
Diagnostic accuracy of imaging studies for initial staging of T2b to T4b melanoma patients: A cross-sectional study



Constanza Riquelme-Mc Loughlin, MD,^a Sebastian Podlipnik, MD,^{a,b} Xavier Bosch-Amate, MD,^a José Riera-Monroig, MD,^a Alicia Barreiro, MD,^{a,b} Natalia Espinosa, MD,^{a,b} David Moreno-Ramírez, MD, PhD,^a Priscila Giavedoni, MD,^a Ramon Vilana, MD,^{b,c} Marcelo Sánchez, MD,^c Sergi Vidal-Sicart, MD, PhD,^{b,d} Cristina Carrera, MD, PhD,^{a,b,e} Josep Malvehy, MD, PhD,^{a,b,e} and Susana Puig, MD, PhD^{a,b,e}
Barcelona, Spain

Background: There is no consensus on the imaging tests that should be performed at the initial staging of melanoma patients.

Objective: To evaluate the diagnostic accuracy of 4 imaging studies for the initial staging of melanoma patients.

Methods: Cross-sectional study with prospectively collected data, from January 2011 to April 2017, including patients with clinical stage T2b to T4b according to 2009 American Joint Committee on Cancer, without evidence of metastasis.

Results: Initial staging of 308 patients detected 16.6% of metastases and 5.8% false-positive results, overall. Regional lymph node ultrasonography showed a metastasis detection rate (MDR) of 12.8%, false-positive rate of 0.8%, and accuracy of 96.0%. Computed tomography (CT) and positron emission tomography-CT had the highest detection rates at stage T4b: MDR, 13.3%; false-positive rate, 8.9%; accuracy, 91.1%; and MDR, 6.9%; false-positive rate, 0%; and accuracy, 93.1%, respectively. Brain magnetic resonance imaging showed a MDR of 2.0% in T4b.

Limitations: Single-center study.

Conclusion: Performing ultrasound scans for assessing lymph node metastasis in patients with American Joint Committee on Cancer T2b stage and above is advisable. In patients with stage T4b, CT or positron

From the Dermatology Department, Hospital Clinic of Barcelona, University of Barcelona^a; Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS)^b; the Radiology,^c and Nuclear Medicine^d Departments, Hospital Clinic of Barcelona, University of Barcelona; and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III.^e
Drs Riquelme-Mc Loughlin and Podlipnik contributed equally to this article.

Funding sources: The study in the Melanoma Unit, Hospital Clínic, Barcelona, was partly supported by grants from Fondo de Investigaciones Sanitarias PI 12/00840, PI 15/00956, and PI 15/00716 Spain; by the Centro de Investigación Biomédica en Red de Enfermedades Raras of the Instituto de Salud Carlos III, Spain, cofunded by "Fondo Europeo de Desarrollo Regional (FEDER), Unión Europea, Una manera de hacer Europa"; by the Agency for Management of University and Research Grants (AGAUR) 2014_SGR_603 and 2017_SGR_1134 of the Catalan Government, Spain; by a grant from "Fundació La Marató de TV3, 201331-30," Catalonia, Spain; by the European Commission under the 6th Framework Programme, Contract No. LSHC-CT-2006-018702 (GenoMEL); by Centres de Recerca de Catalunya (CERCA) Programme/Generalitat de Catalunya; by a

research grant from "Fundación Científica de la Asociación Española Contra el Cáncer" GCB15152978SOEN, Spain; and by a grant from the European Academy of Dermatology and Venereology (EADV) (PPRC-2017/19). The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, approval of the manuscript, or in the decision to submit the manuscript for publication.

Conflicts of interest: None disclosed.

Accepted for publication May 30, 2019.

Reprints not available from the authors.

Correspondence to: Susana Puig, MD, PhD, Melanoma Unit, Dermatology Department, Hospital Clínic Barcelona, Villarroel 170, 08036 Barcelona, Spain. E-mail: susipuig@gmail.com, spuig@clinic.cat.

Published online June 1, 2019.

0190-9622/\$36.00

© 2019 Published by Elsevier on behalf of the American Academy of Dermatology, Inc.

<https://doi.org/10.1016/j.jaad.2019.05.076>

emission tomography-CT are suitable for the detection of metastasis. Brain magnetic resonance imaging at T4b deserves further discussion, considering the ultimate clinical benefit in management and therapeutic options for asymptomatic patients. (J Am Acad Dermatol 2019;81:1330-8.)

Key words: clinical decision making; computed tomography; diagnostic tests; magnetic resonance imaging; melanoma; metastasis; positron emission tomography; prognosis; staging; ultrasonography.

Malignant melanoma denotes an important public health problem, particularly in terms of potential years of life lost, because it represents one of the most frequent forms of cancer in young adults.¹ Several complementary tests have been studied for both the initial staging and the follow-up of patients with high-risk melanoma. The staging assessment can include or combine imaging studies such as computed tomography (CT), regional lymph node ultrasound imaging, positron emission tomography-computed tomography (PET-CT), brain magnetic resonance imaging (MRI), scintigraphy, and total-body MRI, among others.^{2,3} However, there is no current consensus on the optimal initial staging strategy, which staging procedures should be routinely performed, or whether they should be performed at all.⁴ Different international guidelines for the surveillance and management of melanoma patients have been proposed, and most of them differ in the basal imaging studies that should be performed in these patients.⁵⁻¹¹

The decision to perform imaging tests should consider the probability of clinically occult metastases being present, the likelihood of detecting the metastases given the limitations of each imaging test, the potential for false-positive findings, and the cost and morbidity of the study.¹² It is important to determine whether identifying clinically occult metastases by performing imaging studies would change the management plan. Presymptomatic detection of distant metastasis has not yet demonstrated improvement of patient prognosis. However, with the development of immunotherapy and targeted therapies, evidence from clinical trials shows that systemic treatments in melanoma are more effective in patients with earlier, asymptomatic, low-volume metastasis.¹³⁻¹⁸ Therefore, staging and follow-up with imaging techniques could have implications in the development of future clinical guidelines.

This study evaluated the diagnostic accuracy of regional lymph node ultrasound imaging, CT, PET-

CAPSULE SUMMARY

- There is no consensus on the optimal initial staging protocol in patients diagnosed with high-risk melanoma.
- Initial staging detected metastases in 16.6% patients with stage T2b to T4b. This information may assist in the development of optimal staging protocols.

CT, and brain MRI used in the initial staging of patients with intermediate- to high-risk melanoma according to Breslow depth.

METHODS

Study design

This was a cross-sectional study of patients treated at the Hospital Clinic of Barcelona, Spain, from January 2011 to April 2017. The basal demographic characteristics, clinical and histopathologic features, recurrence time, and site were prospectively recorded. This registry mainly includes patients of Mediterranean origin living in the Catalonia region. The Hospital Clinic of Barcelona Clinical Research Ethics Committee approved the study and research protocol. All procedures performed in studies involving human participants were in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was performed following the 2015 Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.¹⁹

Patients

All patients who were diagnosed with an invasive primary melanoma were staged according to the 2009 American Joint Committee of Cancer classification. Patients eligible for inclusion were those with a diagnosis of melanoma with >pT2a (Breslow depth >2 mm, regardless of ulceration, or >1 mm with an ulcerated primary tumor) without clinical evidence of metastasis after a complete physical examination. In sentinel lymph node biopsy candidate patients, basal imaging studies were performed mainly before the procedure. Only imaging studies performed within the first 4 months after the primary melanoma diagnosis were included in the statistical analysis. Exclusion criteria included patients who presented with palpable lymph nodes or clinically evident metastasis before the imaging studies were performed. T1 and T2a subgroups were excluded because imaging studies for initial staging in these patients were not routinely requested.

Abbreviations used:

CT:	computed tomography
FPR:	false-positive rate
MRI:	magnetic resonance imaging
MDR:	metastasis detection rate
PET-CT:	positron emission tomography-computed tomography
PPV:	positive predictive value

Staging protocol

Imaging studies (regional lymph node ultrasound imaging, CT, PET-CT, and brain MRI) were requested according to the standardized protocol of our center (Table I). Ultrasound imaging was performed in patients with T2b and T3a tumors, whereas the rest of the imaging tests were indicated beyond T3b. The patient's clinical history and results of other imaging tests were available to the radiologists and nuclear medicine physicians.

Ultrasound imaging was performed before lymphoscintigraphy and sentinel lymph node biopsy. The regional lymph node areas that were explored according to protocol were the ipsilateral axillary group for upper limb melanoma, ipsilateral inguinal group for lower limb melanoma, bilateral neck and supraclavicular groups for head and neck melanoma, and bilateral axillary and inguinal groups for trunk melanoma. Total-body CT scans were performed of the chest, abdomen, and pelvis. Whole body PET-CT scans were performed using a hybrid PET-CT system (Biograph; Siemen, Erlangen, Germany) equipped with an ECAT EXACT HR+ BGO PET scanner and point spread function algorithms with low-resolution CT without contrast.

Analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value, likelihood ratio, true-positive rate or metastasis detection rate (MDR), false-positive rate (FPR), and accuracy were calculated for each of the 4 imaging index tests. The MDR and diagnostic accuracy measures for CT and PET-CT were calculated excluding lymph node metastases and only considering distant metastases. The study excluded patients with missing data for the reference standard tests. To handle the missing tests in stage T3b patients and above, we evaluated the patterns of missingness of the independent variables of these patients. If the studies were missing completely at random or missing at random (MAR), a pairwise deletion analysis was performed.

For each index test, the definitions of false-negative, false-positive, true-positive, and true-negative results are included in Table II. Imaging

Table I. Standardized staging protocol from our center

Protocol	T1a-T2a	T2b-T3a	T3b-T4a	T4b
Serum biomarkers	+	+	+	+
Ultrasonography		+	+	+
CT*			+	+
PET-CT*			+	+
Brain MRI			+	+

CT, Computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography.

*CT or PET-CT was performed, depending on availability.

studies that were "indeterminate" by the radiologist or nuclear medicine physician were not contemplated as positive studies. By contrast, imaging reports informed as "suspicious for" or "consistent with" metastatic melanoma were considered positive imaging studies.

RESULTS

The study included 308 patients. Figure 1 shows a flowchart of patients throughout the study. Baseline characteristics of the patients are reported in Table III. Participants were a median age of 63 years (interquartile range, 49-74 years), with a male predominance (55.5%). Mean Breslow index was 4.8 mm (standard deviation, 3.4 mm), and ulceration was present in 202 tumors (65.6%). The primary melanoma was most frequently located on the trunk (39.3%), and the most frequent histologic subtype was superficial spreading (37.3%). Globally, initial staging detected metastases in 16.6% of the patients, and an FPR of 5.8% was observed. Table IV reports MDR, FPR, sensitivity, specificity, PPV, negative predictive value, likelihood ratio, and accuracy of the tests performed at each clinical staging.

Lymph node ultrasound imaging was performed in 250 patients. Metastases were detected in 6.3% of T2b to T3a, in 5.8% of T3b to T4a, and in 30.4% of T4b. An overall global MDR of 12.8%, FPR of 0.8%, and accuracy of 96.0% was identified. For ultrasound imaging at stages T3b to T4b for the detection of regional lymph nodes, 58 ultrasound studies were missing. We observed that values were missing completely at random from our data set; therefore, those patients were excluded from the analysis.

CT was performed in 95 patients. Distant metastases were detected in 4.0% of T3b to T4a and in 13.3% of T4b. An overall global MDR of 8.4%, FPR of 11.6%, and accuracy of 88.4% was identified. PET-CT was performed in 61 patients. Distant metastases were detected in 3.1% of T3b to T4a and in 6.9% of T4b. An overall MDR of 4.9%, FPR of 3.3%, and accuracy of 93.4% was identified. In addition, for

Table II. Definition of true positive, false positive, true negative, and false negative for each index test

Index test	True positive	False positive	True negative	False negative
US	US suggesting abnormal lymph nodes or in transit or satellitosis, confirmed by pathology (fine-needle aspiration biopsy, Tru-Cut,* open biopsy, SLNB) or clinical follow-up.	US suggesting abnormal lymph nodes or in transit or satellitosis but disproved by pathology (fine-needle aspiration biopsy, Tru-Cut, open biopsy, SLNB) or follow-up within 4 months.	US with no signs of abnormal lymph nodes or in transit or satellitosis, who remained without recurrence detected by any method within the first 4 months of follow-up.	US with no signs of abnormal lymph nodes or in transit or satellitosis, with later detection by other imaging study or clinical follow-up with histopathologic confirmation within 4 months.
CT	CT suggesting distant metastases, confirmed by another imaging study, pathology, or clinical follow-up.	CT suggesting distant metastases, but disproved by pathology, another imaging study, or clinical/same imaging follow-up within 4 months.	CT with no signs of distant metastases, which remained without recurrence detected by any method within the first 4 months of follow-up.	CT with no signs of distant metastases, with later detection by imaging study or clinical follow-up with histopathologic confirmation, within 4 months of follow-up.
PET-CT	PET-CT scan suggesting distant metastases, confirmed by another imaging study, pathology, or clinical follow-up.	PET-CT scan suggesting distant metastases, but disproved by pathology or another imaging study or clinical follow-up within 4 months.	PET-CT scan with no signs of distant metastases, which remained without recurrence detected by any method within the first 4 months of follow-up.	PET-CT scan with no signs suggesting distant metastases, with later detection by imaging study or clinical follow-up with histopathologic confirmation within 4 months.
Brain MRI	MRI suggesting brain metastases confirmed during follow-up.	MRI suggesting brain metastases but disproved by follow-up within 4 months.	MRI with no signs of brain metastases, which remained without recurrence detected by any method within the first 4 months of follow-up.	MRI with no signs suggesting brain metastases, with later detection by imaging study or at clinical follow-up within 4 months.

CT, Computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography; SLNB, sentinel lymph node biopsy; US, ultrasound.

*Merit Medical, South Jordan, Utah.

PET-CT and CT in stages T3b to T4b for the detection of distant metastasis, 66 tests were missing. We performed the same analysis for missingness, and the data were missing completely at random. We executed the same criteria as for ultrasound imaging.

Brain MRI was performed in 95 patients. Distant metastases were detected in only 1 patient (2.0%) at stage T4b. An overall MDR of 1.1%, FPR of 2.1%, and accuracy of 97.9% was identified.

No significant adverse events occurred as a result of the imaging tests performed.

DISCUSSION

Some authors have suggested that preoperative imaging studies are associated with substantial costs and slight benefit in most patients with melanoma,

arguing that the detection rate of metastatic disease with preoperative imaging has been reported to be lower than the rate of false positivity.^{12,20} In our study, the MDR was higher than the FPR for all stages when performing an ultrasound scan for locoregional lymph node metastases. When analyzing the other imaging tests, the global MDR was lower than the FPR for CT (MDR, 8.4%; FPR, 11.6%), and similar for PET-CT (MDR, 4.9%; FPR, 3.3%) and brain MRI (MDR, 1.1%; FPR, 2.1%). However, when we further analyzed this by stages, the MDR was higher than the FPR for CT, brain MRI, and PET-CT in stage T4b, suggesting that although globally the MDR and FPR are similar to those reported in the literature, the performance of CT, PET-CT, and MRI on the subgroup of T4b patients is adequate.

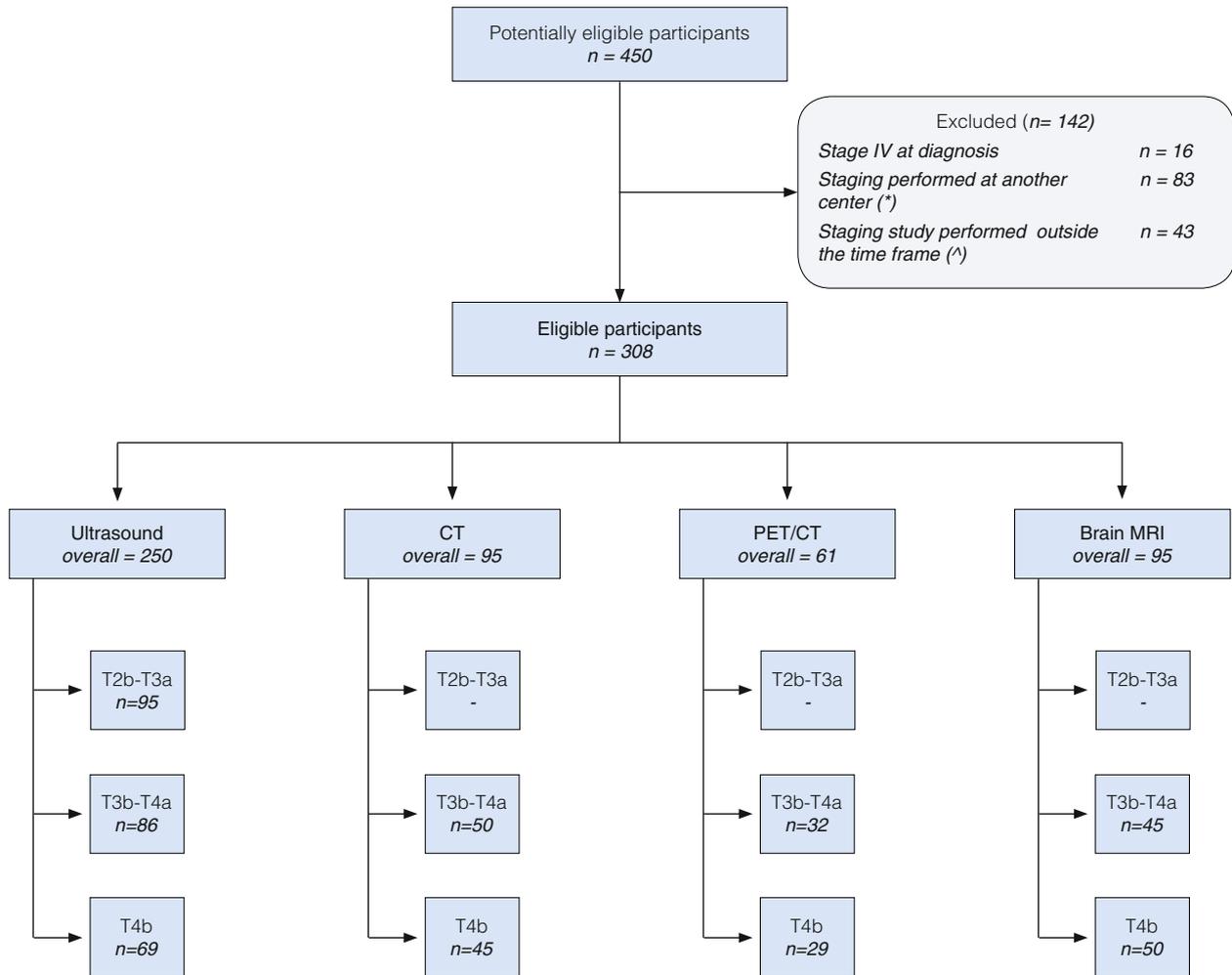


Fig 1. Flowchart of eligible patients. *Where images were not available. ^Time frame of 4 months since the diagnosis of the primary melanoma. *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *PET-CT*, positron emission tomography-computed tomography.

Ultrasound imaging

The value of preoperative ultrasound imaging in different series has been contradictory. Several reports²¹⁻²⁴ have shown the better performance of ultrasound imaging over physical examination in the detection of pathologic lymph nodes, with a higher accuracy when combined with fine-needle aspiration biopsy.^{25,26} In addition, a meta-analysis found ultrasound imaging was superior to CT, PET, and PET-CT in the assessment of lymph node metastasis.²⁷

In our study, the MDR was higher than the FPR, and specificity and accuracy were above 95% in all stages. Bearing in mind that all of our ultrasound studies were performed before lymphoscintigraphy, our results are similar to or higher than other series. Voit et al²⁸ included 127 patients and Testori et al²⁹ 88 patients, reporting a sensitivity of 79% and 94.1%, a specificity of 72% and 89.9%, a PPV of 100% and 64%

(after sentinel lymph node biopsy), and a negative predictive value of 85% and 98.7%, respectively.

Based on these results, we currently favor preoperative ultrasound imaging with fine-needle biopsy (when indicated) in all melanoma patients with stages T2b and above.

CT and PET-CT

Some studies advocate the futility of CT and PET-CT for asymptomatic patients.^{20,30} Yancovitz et al³¹ reported a 0% positive rate for CT and only 1 patient with a true-positive value for PET-CT. However, they only included patients with T1b to T3b melanomas, and only 21 patients belonged to the T3b group. Hafner et al³² reported for PET-CT only 2 FPR of 100 patients. However, they only included 19 patients with T4b melanomas. In our study, the T4b group is where we found MDR to be higher than the FPR. The

Table III. Baseline characteristics of patients

Variable	Patients (N = 309)
Sex, No. (%)	
Male	171 (55.5)
Female	137 (44.5)
Age, median (IQR), y	63 (49-74)
Tumor location, No. (%)	
Trunk	121 (39.3)
Head and neck	59 (19.2)
Lower extremities	50 (16.2)
Upper extremities	34 (11)
Acral	32 (10.4)
Mucosa	12 (3.9)
Breslow, mean (SD), mm	4.8 (3.4)
Ulceration, No. (%)	
Present	202 (65.6)
Absent	104 (33.8)
Missing values	2 (0.6)
Mitosis, median (IQR), No.	5 (2-9)
Histologic subtype, No. (%)	
Superficial spreading	115 (37.3)
Nodular	102 (33.1)
Acral lentiginous	23 (7.5)
Lentiginous malignant	16 (5.2)
Desmoplastic	8 (2.6)
Mucosal	7 (2.3)
Spitzoid	3 (1)
Nevoid	1 (0.3)
Other	24 (7.7)
Missing values	9 (2.9)
AJCC staging group, No. (%)	
T2b-T3a	95 (30.8)
T3b-T4a	117 (38)
T4b	96 (31.2)
Metastasis at initial staging, No. (%)*	
No metastasis	257 (83.4)
Metastasis	51 (16.6)

AJCC, American Joint Committee on Cancer; IQR, interquartile range; SD, standard deviation.

*Including lymph node metastasis detected by imaging methods.

MDR was 13.3% for CT and 6.9% for PET-CT, with a lower FPR of 8.9% and 0%, respectively.

When we compared CT with PET-CT in our T4b patients, CT showed a higher MDR (13.3% for CT vs 6.9% for PET-CT), a lower PPV (60% vs 100%), and lower accuracy (91.1% vs 93.1%). CT also had a higher FPR (8.9% vs 0%). Brady et al³³ found that PET scanning was more sensitive than CT in detecting occult disease (68% vs 48%), but both tests were highly specific (92% vs 95%). We found CT was more sensitive than PET-CT (100% vs 50%), with less specificity (89.7% vs 100%). However, contrary to our study, Brady et al³³ included regional nodal disease, and this was the second most frequent location of distant metastatic disease.

PET and CT have both been found to be cost-effective for evaluating high-risk melanoma patients. Bastiaannet et al³⁴ performed a study of 253 patients with stage III melanoma, where PET exhibited a greater sensitivity and higher predictive value, although CT had a higher specificity for the detection of distant metastasis. Available evidence in a meta-analysis has suggested that a modern PET-CT scan can provide the greatest diagnostic value for detecting distant metastasis for intermediate- to high-risk patients.²⁷

Another factor to consider when performing CT and PET-CT is the lifetime risk of cancer attributable to radiation. An estimated lifetime risk of cancer attributable to an annual total-body CT and PET-CT for 10 years has been estimated as 0.9% and 1.6% for male patients and 1.3% and 1.9% for female patients, respectively.³⁵

According to our results, we support total-body CT or PET-CT for T4b patients and individualizing the indications in T3b-T4a. The tests could be performed depending on the center's availability of imaging tests.

Brain MRI

Studies have suggested that the occurrence of brain metastases as the first site of dissemination is infrequent (0% to 1.1%).^{30,36} These results are similar to our series, where we found only 1 patient in stage T4b with brain metastasis during initial staging (2% of this subgroup). However, these findings need to be taken with precaution. Determining the threshold of advisable MDR is complicated. The only alternative detection of brain metastasis would be the onset of symptomatic disease, associated with a high morbidity and mortality, especially in the current era where offering immunotherapy or target therapy at an early stage would benefit the patient's outcomes.¹⁵⁻¹⁸

Podlipnik et al^{2,37} recently analyzed the performance of the same tests during the follow-up of stage IIB, IIC, and III in patients with melanoma, showing the cost-effectiveness during the first year of follow-up. In this context, the possibility to have basal explorations should be considered, reinforcing its use not only for the initial staging but also as the starting point for further follow-up. Future studies are needed to validate our findings in larger populations and across different geographic institutions. In addition, a cost-effectiveness analysis should be considered.

Limitations

Ultrasound imaging was performed on regional lymph node areas, according to our protocol, before

Table IV. Diagnostic accuracy by T stage

Imaging study	Overall	T2b-T3a	T3b-T4a	T4b
Ultrasound	(N = 250)	(n = 95)	(n = 86)	(n = 69)
Metastasis detection rate, %	12.8	6.3	5.8	30.4
False-positive rate, %	0.8	1.1	0	1.4
Sensitivity, %	80.0	66.7	62.5	91.3
Specificity, %	99.0	98.8	100	97.8
Positive-predictive value, %	94.1	85.7	100	95.5
Negative-predictive value, %	96.3	96.6	96.3	95.7
Likelihood ratio	84.0	57.3	...	42.0
Accuracy, %	96.0	95.8	96.5	95.7
CT*	(N = 95)		(n = 50)	(n = 45)
Metastasis detection rate, %	8.4		4.0	13.3
False-positive rate, %	11.6		14.0	8.9
Sensitivity, %	100		100	100
Specificity, %	87.4		85.4	89.7
Positive predictive value, %	42.1		22.2	60.0
Negative predictive value, %	100		100	100
Likelihood ratio	7.9		6.9	9.8
Accuracy, %	88.4		86.0	91.1
PET-CT*	(N = 61)		(n = 32)	(n = 29)
Metastasis detection rate, %	4.9		3.1	6.9
False-positive rate, %	3.3		6.3	0.0
Sensitivity, %	60.0		100	50.0
Specificity, %	96.4		93.5	100
Positive predictive value, %	60.0		33.3	100
Negative predictive value, %	96.4		100	92.6
Likelihood ratio	16.8		15.5	...
Accuracy, %	93.4		93.8	93.1
Brain MRI	(N = 95)		(n = 45)	(n = 50)
Metastasis detection rate, %	1.1		0	2.0
False-positive rate, %	2.1		4.4	0
Sensitivity, %	100		...	100
Specificity, %	97.9		95.6	100
Positive predictive value, %	33.3		0	100
Negative predictive value, %	100		100	100
Likelihood ratio	47.0	
Accuracy, %	97.9		95.6	100

CT, Computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

*CT and PET-CT excluding lymph node metastasis.

lymphoscintigraphy. However, lymph node basin metastasis is not predictable on the sole basis of anatomic proximity of a lymphatic area.

The quality and expertise in radiologic imaging could be center and physician dependent, respectively. Extrapolating our data to other settings should consider the high-level of expertise in melanoma imaging of our hospital radiologists and nuclear medicine physicians.

The time frame of 4 months assigned to determine whether a test result was true or false positive does not warrant the result. Low-burden metastatic disease and slow progressive disease could occur, and long-term follow-up is needed to confirm the outcomes of melanoma patients.

This was a protocolized staging system; nevertheless, following the guidelines in all of the patients is not always possible in real clinical practice. However, the missing imaging tests in patients from stages T3b and above were further analyzed and considered to be missing completely at random.

Conclusion

There are currently no consistent or collectively agreed guidelines concerning the stage-specific use of imaging studies for patients with melanoma. Based on our results, the review of the literature, and extrapolating the results to be compatible with the new American Joint Committee of Cancer

classification, we support the following protocol for staging in melanoma patients.

In all patients from T2b onward, ultrasound imaging is favored for the assessment of lymph node metastasis.

In patients with a T3b to T4a tumor, an individualized decision is advised. It can be discussed that CT or PET-CT can be performed only in symptomatic patients. In addition, it can be argued that an initial staging examination involving CT scans is reasonable to provide a baseline. This may be particularly useful during follow-up in case suspicious findings occur; thus, false-positive scans will be discarded by being unchanged at follow-up. In patients with stage T4b, CT or PET-CT are suitable for the detection of distant metastases or when distant metastases are clinically detected.

An MRI should be performed depending on the MDR threshold that one wishes to detect and on the expected clinical benefit for asymptomatic patients.

We thank members of the Hospital Clínic of Barcelona Melanoma Unit, especially Oriol Yélamos for his contribution. We thank our patients and their families who are the main reason for our studies; the nurses from the Hospital Clínic of Barcelona Melanoma Unit: Maria E. Moliner, Pablo Iglesias, and Daniel Gabriel, and all melanoma scholarship fellows who play a fundamental role in our unit.

REFERENCES

1. Siegel R, Miller KD, Ahmedin J. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67(1):7-30.
2. Podlipnik S, Carrera C, Sánchez M, et al. Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: a prospective cohort study. *J Am Acad Dermatol*. 2016;75(3):516-524.
3. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. *Lancet Oncol*. 2005;6(August):608-621.
4. Forschner A, Eigentler TK, Pflugfelder A, et al. Melanoma staging: facts and controversies. *Clin Dermatol*. 2010;28(3):275-280.
5. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2018;80(1):208-250.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Melanoma (version 1.2018). <http://www.acmonline.it/wp-content/uploads/2018/01/melanoma1.18.pdf>; 2017. Accessed January 3, 2019.
7. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised UK guidelines for the management of cutaneous melanoma 2010. *J Plast Reconstr Aesthet Surg*. 2010;63(9):1401-1419.
8. Australian Cancer Network and New Zealand Guidelines Group. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. <http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ClinicalPractic>. Accessed January 3, 2019.
9. Pflugfelder A, Kochs C, Blum A, et al. Malignant melanoma S3-guideline "diagnosis, therapy and follow-up of melanoma". [in German] *J Dtsch Dermatol Ges*. 2013;11(SUPPL. 6):1-126.
10. Dummer R, Hauschild A, Guggenheim M, Keilholz U, Pentheroudakis G. Group on behalf of the EGW. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl_7):vii86-vii91.
11. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline—update 2016. *Eur J Cancer*. 2016;63:201-217.
12. Sabel MS, Wong SL. Review of evidence-based support for pretreatment imaging in melanoma. *J Natl Compr Cancer Netw*. 2009;7(3):281-289.
13. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356.
14. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379(8):722-730.
15. Warner AB, Postow MA. Bigger is not always better: tumor size and prognosis in advanced melanoma. *Clin Cancer Res*. 2018;24(20):4915-4917.
16. Huang AC, Postow MA, Orlowski RJ, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature*. 2017;545(7652):60-65.
17. Joseph RW, Ellassaiss-Schaap J, Kefford R, et al. Baseline tumor size is an independent prognostic factor for overall survival in patients with melanoma treated with pembrolizumab. *Clin Cancer Res*. 2018;24(20):4960-4967.
18. Poklepovic AS, Carvajal RD. Prognostic value of low tumor burden in patients with melanoma. *Oncology (Williston Park)*. 2018;32(9):e90-e96.
19. Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open*. 2016;6(11):1-18.
20. Haddad D, Garvey EM, Mihalik L, Pockaj BA, Gray RJ, Wasif N. Preoperative imaging for early-stage cutaneous melanoma: predictors, usage, and utility at a single institution. *Am J Surg*. 2013;206(6):979-986.
21. Binder M, Kittler H, Steiner A, Dorffner R, Wolf K, Pehamberger H. Lymph node sonography versus palpation for detecting recurrent disease in patients with malignant melanoma. *Eur J Cancer*. 1997;33(11):1805-1808.
22. Blum A, Schlagenhauff B, Stroebel W, Breuninger H, Rassner G, Garbe C. Ultrasound examination of regional lymph nodes significantly improves early detection of locoregional metastases during the follow-up of patients with cutaneous melanoma: results of a prospective study of 1288 patients. *Cancer*. 2000;88(11):2534-2539.
23. Rossi CR, Seno A, Vecchiato A, et al. The impact of ultrasound scanning in the staging and follow-up of patients with clinical stage I cutaneous melanoma. *Eur J Cancer*. 1997;33(2):200-203.
24. Machet L, Nemeth-Normand F, Giraudeau B, et al. Is ultrasound lymph node examination superior to clinical examination in melanoma follow-up? A monocentre cohort study of 373 patients. *Br J Dermatol*. 2005;152(1):66-70.
25. Voit C, Mayer T, Proebstle TM, et al. Ultrasound-guided fine-needle aspiration cytology in the early detection of melanoma metastases. *Cancer*. 2000;90(3):186-193.
26. Rossi CR, Mocellin S, Scagnet B, et al. The role of preoperative ultrasound scan in detecting lymph node metastasis before sentinel node biopsy in melanoma patients. *J Surg Oncol*. 2003;83(2):80-84.
27. 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*. 2010;103:129-142.

28. Voit C, Kron M, Schäfer G, et al. Ultrasound-guided fine needle aspiration cytology prior to sentinel lymph node biopsy in melanoma patients. *Ann Surg Oncol*. 2006;13(12):1682-1689.
29. Testori A, Lazzaro G, Baldini F, et al. The role of ultrasound of sentinel nodes in the pre-and post-operative evaluation of stage I melanoma patients. *Melanoma Res*. 2005;15(3):191-198.
30. Aloia TA, Gershenwald JE, Andtbacka RH, et al. Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. *J Clin Oncol*. 2006;24(18):2858-2865.
31. Yancovitz M, Finelt N, Warycha MA, et al. Role of radiologic imaging at the time of initial diagnosis of stage T1b-T3b melanoma. *Cancer*. 2007;110(5):1107-1114.
32. Hafner J, Hess M, Schmid W, et al. Baseline staging in cutaneous malignant melanoma. *Br J Dermatol*. 2004;5(150):677-686.
33. Brady MS, Akhurst T, Spanknebel K, et al. Utility of preoperative [(18)F] fluorodeoxyglucose-positron emission tomography scanning in high-risk melanoma patients. *Ann Surg Oncol*. 2006;13(4):525-532.
34. Bastiaannet E, Groot CAU, Brouwers AH. Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma. *Ann Surg*. 2012;255(4):771-776.
35. Wen JC, Sai V, Straatsma BR, McCannel TA. Radiation-related cancer risk associated with surveillance imaging for metastasis from choroidal melanoma. *Arch Ophthalmol*. 2013;131(1):56-61.
36. Miranda EP. Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. *Arch Surg*. 2004;139(8):831.
37. Podlipnik S, Moreno-Ramírez D, Carrera C, et al. Cost-effectiveness analysis of imaging strategy for an intensive follow-up of patients with AJCC stage IIB, IIC and III malignant melanoma. *Br J Dermatol*. 2019;180(5):1190-1197.