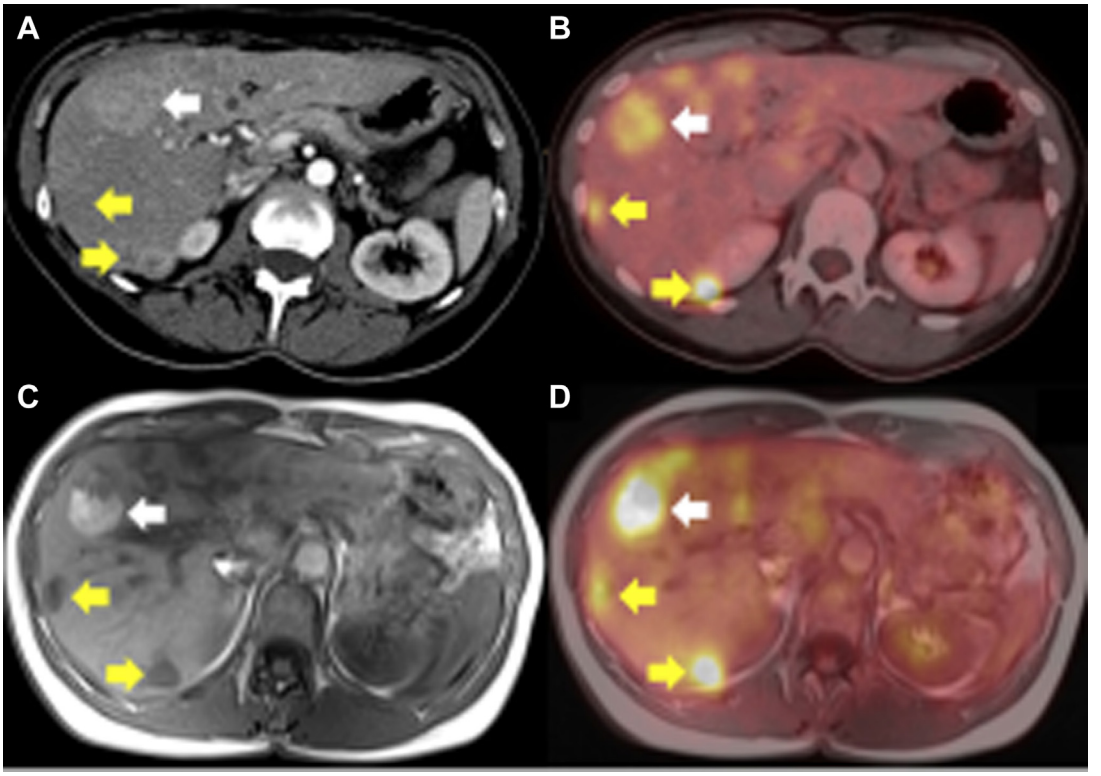

Fig. 3. Patient after surgical resection of primary nodular melanoma of the cheek. Contrast-enhanced arterial phase CT (*A*) and corresponding fused PET/CT images (*B*); at least 5 hepatic lesions (*white and yellow arrows*) are seen. PET/MRI images (*C*) also reveal multiple partly hyperintense lesions owing to melanin contact or intralesional hemorrhage (*white arrow*), with a pathologic focal tracer uptake on the PET component of the fused PET/MRI image (*D*). (*From* Berzaczy D, Fueger B, Hoeller C, Haug AR, Staudenherz A, Berzaczy G, Weber M, Mayerhoefer ME. Whole-Body [18F]FDG-PET/MRI vs. [18F]FDG-PET/CT in Malignant Melanoma. Mol Imaging Biol. 2020 Jun;22(3):739-744; with permission.)

regional lymph node dissection. If SLNB does not show metastasis on histopathological examination, such cases can be spared lymph node dissection. The SLN lymphoscintigraphy procedure (**Box 1**) and biopsy remain the standard for staging locoregional lymph nodal involvement. This procedure can be performed either in a -one or a 2-day technique, with the 1-day method requiring a single injection of radionuclide for both diagnostic lymphoscintigraphy and surgery, whereas the 2-day technique requires 2 injections separated by 24 hours, with surgery performed with a gamma probe to aid in localization of nodes with radiotracer. In addition, a blue dye may be injected into the lesion at the time of surgery, and lymphatic drainage patterns are observed to aid in identification of nodal basins and have been shown to be a complementary procedure to lymphoscintigraphy, with an 80% sensitivity.[58] In the head and neck, however, reliable and accurate observation of lymphatic spread is much more difficult because of the complex anatomy and variability of lymphatics, which can result in higher rates of false negative results (reported up to 44%)[59] in comparison with tumors in other sites in the body.[60–62] Introduction of the use of single-photon emission tomography/computed tomography (SPECT/CT) in combination with lymphoscintigraphy aids in better nodal localization by demonstrating anatomic tomographic slices of radiotracer distribution in the tissues, increasing the likelihood of SLN detection and removal of any positive nodes.[63] In a recent study by Kwak and colleagues,[64] the "hottest" node seen on SPECT/CT was also the "hottest" node intraoperatively using the gamma probe in 85% of patients. Moreover, the use of this imaging technique in combination with lymphoscintigraphy has shown a significant impact on surgical approach, particularly in head and neck melanoma, as studies have shown a change of 41.6% and 49.38% in surgical management based on findings of SPECT/CT-enhanced SLNB as opposed to the use of lymphoscintigraphy alone.[65,66] Some of the advantages of

Box 1
Outline of lymphoscintigraphy procedure

Lymphoscintigraphy

Radiopharmaceutical:

- *^{99m}Tc-sulfur colloid* is the most commonly used radiopharmaceutical.
- It can be filtered with a 100-nm to 200-nm membrane filter to obtain particles of uniform size.
- Other radiopharmaceuticals used are ^{99m}Tc-dextran (mean particle size 2–3 nm), ^{99m}Tc-DTPA mannosyl dextran (mean particle size 6–8 nm), ^{99m}Tc-labeled human serum albumin colloid, ^{99m}Tc-human serum albumin (mean particle size 2–3 nm).

Preparation of ^{99m}Tc-sulphur colloid:

The preparation kit comprises 3 different components:

- *Component A*: 0.5 mL of 0.3 N HCl (hydrochloric acid)
- *Component B*: 1 mL of solution with 10% sodium thiosulphate and 3.5% gelatin
- *Component C*: 1 mL of 0.08 M phosphate buffer at pH 7.4 with 136 mg of Na_2HPO_4 and 12 mg of NaH_2PO_4
- *Components A and C* are stored at room temperature, and *component B* has to be refrigerated at 2°C-8°C

Radiolabeling[70–72]:

- A maximum of 100 μCi (3.7 MBq) of $^{99m}TcO_4^-$ in 3-mL solution is added to component A. This cocktail forms the *reaction vial.*
- 0.5 mL of component B is transferred to the reaction vial. It is mixed well and placed in a boiling water bath for 3 to 5 minutes.
- The vial is allowed to cool to room temperature (5 minutes).
- 0.5 mL of component C is then transferred into the reaction vial and mixed well.
- ^{99m}Tc-sulfur colloid will be ready for use after 5 minutes.

Labeling features:

- A 99mTc-sulphur colloid in colloidal suspension
- pH 4 to 7
- Radiochemical purity: greater than 95%
- Free pertechnetate ($^{99m}TcO_4^-$): less than 5%

Quality control procedure:

- Radiochemical purity is assessed by ascending chromatography using instant thin-layer chromatography or Whatman no. 1 paper.
- RF (relative front) values in acetone or saline for ^{99m}Tc-sulphur colloid is 0.0–0.1 and for $^{99m}TcO_4$ is 0.9–1.0.

Dosimetry:

- Current dosimetric data are obtained from SLN lymphoscintigraphy procedures in breast cancer.[73,74]
- Radiation dose to the patient depends on (a) amount of injected dose; (b) time to surgery.
- The recommended dose for injection: ranges from 15-Mbq (single-day procedure) to 120-MBq (2-day procedure) in a total volume of 0.4 to 1.0 mL. The intention is to achieve at least activity of 10 MBq at the time of surgery.
- Most centers perform SLNB within 24 hours of lymphoscintigraphy.
- The safety of SLNB is confirmed by studies from Memorial Sloan Kettering Cancer Center. The effective dose from the procedure is calculated to be around 0.2 mSv.[75]

Procedure:

- Patients should be informed about the procedure, discomfort involved, and potential risk of bleeding. Written informed consent must be obtained before the procedure.

- *Injection*: Tuberculin syringe with 25- or 27-gauge needle and minimal dead space are recommended (Fig. 4).
- *Activity for injection*: Varies from 15 to 120 MBq between studies.
- *Site*: Tracer should be injected at about 0.1 to 0.5 cm from the tumor margin.
- Aliquots vary according to the size and location of the tumor.
- Tumors in the floor of the mouth require 4 separate submucosal injections around the lesion.
- For tumors in other head and neck noncutaneous sites like tongue, a tracer should be injected according to the depth of the lesion too.
- The first-echelon and second-echelon lymph nodes should separately be marked on the skin using indelible markers of different colors, guided by a gamma camera and a handheld gamma probe or a radioactive point source (Fig. 5).
- *Dynamic and static images should be taken, and topographic localization using ^{57}Co flood source for simultaneous emission and transmission imaging and SPECT/CT should be performed* (Figs. 6–9).
- The patient should be asked to rinse the oral cavity after injection to prevent the pooling of the tracer.

SPECT/CT include the following: (a) identification of missed SLN and exclusion of ambiguous SLN; (b) compared with planar imaging, SPECT/CT identifies at least 1 additional lymph node; (c) better anatomic localization in 30% to 47% cases; (d) it can identify SLN located close to the primary tumor, which is commonly missed by the intraoperative gamma probe; (e) high-quality CT helps identify subcentimeter SLN and hence improved intraoperative SLN localization. The benefits of SPECT/CT have not been universally accepted; however, both planar and SPECT/CT images have been shown to demonstrate good interobserver and intraobserver agreement for evaluation of SLN,[67] with kappa values ranging from 0.68 to 0.89. This procedure is not without its risks of adverse and/or allergic reactions, as such reactions to human serum albumin colloid have been

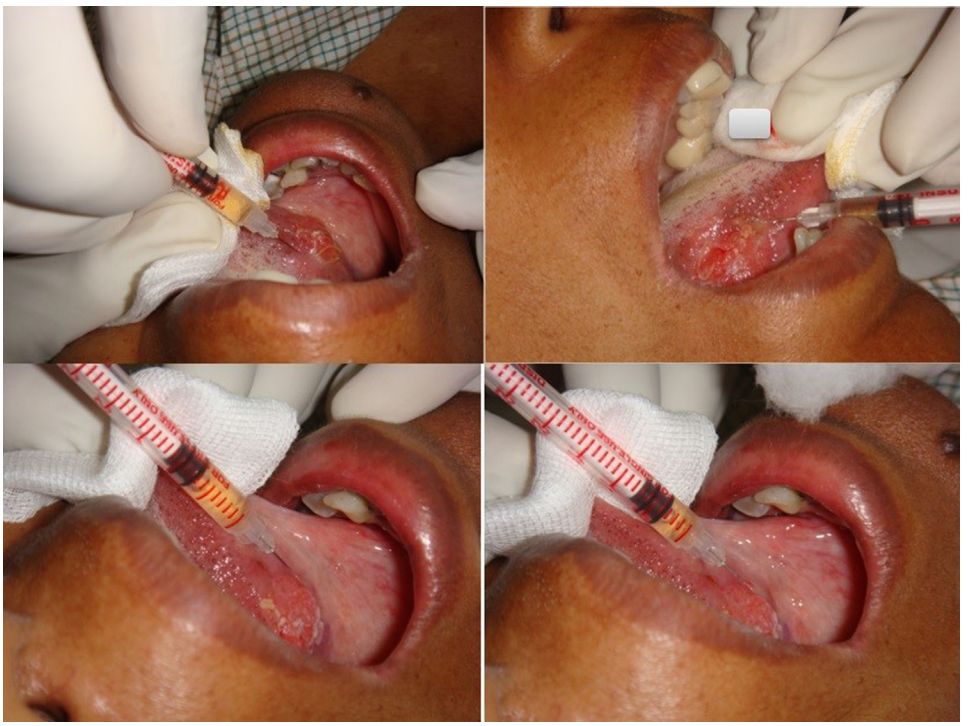

Fig. 4. Peritumoral injection of ^{99m}Tc-sulphur colloid.

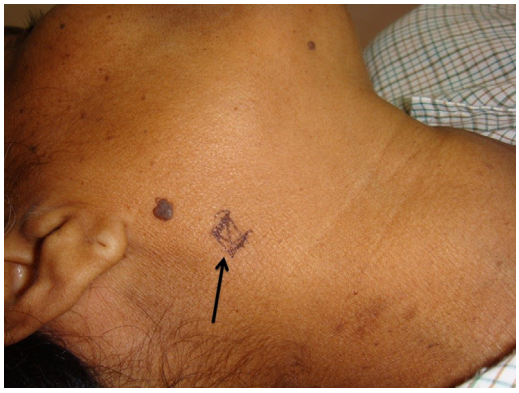

Fig. 5. Skin marking of SLN.

reported in the literature.[68,69] Another group wherein caution must be taken is in pregnant and lactating women, with associated potential risks to the child. Fetal-absorbed dose from a tracer activity of 18.5 MBq has been calculated to be 0.013 mSv, with congenital malformations primarily observed at exposures greater than 200 mSV. Given this, SLNB is not contraindicated during pregnancy; however, it is preferable to perform a single-day procedure with a lower injected dose. In lactating women, it is advised that they stop breastfeeding for 24 hours following SLNB procedures.

The use of US in patients with melanoma has been shown to have multiple applications, in assessment of the primary tumor itself as well as in detection of regional metastasis. It is well known that the thickness of melanoma is a major prognostic factor and also determines the margins of surgical excision. High-resolution US imaging has been used to accurately measure tumor thickness and has shown promising results. A systematic review by Machet and colleagues[76] that included 14 studies compared both US and

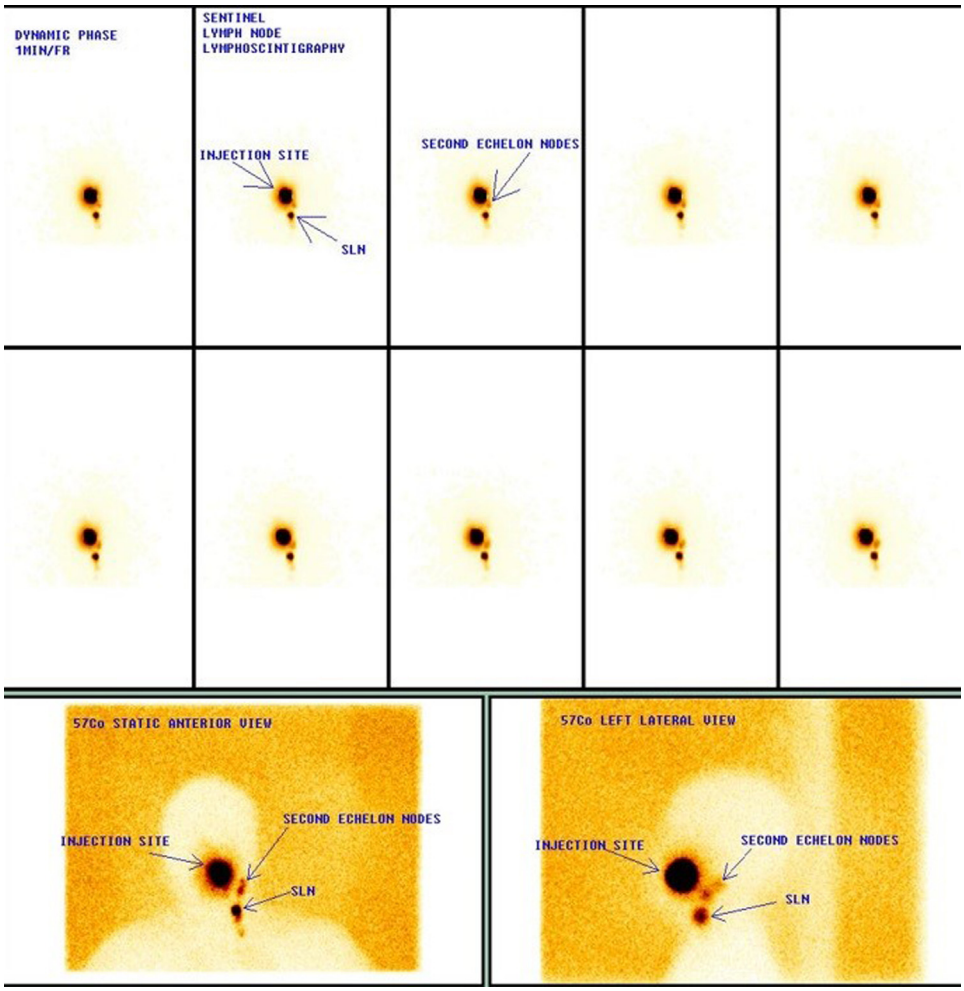

Fig. 6. Dynamic lymphoscintigraphy demonstrating first- and second- echelon lymph nodes.

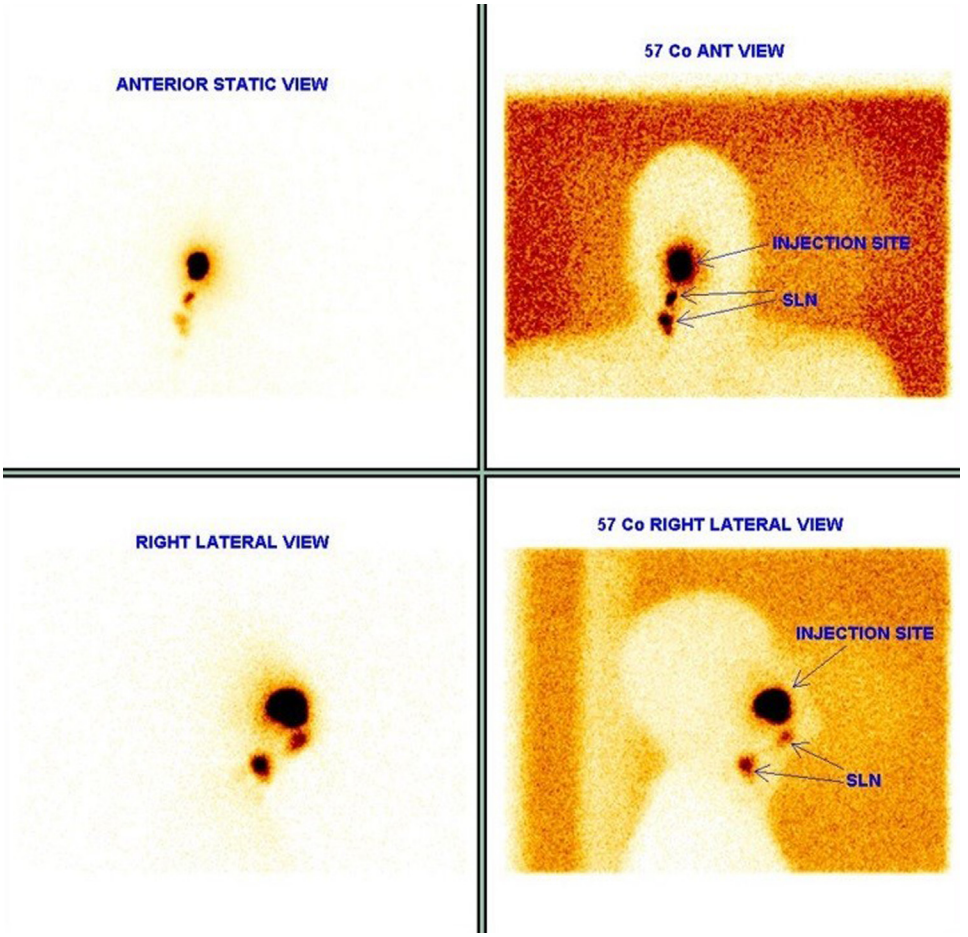

Fig. 7. Topographic localization using ^{57}Co transmission source.

histologic measurements of tumor thickness in a total of 869 patients and showed a correlation coefficient of greater than 0.9 between the 2 methods and that adequate surgical margins were obtained based on US measurements in 72% of lesions. Less reliable results were obtained in thin tumors measuring less than 0.4 mm in thickness and in very thick tumors greater than 7.6 mm. US used in combination with fine-needle aspiration biopsy has also been used in detection of lymph node involvement in patients with melanoma, although its use has not yet been well established based on varying results. Bossi and colleagues[77] demonstrated in their study a sensitivity and specificity of 89.4% and 90.3%, respectively, using this method of lymphatic assessment, whereas Kahle and colleagues[78] were able to show that it was possible to demonstrate the localization of SNs successfully in 85% of patients. However, in a later study by Sanki and colleagues,[79] they were only able to demonstrate a 24.3% sensitivity in detection of SNs, with a resulting very high rate of false negatives. The sensitivity of US in this setting has been shown to increase in high-risk patients, with higher Breslow thickness (>4 mm) and increased tumor volume (>1.00 mm^3), increasing the sensitivity in some studies to 76%.[80]

LABORATORY TESTING

Evaluation of a patient's serum for prognostic biomarkers represents an easy, noninvasive, rapid, and potentially valuable method in the detection of disease burden, particularly in the early stages. Because of tumor biology and clinical heterogeneity of melanoma, tumor behavior, and thus prognosis, can vary significantly within the same stage of disease.[81] Thus, the investigation of biochemical serum markers is particularly important to determine the specific tumor profile in order to identify the behavior pattern of a particular patient's disease process to more accurately determine their level of disease burden, and overall treatment options and prognosis.

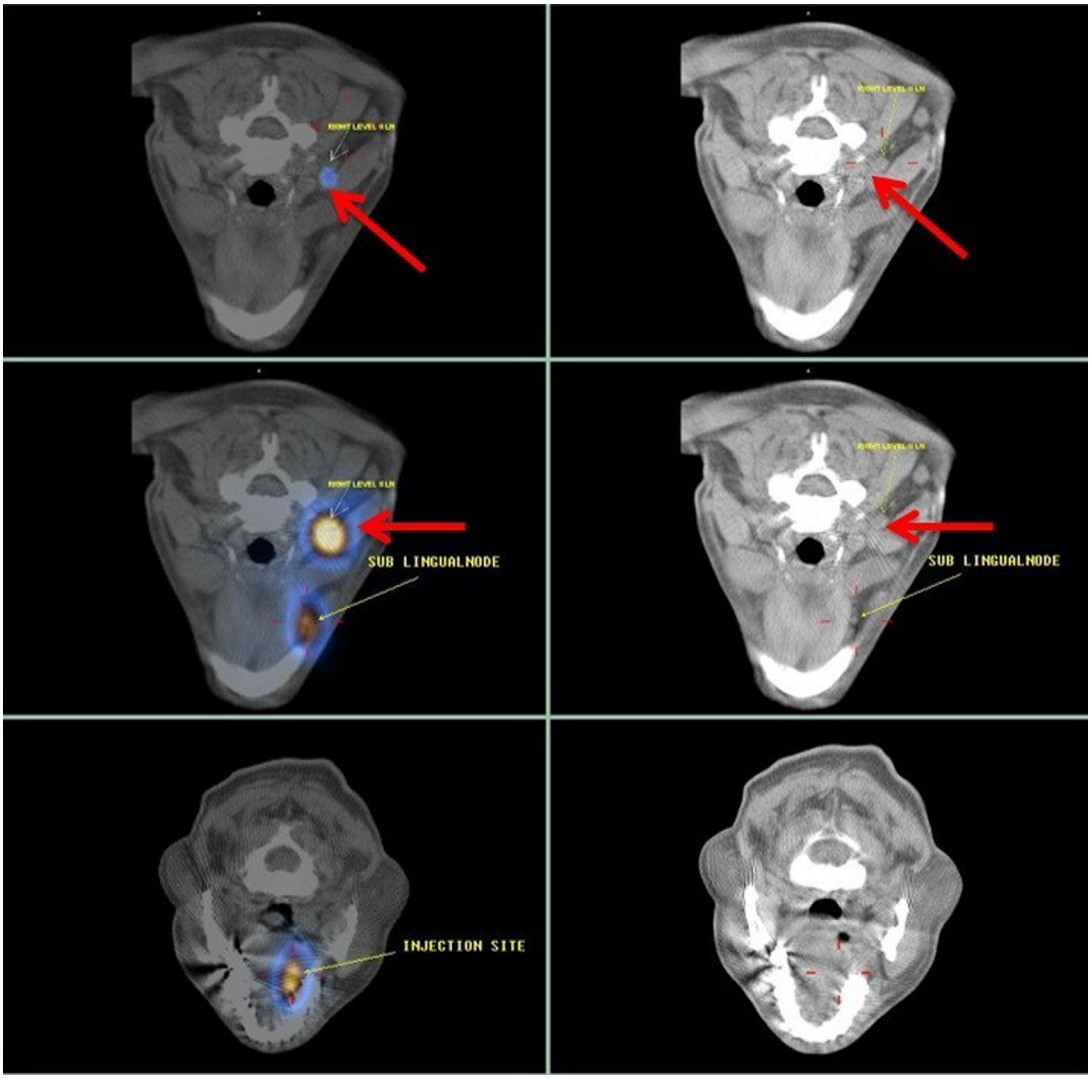

Fig. 8. SPECT/CT image showing injection site and lymph nodes in CT and fusion images. Red arrow demonstrates right level II cervical lymph node. Right sublingual lymph node and injection site are also represented in the picture.

An example of a serum biomarker for melanoma is lactate dehydrogenase (LDH), which, given the hypoxic environment of melanoma cells, catalyzes the conversion of pyruvate to lactate when oxygen levels are low. LDH does not represent a secreted enzyme, so an elevated serum level is thought to be secondary to spillage of the enzyme when melanoma cells outgrow their blood supply.[2] Despite the fact that it is not a specific marker for melanoma, the presence of elevated serum levels of this enzyme can be an indicator of distant metastasis in these patients. In a study of 121 melanoma patients by Finck and colleagues,[82] it was found that as an indicator of liver metastasis, the sensitivity and specificity of this biomarker in stage II patients were 95.1% and 82.8%, respectively, and 86.5% and 57.1% in stage III patients, respectively. Currently, LDH is the only serologic biomarker included in the American Joint Committee on Cancer staging system and is used to subclassify stage IV melanoma patients into an M1c category, which decreases the 1- and 2-year overall survival by about 50%.[83]

Another biomarker to receive some more recent attention is S100B, a small, acidic molecule involved in a variety of cellular functions, including tumor promotion, as it suppresses p53 function, and is part of the S100 molecule group, which is already recognized as a marker for melanoma tumors. Several studies have found that abnormally

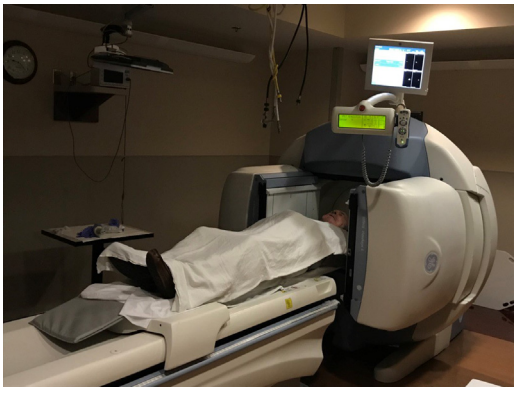

Fig. 9. SPECT-CT scanner with patient in position. Imaging duration can vary based on tracer drainage into the SN. Drainage pattern is visualized on the monitor above the scanner.

high levels of S100B in the serum of patients with melanoma are seen in disseminated disease, with Guo and colleagues[84] demonstrating its elevation in 73.9% of stage IV disease. In this same study, S100B was found to only be elevated in 1.3% and 8.7% of stage I and II patients, respectively, and thus does not represent a useful screening tool nor is it very useful in early detection. Increased levels of serum S100B have also been correlated to more aggressive disease profiles and resultant reduced survival.[85] In a meta-analysis by Mocellin and colleagues[86] including 3393 patients across all stages, they found that elevated S100B correlated with statistically significant poorer survival statistics and was found to be an independent prognostic factor at multivariate analysis. Moreover, another report demonstrated a direct correlation between S100B levels and Breslow tumor thickness, showing that a combined level of greater than 0.22 μg/L and Breslow thickness greater than 4 mm together had a sensitivity and specificity of 91% and 95%, respectively, for the presence of distant metastasis.[87] In a direct comparison of LDH and S100B by Wevers and colleagues,[88] they were able to show a correlation between disease-free survival and elevated S100B levels in patients with stage III melanoma, thus potentially representing a similar relationship as with LDH in stage IV patients, although S100B also has shown a relationship with elevated tumor burden in stage IV cases.[89] Unfortunately, given their poor sensitivity and specificity in stage I and II disease, they have limited use and value in early disease.

Cytokine profiles, both proinflammatory and anti-inflammatory, represent a valuable set of biomarkers that are easily accessed and measured and can aid in profiling tumors and their biologic behavior patterns. In a study examining 348 melanoma patients, Ortega-Martinez and colleagues[90] showed that serum levels of dermcidin (DCD) had prognostic value in patients with stage I and II melanoma, interestingly demonstrating that although DCD levels are elevated in patients with melanoma relative to healthy control subjects, patients with early disease who developed metastasis had a sharp decrease in levels of DCD, showing that patients with levels less than 2.98 μg/mL were more likely to develop metastasis. In the same study, they also examined vitronectin (VN) and found that patients with stage I and II disease with elevated levels of VN were 2.8 times more likely to develop metastasis, indicating that destruction of the basement membrane and extracellular matrix by tumor propagates the release of VN among other components into the serum, indicating potential metastatic activity.

Additional serum markers, such as IL-2 receptor, sICAM-1, IL-10, MIA, tyrosinase, VEGF, IL-6, and IL-8, to name a few, are currently being studied and have shown some relationship with advanced stage of disease and poor prognosis; however, they have yet to be further investigated.[91,92]

The liver represents one of the most common sites of metastasis of malignant melanoma and thus confers a poor prognosis and decreased survival. Assessment of liver enzyme levels and liver function tests, such as alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, and total bilirubin, can also be used in screening for and assessment of metastatic disease for the liver. This is well established in the monitoring of uveal melanoma, which shows levels rising at least 6 months before clinical detection of metastasis has occurred.[93] Despite this, measurement of serum liver enzymes and functional evaluation is not a part of the routine workup of metastatic melanoma.

SUMMARY

Melanoma represents a devastating disease process with a relatively high mortality, and in which early detection and accurate staging are crucial in terms of prognosis. Unfortunately, diagnostic testing, such as advanced imaging and serum biomarkers, is currently inadequate for reliable identification of regional and distant metastasis, especially in early stages of the disease process and in routine surveillance. Fusion of some of the available imaging modalities and the combination of laboratory testing with certain tumor characteristics have resulted in improved detection rates; however, further research is needed to yield

more reliable results, particularly in early-stage disease.

CLINICS CARE POINTS

- When performing a diagnostic workup of a patient with melanoma, ensure the correct staging of the disease process, as this has a very significant impact on treatment and prognosis.
- Keep in mind that different imaging modalities are indicated based on site-specific evaluation in melanoma, and that use of more than one imaging technique may be indicated.
- Perform sentinel lymph node biopsy in conjunction with lymphoscintigraphy whenever possible, as this represents an excellent and well-proven modality in the assessment of regional lymph nodes.

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