PREOPERATIVE AND PRETREATMENT INVESTIGATIONS FOR MALIGNANT MELANOMA

Effective Date: February 2013

The recommendations contained in this guideline are a consensus of the Alberta Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Pre-operative or pre-treatment investigations in patients with malignant melanoma are important for establishing baseline values, confirming or re-evaluating treatment plans, or possibly identifying patients who may be suitable for inclusion in a clinical trial. [1]

The purpose of this guideline is to develop a consensus based guideline that outlines which tests should be included in the pre-operative and pre-treatment investigation (herein referred to as 'work-up') of patients with malignant melanoma.

GUIDELINE QUESTION

Which tests should be included in the work-up of patients with malignant melanoma?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

The MEDLINE (1966 through January 5, 2011), CINAHL, Cochrane, ASCO Abstracts and proceedings, and CANCERLIT databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Search terms included: magnetic resonance imaging, computed tomography, positron emission tomography, imaging, sentinel node biopsy, chest x-ray, lactate dehydrogenase, fine needle aspiration, biopsy, complete blood count, or pre-operative and melanoma.

For the 2013 update of the guideline, PubMed was searched for evidence on imaging and blood work for cutaneous melanoma. The search term "melanoma" was used and results were limited to clinical trials, published between January 2012 and January 2013. Citations were hand-searched for studies pertaining to imaging and blood work, resulting in a total of two prospective studies. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no changes were made to the recommendations.

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with malignant melanoma. Different principles may apply to pediatric patients.

RECOMMENDATIONS

For staging definitions please refer to the Appendix.

Clinical Presentation and Preliminary Work-up [1]

- Once melanoma has been confirmed, each of the following should be documented, as per the College of American Pathologists Protocol for the Examination of Specimens from Patients with Melanoma of the Skin (February 2011): [2]
    - Breslow thickness (specify mm, indeterminate)
    - Ulceration (present, not identified, indeterminate)
    - Clark level
    - Microscopic satellitosis (not identified, present, indeterminate)
    - Macroscopic pigmentation (optional; not identified, present, present, patchy/focal, indeterminate)
    - Mitotic rate (less than 1 per mm^2 or specify number per mm^2)
    - Peripheral and deep margin status of biopsy (cannot be assessed, uninvolved by invasive melanoma, involved by invasive melanoma, uninvolved by melanoma in situ, involved by melanoma in situ)
    - Specimen laterality (right, left, midline, not specified)
    - Tumour site
    - Tumour size
    - Tumour regression (not identified, present involving less than 75% of lesion, present involving 75% or more of lesion, indeterminate)
    - Histologic sub-type (melanoma not otherwise classified, superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral-lentiginous melanoma, desmoplastic and/or desmoplastic neurotropic melanoma, melanoma arising from blue nevus, melanoma arising in a giant congenital nevus, melanoma of childhood, nevoid melanoma, persistent melanoma, other)
    - Tumour infiltrating lymphocytes (optional; not identified, present non-brisk, present brisk)
    - Growth phase (optional; radical, vertical, indeterminate)
    - Lymph-vascular invasion (not identified, present, indeterminate)
    - Perineural Invasion (optional; not identified, present, indeterminate)
- Preliminary work-up should then include the following:
    - H&P with attention to locoregional area, draining lymph nodes, and skin type
    - Complete skin exam
    - Family history of melanoma, prior primary melanoma, atypical moles, or dysplastic nevi

Work-up by Clinical Stage [1]

Stage 0, in situ (Tis, N0, M0)
- None

Stage IA, low risk primary (≤1.0 mm thick, without ulceration and mitotic index <1/mm^2) N0, M0
- Further imaging (CT scan, PET, MRI) only to evaluate specific signs or symptoms
- Consider discussion of sentinel node biopsy

Stage IB, intermediate risk primary (≤1.0 mm thick, with ulceration or mitotic index ≥1/mm^2 or 1.01-2.0 mm thick without ulceration) N0, M0
- Chest x-ray (optional; however, for tumours >4 mm, baseline chest x-ray is indicated)
- Further imaging to evaluate specific signs or symptoms for Stage IIB, IIC patients (CT scan, PET, MRI)

Stage II, high risk primary (1.01-1.0 mm thick with ulceration or >2.01 mm thick any ulceration) N0, M0
- Chest x-ray (optional; however, for tumours >4 mm, baseline chest x-ray is indicated)
- Further imaging to evaluate specific signs or symptoms for Stage IIB, IIC patients (CT scan, PET, MRI)

Stage III (any thickness), N1a-3 (sentinel lymph node), M0
- Consider baseline imaging (abdominal/chest imaging: x-ray, CT ± PET) and to evaluate specific signs or symptoms.
- LDH (optional)

Stage III (any thickness) ≥N1 (clinical), M0
- FNA preferred, if feasible, or lymph node biopsy
- Consider baseline imaging (abdominal/chest imaging: x-ray, CT ± PET) and to evaluate specific signs or symptoms.
- LDH (optional)

Stage III in-transit (any thickness) N3, M0
- Biopsy preferred; FNA if biopsy not possible
- Consider baseline imaging (abdominal/chest imaging: x-ray, CT ± PET) and to evaluate specific signs or symptoms
- LDH (optional)

Stage IV metastatic
- FNA preferred, if feasible or biopsy
- Chest x-ray and/or chest CT
- LDH
- Recommend abdominal and pelvic CT with MRI or CT of head, and/or PET
- Further imaging studies to evaluate specific signs or symptoms

Recurrences

True local scar recurrence
- Biopsy to confirm
- Chest x-ray optional
- CBC, LDH optional
- CT scan, PET, MRI, as indicated

Local, satellitosis, and/or in-transit recurrence
- FNA (preferred) or excisional biopsy
- Chest x-ray and/or chest CT
- CBC, LDH optional
- Pelvic CT if inguinofemoral nodes clinically positive
- Other CT scans or other imaging studies if clinically indicated

Nodal recurrence

- FNA (preferred) or lymph node biopsy
- Chest x-ray and/or chest CT
- LDH
- Pelvic CT if inguinofemoral nodes clinically positive
- Abdominal and pelvic CT ± MRI head, PET scan as indicated

Distant recurrence

- FNA (preferred) or biopsy
- Chest x-ray and/or chest CT
- LDH
- Abdominal/pelvic CT, MRI brain, PET scan as indicated

DISCUSSION

There are currently no randomized trials on the use of pre-operative or pre-treatment investigations for malignant melanoma; as such, it is impossible to make any definitive conclusions on its usefulness. Furthermore, there are no studies providing an economic evaluation. [3]

In general, care must be taken when interpreting the results of blood or imaging tests, given the relatively low sensitivity of some of these tests. Mansour, et al. (2010) conducted a post-hoc analysis of prospective data from patients with cutaneous melanoma (n=342) who underwent a whole-body F-18-deoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) scan for staging purposes and to confirm melanoma; the false-positive rate was 13.9% overall and a relative risk of 5.33 (95% CI 2.85-9.94) for a false positive result. [4]

A summary of the literature by the National Health and Medical Research Council of Australia and New Zealand (2008) [3] concluded that for locoregional disease, the true-positive rate is less than 2% and the false-positive rate is about 10% for routine radiological scans; routine CT or PET scans can detect stage IV disease in up to 20% of macroscopic stage III patients, which may influence clinical management in up to 49% of patients. [3]

For metastatic melanoma, chest CT scan is superior for the detection of pulmonary metastases; for most other sites of metastases, PET scan is generally more sensitive than CT scan, except for brain (MRI is generally more accurate) and several others; and for patients with stage IV disease, the routine use of CT, MRI or PET scan may influence clinical management in up to 49% of patients. A prospective study by Veit-Haibach, et al. (2009) among patients with newly diagnosed and resected cutaneous malignant melanoma (n=56) who underwent contrast-enhanced FDG-PET/CT, PET-only, or CT-only for the purposes of detecting lymph node and distant metastasis demonstrated sensitivities of 38.5% and 41.7%, respectively, for PET/CT, 38.5% and 33.3%, respectively, for PET-only, and 23.1% and 25.0%, respectively, for CT-only (no significant differences). [5] The use of FDG-PET-CT within 36 days of staging contrast-enhanced CT among patients with oligometastatic stage IV or clinically evident stage III melanoma (N=32) demonstrated the identification of unexpected metastases in 12% of scans, resulting in a change of management in four patients (12%). False-positive FDG-PET-CT findings occurred in 9% (three scans). [6] A study looking at the cost-effectiveness of PET-CT, CT only, and PET only, as staging tests among melanoma patients with palpable proven lymph node metastases, found that CT alone

decreased the cost of treatment by 5.5%, whereas PET alone and CT-PET increased the cost of diagnostic work-up and treatment by 7.2% and 15.1% respectively. [7]

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CBC	complete blood count
CT	computed tomography
FNA	fine needle aspiration
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
PET	positron emission tomography

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2015. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

[1] National Comprehensive Cancer Network. Melanoma Guidelines, v.1.2012. URL: http://www.nccn.org/professionals/physician_gls/PDF/melanoma.pdf

[2] College of American Pathologists. Protocol for the Examination of Specimens from Patients with Melanoma of the Skin. Version 3.1.0.0. February 1, 2011. URL: http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/SkinMelanoma_11protocol.pdf.

[3] National Health and Medical Research Council. Clinical practice guidelines for the management of melanoma in Australia and New Zealand: Ocular and Periocular Melanoma: Supplementary Document, 2008. URL: http://www.nhmrc.gov.au/publications/synopses/_files/cp111-ocular-melanoma.pdf

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[8] Balch, C.M. et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009; 27(36): 6199-206.

APPENDIX

AJCC 2009 (7th Edition) Anatomic Stage Groupings for Cutaneous Melanoma [8]

	Clinical Staging [a]				Pathologic Staging [b]			
	T	N	M		T	N	M	5-year Survival (%)
0	Tis	N0	M0	0	Tis	N0	M0	100%
IA	T1a	N0	M0	IA	T1a	N0	M0	95%
IB	T1b T2a	N0	M0	IB	T1b T2a	N0	M0	90%
IIA	T2b T3a	N0	M0	IIA	T2b T3a	N0	M0	78%
IIB	T3b T4a	N0	M0	IIB	T3b T4a	N0	M0	65%
IIC	T4b	N0	M0	IIC	T4b	N0	M0	45%
III	Any T	N > N0	M0	IIIA	T1-4a T1-4a	N1a N2a	M0	66%
				IIIB	T1-4b T1-4b T1-4a T1-4a T1-4a	N1a N2a N1b N2b N2c		50%
				IIIC	T1-4b T1-4b T1-4b Any T	N1b N2b N2c N3		27%
IV	Any T	Any N	M1	IV	Any T	Any N	M1	13%

[a] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[b] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

AJCC 2009 (7th Edition) TNM Staging Categories for Cutaneous Melanoma [8]

T	Thickness (mm)	Ulceration Status/Mitoses	
Tis	NA	NA	
T1	≤ 1.00	a: without ulceration and mitosis < 1/mm^2 b: with ulceration or mitoses ≥ 1/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	
N	Number of Metastatic Nodes	Nodal Metastatic Burden	
N0	0	NA	
N1	1	a: micrometastasis[a] b: macrometastais[b]	
N2	2-3	a: micrometastasis[a] b: macrometastais[b] c: in transit metastases/satellites without metastatic nodes	
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/ satellites with metastatic nodes		
M	Site		Serum LDH (lactate dehydrogenase)
M0	No distant metastases		not applicable
M1a M1b M1c	Distant skin, subcutaneous or nodal metastases Lung metastases All other visceral metastases Any distant metastases		Normal Normal Normal Elevated

[a] Micrometastases are diagnosed after sentinel lymph node biopsy.
[b] Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.