



PRINCESS MARGARET CANCER CENTRE CLINICAL PRACTICE GUIDELINES

MELANOMA

Melanoma Site Group – Melanoma

Authors: Carolyn Nessim MD, Lorne Rotstein MD, David Goldstein MD, Alex Sun MD, David Hogg MD, David McCready MD, Danny Ghazarian, MD

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1. Introduction

Melanoma is the 8th most common malignancy across Canada and its incidence is slowly rising. In 2011, 5300 new cases and 950 deaths from melanoma were estimated, with 44% of the cases being from Ontarioⁱ. The most significant risk factors includeⁱⁱ:

1- Genetic mutations: Approximately 10% of melanomas are familial. Genetic mutations are variable and heterogeneous among different families.

2- Sun or UVB exposure: Patients that have prolonged or short intense exposure to the sun are more likely to be affected with malignant melanoma. UV exposure from tanning beds, especially if used before the age of 35, has also been associated with an increased risk of malignant melanoma.

3- Phenotypic traits: Fair skin, blond/red hair, high-density freckling and light coloured eyes (blue/green/hazel) have also been associated with an increased risk of melanoma.

4- Atypical nevi: 2-30 fold increased risk of developing malignant melanoma when compared to the general population

5- High nevus count: There is a high association between high nevus count (>25) and the development of malignant melanoma

2. Prevention

UVB protection by using SPF sunscreen is an essential component of melanoma prevention. Wearing a hat when exposed to the sun and UVB protection sunglasses are also beneficial as prevention strategies. Avoiding tanning beds should also be advocated.

3. Screening

There is no accepted populational screening tool for melanoma. There aren't any randomized trials showing any benefit in screening the entire population. However, Cancer Care Ontario has made the following recommendations based on expert consensusⁱⁱⁱ.

Very high risk of skin cancer

Individuals with any of the following risk factors have a very high risk of skin cancer (approximately 10 or more times the risk of the general population):

- on immunosuppressive therapy after organ transplantation
- a personal history of skin cancer
- two or more first-degree relatives with melanoma
- more than 100 nevi in total or 5+ atypical nevi

- have received more than 250 treatments with psoralen-ultraviolet A radiation (PUVA) for psoriasis
- received radiation therapy for cancer as a child

High risk of skin cancer

Individuals with two or more of the main identified susceptibility factors are at a high risk for skin cancer (roughly 5 times the risk of the general population):

- a first-degree relative with melanoma
- many (50-100) nevi
- one or more atypical (dysplastic) nevi
- naturally red or blond hair
- a tendency to freckle
- skin that burns easily and tans poorly or not at all
- use of tanning beds during teens and twenties, radiation therapy as an adult, outdoor occupation, childhood spent at a latitude less than 350*

*Other factors that may influence the risk of skin cancers.

Individuals at very high or high risk should be identified by their primary health care provider and offered total body skin examination by a dermatologist or a trained health care provider, respectively, on a yearly basis. They should also be counselled about skin self-examination and skin cancer prevention by a health care provider (e.g., physician, nurse practitioner, or public health nurse). In the case of cancer survivors, the site of radiation therapy should be closely monitored.

The general population not at increased risk of skin cancer

There is at this time no evidence for or against skin cancer screening of the general population at average risk of developing skin cancer. Based on the limited evidence available at present, routine total body skin examination by primary care providers and routine counselling about skin self-examination is not recommended for individuals at average or low risk for skin cancer.

4. Diagnosis and Pathology

4.1 Diagnosis

The clinical features of malignant melanoma can be summarized as follows:

- A- Asymmetrical
- B- Border Irregularity
- C- Colour Variegation (i.e. different colours within the same region)
- D- Diameter > 6mm
- E- Enlargement or evolution of colour, shape or symptoms

A) Diagnostic Biopsy:

- <1.0 cm: an EXCISIONAL biopsy is the ideal type of biopsy.
- >1.0 cm or difficult location: a large PUNCH biopsy is the ideal, in the center or most suspicious looking part of the lesion

**Shave biopsies are often inadequate and make pathologic diagnosis difficult as they cannot evaluate the true depth of a melanoma, which is quite important in determining the best treatment plan for the patient.*

B) Imaging and Laboratory Studies:

Stage I and II: (T1-4a/bN0M0)

- No imaging or laboratory tests for metastatic work-up is indicated in patients with melanoma of the trunk and extremities.^{iv,v}. Yield is very low at 0.1% and false positive rate is high at 15%
- In patients with head and neck intermediate thickness melanoma, US or CT Scan of the head and neck are done to evaluate the presence of nodal disease. If positive, lymphadenectomy is preformed without doing a prior SLNB.

Stage III: (T1-4a/bN1-3M0)

- **Sentinel Lymph node (SLN) positive:**
 - If limited disease in the SLN, thin or intermediate thickness melanoma (0-4 mm) and no ulceration^{vi, vii, viii}:
 - No imaging or laboratory tests indicated prior to completion lymphadenectomy
 - Yield is low and false positive rate is high
 - If extensive disease in the SLN, thick melanoma (>4 mm) or ulcerated^{6, 7, 8}:
 - CT Chest/Abdomen/Pelvis +/- MRI Brain prior to completion lymphadenectomy
 - Must still be aware of high false positive rate and if unsure, biopsy to prove metastasis may be warranted
- **Palpable lymph node at presentation / FNA positive:**
 - CT Chest/Abdomen/Pelvis and MRI Brain prior to completion lymphadenectomy
 - Must still be aware of high false positive rate and if unsure, biopsy to prove metastasis may be warranted

Stage IV: (Any T, Any N, M1a-c)

- **Widespread metastases:**
 - CT Chest/Abdomen/Pelvis and MRI Brain
 - LDH

- **Oligometastatic:** (If being considered for surgical resection)
 - CT Chest/Abdomen/Pelvis and MRI Brain
 - PET-Scan prior to resection is warranted
 - LDH

4.2 Pathology

Immunohistochemistry can be useful in difficult cases and for nodal evaluation. The markers most commonly used are S-100, HMB-45 and Melanoma Cocktail (HMB-45 + MART-1). When these markers still show inconclusive results, Microphthalmia transcription factor, Tyrosinase, Sox-10 and WT-1 may be used.

There are 4 main pathological subtypes of Melanoma:

1- Superficial Spreading Melanoma: The most common subtype, making up 70% of cases. More than 60% of this subtype, are thin melanomas <1mm and can be found at any anatomic site but have a predilection for the back in men and the lower extremities in women. They present as a variably pigmented plaque or macule with an irregular border. It may have multiple shades of red, blue, black, gray and white. The majority arise de-novo and one fourth are associated to a pre-existing nevus such as a dysplastic or congenital nevus. Their main pathologic characteristic includes a radial (lateral) growth pattern for a period of time before developing vertical (invasive) growth.

2- Nodular Melanoma: This is the second most common subtype and comprises 15-30% of all cases. They appear as darkly pigment, pedunculated or polypoid nodules. Rarely, they may be amelanotic (unpigmented). This subtype has a worse prognosis by the mere fact that more than 50% present at a depth >2mm. Its main pathologic characteristic is its vertical growth pattern.

3- Lentigo Maligna Melanoma: This subtype accounts for 10-15% of all cases. It is often found on sun-damaged areas of skin of older individuals, namely the face. It often arises from an original “in-situ lentigo maligna” as a tan-brown macule that eventually grows, darkens with irregular borders with colour variegation, becoming raised signifying the vertical growth component of this lesion.

4- Acral Lentiginous Melanoma: This subtype accounts for less than 5% of all cases. It is however most common in Asians and dark-skinned individuals. It is found on the palmar surfaces of the hand, plantar surfaces of the feet as well as in subungual locations. It appears as a dark brown or black irregularly pigmented plaque or macule.

5- Other Variants: More rare subtypes include nevoidal, desmoplastic, amelanotic and mucosal (sinus, oral mucosa, vulvar, vaginal, penile, urethral, ano-rectal etc).

4.2.1 Synoptic Pathological Reporting

A) Primary Lesion:

- The following parameters are included in the synoptic report:
 - Type of biopsy performed (excisional, incisional, punch, shave)
 - Site of the lesion and specimen laterality (left, right, midline, NOS)
 - Macroscopic Pigmentation (Not identified (NI)/ Present (diffuse or patchy) / Indeterminate)
 - Macroscopic Satellite nodules (NI / Present / Indeterminate)
 - Histologic Type (Superficial Spreading, Nodular, Lentigo Maligna, Acral Lentiginous etc.)
 - Melanoma cell type (epithelioid, spitzoid, spindle etc.)
 - Tumor Size (mm)
 - Maximum tumor thickness (mm)
 - Anatomic (Clark's) Level (I-V)
 - Ulceration (NI (Crust present or not) / Present (Focal, Extensive, post-trauma)
 - Peripheral margins (mm) closest to in-situ and invasive
 - Deep margin (mm) closest to invasive
 - Mitotic index ($<1/\text{mm}^2$ / specific number/ mm^2)
 - Microsatellitosis (NI / Present / Indeterminate)
 - Lympho-vascular invasion (NI / Present / Indeterminate)
 - Perineural invasion (NI / Present / Indeterminate)
 - Tumor infiltrating lymphocytes (NI / Present (brisk or non-brisk)
 - Tumor Regression (NI / $>75\%$ lesion / $<75\%$ lesion / Indeterminate)
 - Growth phase (Radial / Vertical / Indeterminate)
 - Lymph nodes (if present then evaluated)

B) Sentinel Lymph node:

- 6 levels per mm of the lymph node are sampled = 24um of tissue
- *Negative lymph nodes:*
 - X number of lymph node(s) identified, negative for metastatic melanoma (0/X) – using sentinel lymph node protocol
- *Positive lymph nodes:*
 - X number of lymph node(s) identified – one out of X involved by (micro/macro)metastatic melanoma (micro = 0.2-2mm, macro $>2\text{mm}$)
 - Size of node –
 - Number of foci –
 - Site of foci – (subcapsular or parenchymal)
 - Size of largest focus –
 - Cell type –
 - S-100 protein –
 - HMB45 –
 - Melanoma-cocktail (Mart-1 and HMB-45) –
 - Extranodal extension -

4.3 Staging

Melanoma staging is based on the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. Poor prognostic factors include increased tumor thickness, ulceration, mitoses $\geq 1/\text{mm}^2$ in thin T1 melanomas, nodal involvement and metastases (especially if LDH is elevated)^{ix}.

T (primary tumor)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	In-situ
T1	≤ 1.0 mm a: without ulceration and mitoses $< 1/\text{mm}^2$ b: with ulceration or mitoses $\geq 1/\text{mm}^2$
T2	1.01-2.0 mm a: without ulceration b: with ulceration
T3	2.01-4.0 mm a: without ulceration b: with ulceration
T4	> 4.0 mm a: without ulceration b: with ulceration
N (regional lymph nodes)	
NX	Cannot be assessed
N0	No regional metastases detected
N1	One lymph node a: micrometastasis* b: macrometastasis**
N2	Two or three lymph nodes a: micrometastasis* b: macrometastasis** c: in-transit met(s)/satellite(s) without metastatic lymph nodes ⁰
N3	Four or more metastatic lymph nodes or matted lymph nodes or in-transit met(s)/satellite(s) with metastatic lymph node(s)
M (distant metastasis)	
M0	No detectable evidence of distant metastasis
M1a	Metastases to skin, subcutaneous, or distant lymph node, normal serum LDH
M1b	Lung metastases, normal LDH
M1c	Metastasis to other visceral metastases with a normal LDH, or any distant metastases and an elevated LDH

* Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

** Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

⁰ In-transit is a lesion > 2 cm from the index lesion, satellite is a lesion within 2 cm of the index lesion

Despite the different definition of these two types of lesions, they are of equal prognostic significance. They have therefore been merged together under the term intralymphatic metastases in the new 7th edition of the AJCC Staging system.

Intralymphatic metastases:

- *Satellite metastases:* Skin or subcutaneous lesions that recur within 2 cm of the site of the primary tumor and are considered intralymphatic extensions of the primary tumor
- *In-transit metastases:* Develop within regional dermal and subdermal lymphatics prior to reaching the regional lymph nodes. They are any skin or subcutaneous metastases that are more than 2 cm from the primary lesion but are not beyond the regional nodal basin.

Pathologic Stage	
0	TisN0M0
IA	T1aN0M0
IB	T1bN0M0 T2aN0M0
IIA	T2bN0M0 T3aN0M0
IIB	T3bN0M0 T4aN0M0
IIC	T4bN0M0
IIIA	T1-4aN1aM0 T1-4aN2aM0
IIIB	T1-4bN1aM0 T1-4bN2aM0 T1-4aN1bM0 T1-4aN2bM0 T1-4aN1cM0
IIIC	T1-4bN1bM0 T1-4bN2bM0 T1-4bN2cM0 Any T N3M0
IV	Any T Any N M1

5. Management Algorithms

5.1 EARLY STAGE MELANOMA

5.1.1 Surgery

A) Wide local excision:

At the current time, the standard of care for primary melanoma is wide local excision (WLE) down to the deep fascia, with varying margins depending on the depth of the melanoma^{x, xi, xii, xiii}.

Breslow depth	Margin of excision
In-situ	0.5 cm
≤1 mm	1 cm
1.01-2.0 mm	1-2 cm
2.01-4.0 mm	2 cm
> 4 mm	2 cm

*Some special circumstances include: If a lesion is deemed in-situ but has regression on pathologic examination, a 1 cm margin should be performed. When primary closure is not possible, skin flaps and skin grafts may be used. In patients that have melanoma of the head and neck, a 2 cm margin may be quite deforming and in these circumstances a 1-2 cm margin is reasonable.

For melanomas of the fingers, toes, palmar and plantar surfaces, the following excisions are recommended. Preservation of important joints is recommended, as much as oncologically possible, in order to maintain good patient function:

Anatomic site of melanoma	Amputation required
Distal / Subungual Thumb / Fingers	At the distal inter-phalangeal joint
Proximal Thumb / Finger	WLE if feasible with flap or skin graft
Distal / Subungual Great Toe	At the distal inter-phalangeal joint
Proximal Great Toe	WLE if feasible with flap or skin graft
Other toes	At Metatarsal-phalangeal joint
Palmar / Plantar surfaces	WLE with flap or skin graft

Mucosal melanomas are extremely rare and make up 1.3% of all cases. They also have special surgical considerations.

Site of mucosal melanoma	Surgery recommended
Nasal cavity / oral mucosa /sinuses/ larynx	WLE if possible +/- Radiation. If not surgically feasible, radiation therapy
Vulva	WLE with 1-2 cm margins down to fascia, Total Vulvectomy may be necessary
Vagina	WLE with 1-2 cm margins + Radiation
Ano-rectal	Sphincter-sparing WLE with 1-2 cm margins Abdomino-perineal resection has not shown to improve survival and is reserved on a case to case basis of a very bulky primary tumor

B) Lymphatic Mapping:

No clinical evidence of nodal disease (microscopic disease)

For patients that have clinically negative nodal basins, a sentinel lymph node biopsy (SLNB) may be offered.

- The sentinel lymph nodes (SLN) are the first few nodes that drain the area of skin where the primary tumor is located.
- It is identified with the help of a radioactive colloid and patent blue dye, injected intra-dermally around the primary tumor site and a gamma probe in the OR.
- Lymphoscintigraphy helps map the location of the SLNs (especially useful in melanomas of the trunk and head & neck as they may drain to various basins).
- All basins identified by lymphoscintigraphy must be evaluated with SLNB for an accurate nodal evaluation.

- **Sentinel Lymph Node Biopsy** is offered to:
 - All patients with a melanoma of the trunk and extremities >1 mm in depth^{xiv}.
 - Patients with thick melanomas >4 mm may benefit from SLNB^{xv, xvi} as it is a useful prognostic tool that can guide adjuvant therapy or eligibility for a clinical trial and it is thus offered in patients with melanoma of the trunk and extremities.
 - All patients with a melanoma of the head and neck >0.75 mm^{xvii}.
 - Patients with thin melanomas ≥ 0.75 -1.00 mm in depth if they have the following poor prognostic factors^{xviii}.
 - Ulceration
 - Mitoses $\geq 1/\text{mm}^2$
 - Or if they had a shave biopsy where pathologic examination cannot evaluate the entire depth of the lesion (deep margin is positive)

- **Special Considerations:**
 - Ideally, WLE and SLNB should be concurrently performed during the same operation, however,
 - Trunk & Extremities:
 - SLNB, as a second operation, can still be performed on patients that have already had a WLE with primary closure or skin graft^{xix}.
 - If they have already had a rotational flap reconstruction, SLNB is unreliable and is thus not often performed, but may be considered¹⁹. Close observation of the nodal basins is practiced if not performed.
 - Head & Neck:
 - For patients who have already had a WLE and primary closure, skin graft, or rotational flap reconstruction, SLNB as a second operation is often unreliable and is therefore, not performed. Close observation of nodal basins is practiced.

There is much controversy as to the approach to take if a SLNB is positive with disease. It is unknown if completion lymph node dissection has any therapeutic benefit on outcome^{xx}. Patients that have additional non-sentinel node positive disease in their completion dissection have a very poor prognosis^{xxi, xxii}. It is possible that the SLNB alone, if no other nodes are positive may be therapeutic in and of itself. The MSLT-2 trial is currently ongoing to answer this question. At the current time, if a patient has a positive SLNB, completion lymph node dissection or the MSLT-2 trial is offered. The completion nodal dissections are described in the locally advanced section below.

5.1.2 Systemic Therapy

Interferon-a (IFNa) treatment schedule:

- Intravenous therapy at a dose of 20 million units/m² five days per week for four weeks
- followed by 10 million units/m² subcutaneously three times weekly for an additional 11 months.

Multiple randomized controlled trials have been performed to determine the effectiveness of Interferon-a in the adjuvant setting and results have been conflicting, some showing benefit while others did not. A large meta-analysis suggests that disease free survival is improved by 20-30% and overall survival is improved by 3-10% especially in patients with positive sentinel lymph nodes or ulcerated primary tumors more so than patients with thick >4 mm melanomas or palpable nodal disease^{xxiii}.

Since there are no other alternatives for adjuvant treatment at the current time, IFNa is offered as adjuvant treatment, for patients <70 years old:

- With positive nodal disease either by SLNB or palpable disease
- With T4 lesions that are node negative
- May be considered for patients with T2 lesions that are ulcerated, in the absence of nodal disease

5.1.3 Radiation Therapy

Although there aren't any randomized controlled trials studying the benefit of adjuvant radiation therapy in melanoma patients, some series and non-randomized prospective trials would suggest improved local control in patients that are at increased risk for local recurrence.

Radiation therapy to the primary site is considered for the following patients^{xxiv}:

- Patients that have positive margins and further excision is not feasible
- Following resection of melanomas with desmoplastic or neurotropic features
 - Thick (>4 mm) melanomas especially if ulcerated or associated with satellitosis
 - Melanomas of the head and neck especially of the mucosal type

Radiation therapy to the nodal basin is considered for the following patients^{xxv}:

- Nodes with extracapsular extension
- ≥ 4 nodes involved with disease
- Bulky adenopathy (≥ 3 cm in size)
- Cervical lymph node location
- Positive SLNB and completion dissection is not planned

5.2 LOCALLY ADVANCED MELANOMA

5.2.1 Surgery

A) Wide Local Excision:

- The same recommendations apply as for early stage melanoma (as discussed above)

B) Lymph Node Evaluation:

Clinically palpable disease (macroscopic disease)

For patients that have clinical evidence of lymph node metastases, a fine needle aspiration biopsy of the node is recommended to confirm the diagnosis. At the present time, patients with clinically and pathologically positive disease are recommended to undergo a complete lymph node dissection^{xxvi} (removal of all lymph nodes in the nodal basin). Before any complete nodal dissection, metastatic disease should be ruled out by means of a CT Chest/Abdomen/Pelvis and MRI brain as discussed above.

Groin dissection:

Superficial groin dissection = Iguinal nodal dissection

- All nodal tissue bound by the inguinal ligament superiorly, the adductor muscle medially and the sartorius muscle laterally.
- The inferior apex landmark is where the adductor and sartorius meet. Saphenous vein may be ligated or spared if possible.
- Includes Cloquet's node which is the **first node of a deep groin dissection**

Iliac dissection (sometimes referred to as a deep groin dissection)

- All nodal tissue superior and deep to the inguinal ligament around the obturator artery and vein and along the iliac artery and vein
- Iliac dissection *may* be performed if:
 - Cloquet's node is positive with disease
 - Suspiciously enlarged deep nodes are seen on pre-operative CT-Scan
 - ≥ 3 nodes are grossly involved in the superficial dissection

Axillary Dissection:

Level III dissection

- All nodal tissue in Levels I, II and III of the axilla should be removed
- Level I is lateral to the pectoralis minor muscle and is bound by the axillary vein superiorly, the pectoralis major muscle medially and the latissimus dorsi muscle laterally
- Level II – is underneath the pectoralis minor muscle
- Level III – is medial to the pectoralis minor muscle and inferior to the subclavian vein. The pectoralis minor is often divided to properly access the Level III nodes

Neck Dissection: (*Selective neck dissection is recommended*)

Lesions of the upper neck, face, and scalp anterior to the ear

- Parotidectomy and Levels I-IV of the neck

Lesions of the upper neck and scalp posterior to the ear

- Levels II-V of the neck

Lesions of the inferior neck

- Levels III-V of the neck

Lesions of the ear and of the scalp and neck at the level of the ear

- Parotidectomy and complete (levels II-V) neck dissections

C) Complications post Lymphadenectomy:

Lymphadenectomy can be a highly morbid procedure^{xxvii}

- Infection and dehiscence: 7%
- Lymphedema: 5-30% (highest risk with groin dissection)
- Seroma / Hematoma: 6%
- Sensory nerve injury: 1.8%

5.2.2 Systemic Therapy

- The same recommendations apply as those noted above for early stage disease

5.2.3 Radiation Therapy

- The same recommendations apply as those noted above for early stage disease

5.3 LOCALLY RECURRENT MELANOMA

- Although intralymphatic metastases (satellite and in-transit lesions) may occur at the same time as the primary melanoma lesion (index lesion), they are often a very common type of local recurrence.

5.3.1 Surgery

Whenever feasible, these lesions are surgically resected for an R0 resection (microscopically negative margins). If margins come back positive, re-resection may be considered if feasible. Multiple resections can be done if multiple recurrences happen as long as it remains surgically feasible with low volume disease.

Although there aren't any trials in this clinical scenario, at the time of resection, SLNB can be attempted to add to prognostic information and the need for systemic therapy.

5.3.2 Systemic Therapy

IFNa has not been shown to be beneficial in patients with in-transit or satellite metastases alone and is therefore not routinely offered.

When there are very numerous lesions, not amenable to surgical resection, some centers perform hyperthermic systemic limb perfusion or infusion with melphalan chemotherapy^{xxviii}.

5.3.3 Radiation Therapy

There is no evidence that radiation therapy is beneficial to improve local control of resected in-transit or satellite lesions or to be used alone for the treatment of multiple lesions in situ. It may, however, offer some palliation on a case by case basis.

5.3.4 Other Therapy

When these lesions are too numerous and therefore cannot be resected we may consider direct intra-lesional injection of Interleukin-2 (IL-2) which has shown quite a remarkable response rate in some patients (70% complete response rate)^{xxxix}.

5.4 METASTATIC DISEASE (at presentation or later)

5.4.1 Surgery

Usually surgery is not beneficial for patients with metastatic melanoma. Some exceptions may be patients that present with one or few solitary metastases that are resectable either in the small bowel, liver, lung or brain. As noted in some series^{xxx, xxxi} in these very select patients, a 5-year survival of 40% can be achieved. These cases must be discussed in multidisciplinary tumor boards for evaluation. PET scanning in this context is useful to ensure that there are no other sites of disease, prior to surgery.

5.4.2 Systemic therapy

Palliative chemotherapy is the mainstay of treatment for patients with metastatic melanoma. DTIC is the most common chemotherapy used, however does not have impressive response rates.

5.4.3 Radiation Therapy

- **Widespread metastases**
 - Palliative radiation can be beneficial to patients with symptomatic metastases to:
 - Bone
 - Lung
 - Pelvis
 - Brain
 - Liver

- **Solitary Brain Metastasis**
 - Surgical excision followed by whole brain radiation therapy (WBRT), if feasible, is the preferred method of treatment^{xxxii}.
 - However, if the lesion is surgically inaccessible, Stereotactic Radiosurgery followed by WBRT is recommended^{xxxiii}.

5.4.4 Other Therapy

With the advent of molecular profiling in melanoma^{xxxiv}, newer targeted therapies^{xxxv} have shown some promise in metastatic melanoma showing improved progression-free and overall survival. Mutually exclusive oncogenic mutations in cutaneous melanomas involving BRAF (50%), NRAS (15-20%) and C-KIT (up to 17%) have been identified. Moreover, clinical characteristics have been noted with each type of mutation^{xxxvi}. For example, patients that have BRAF mutations are more likely to be young, with non-

chronically sun-damaged skin and are often histologically superficial spreading, while patients with C-KIT mutations are more likely to be older with chronically sun-damaged skin and of the acral lentiginous histology. Targeted therapy such as Vemurafenib^{xxxvii} in patients with BRAF mutations and Imatinib^{xxxviii} in patients with C-KIT mutations have shown some promising results in metastatic melanoma patients.

BRAF inhibitors

Patients are tested for the V600E and V600K BRAF mutation and if positive are treated with BRAF inhibitors. 40-60% of patients with melanoma carry the mutation.

C-kit inhibitors

Patients are also tested for c-kit mutations and if positive may be offered Gleevec. 30% of patients carry the mutation.

Ipilimumab

In patients that have neither mutation, immunotherapy with Ipilimumab^{xxxix, xl} may be beneficial, especially for patients with CNS metastases. It is a monoclonal antibody that targets CTLA-4.

5.5 Oncology Nursing

Refer to [general oncology nursing practices](#)

6. Supportive Care

6.1 Patient Education

Refer to [general patient education practices](#)

6.2 Psychosocial Care

Refer to [general psychosocial oncology care guidelines](#)

6.3 Symptom Management

Refer to [general symptom management care guidelines](#)

6.4 Clinical Nutrition

Refer to [general clinical nutrition care guidelines](#)

6.5 Palliative Care

Refer to [general oncology palliative care guidelines](#)

7. Follow-up Care

There is no benefit for routine use of imaging or laboratory tests in follow-up. These studies are ordered based on patient symptoms. Although, there aren't any standardized recommendations for the frequency of follow-up, our recommendations are as follows:

Every 6 months for five years and then yearly after that, including the following:

- Full history to evaluate any symptoms concerning for metastatic disease
- Full body skin check by a dermatologist specialized in melanoma, especially to rule out a new primary melanoma (lifetime risk is 2-5%)
- Evaluation of the scar of the primary WLE to rule out recurrent satellite or in-transit lesions
- Evaluation of the nodal basin that was operated as well as other nodal basins to rule out recurrent nodal disease

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