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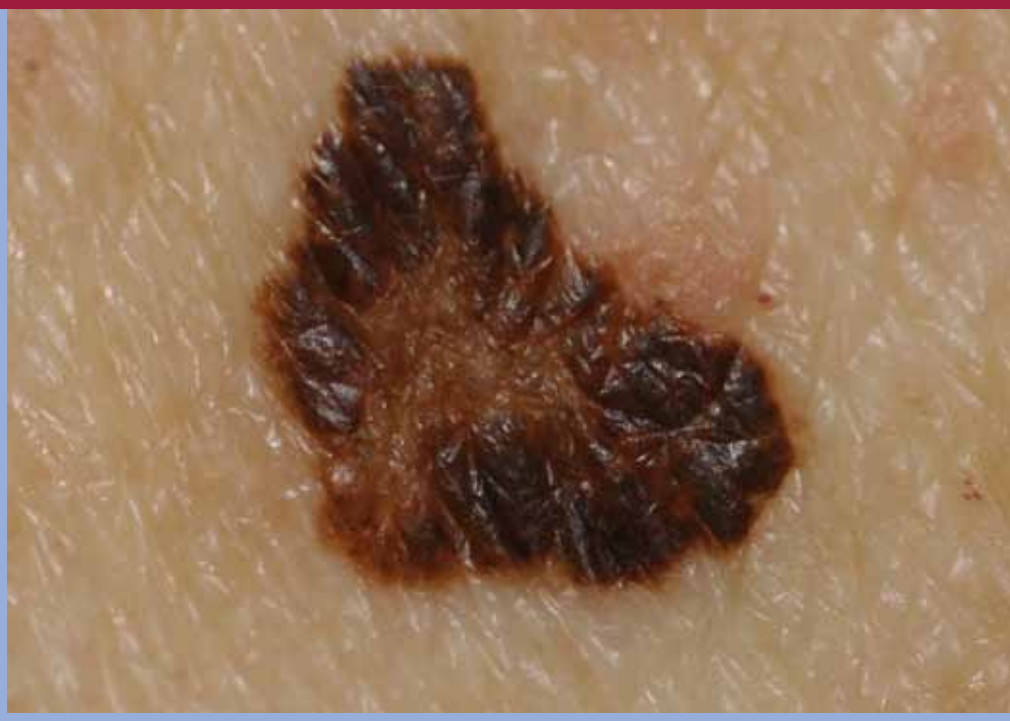
Oncology Education for Health Professionals



Skin Cancer

An Overview of Non-melanoma Cancers and Melanoma

- Precursors
- Diagnosis
- Treatment
- Outcomes
- Prevention

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Note: The information provided in this booklet is intended for educational purposes. To review Clinical Practice Guidelines, please refer to Guidelines for the Management of Malignant Melanoma, *Cancer Care Nova Scotia, www.cancercare.ns.ca (hyperlink to CCNS/ health professionals/resources and tools)*

Key Points

Non-Melanoma Skin Cancer

- There are two major types of non-melanoma skin cancers (NMSC): squamous cell carcinoma (SCC) and basal cell carcinoma (BCC).
- NMSCs are the most common cancers in humans in North America.
- Basal cell carcinoma is the most common type of skin cancer.
- It is locally destructive and causes significant morbidity, but rarely metastasizes.
- New growths or sores that don't heal are a warning sign for skin cancer.

Skin Cancers in Skin of Colour

- Skin cancers in skin of color often present atypically or with advanced stage, often due to delay in diagnosis, in comparison to Caucasian patients.
- Health professionals must maintain a high index of suspicion when examining skin lesions in patients with skin of color.
- Tools for the self assessment of skin sun sensitivity (e.g. The Fitzpatrick Skin Type Classification Scale) typically are not relevant for those with skin of colour. Health professionals may find it helpful to use culturally-neutral words (eg, the skin gets darker, itches, hurts) rather than the words "burn" or "tan" to enhance this aspect of skin cancer risk assessment.

Melanocytic Nevi

- Dysplastic nevi (clinically atypical nevi) are a type of acquired melanocytic lesion that has been identified as a marker and potential precursor for cutaneous melanoma.
- May be sporadic or familial.
- Changing lesions or atypical lesions, in which differentiation of early melanoma is not possible, should be excised.

Cutaneous Melanoma

Early diagnosis and complete surgical excision are critical to improving the prognosis of melanoma. Melanomas diagnosed at an early stage are highly curable (melanoma in situ – five year survival rate = 100%), whereas the median survival for metastatic melanoma is poor (median survival = 6-10 months for Stage IV melanoma), encouraging efforts to improve early diagnosis. The lifetime risk of developing melanoma in Canada has been estimated as 1:63 for males and 1:79 for females.

Classification:

1. Superficial spreading melanoma
2. Acral lentiginous melanoma
3. Lentigo maligna melanoma
4. Nodular melanoma

Diagnosis:

Risk factors

- light skin pigmentation
- number of melanocytic nevi
- ease of developing sunburn
- family history of melanoma (two first-degree relatives)
- blue-green eyes
- presence and number of atypical/ dysplastic nevi
- blond or red hair
- freckling
- prior history of melanoma
- history of blistering sunburn

History and Clinical Examination

- A cardinal feature of melanoma is a change observed over a period of months, either in a pre-existing nevus or a new pigmented lesion
- The development of any symptoms (itching) or signs (enlargement, asymmetry, darkening, bleeding, ulceration) should prompt referral for assessment of a pigmented lesion.
- Criteria for clinical recognition of an early melanoma is summarized by the ABCDE acronym: A = Asymmetry; B = Border irregularity; C = Color variation; D = Diameter > 6 mm; E = Evolution
- Small superficial spreading, nodular and amelanotic melanomas may lack some or all of these clinical criteria.

Management:

- Any pigmented lesion in which the diagnosis of melanoma is suspected should be biopsied (complete excision with narrow margins).
- Thickness, mitoses and ulceration are the most important histologic factors in determining prognosis of primary cutaneous melanoma.
- It is recommended that sentinel lymph node biopsy be considered for stage T1b (>1.00 mm in thickness) and upward.
- Advanced melanoma may be treated with adjuvant therapy (interferon alpha 2b for stage IIB-III) or radiotherapy.
- Local recurrence is often associated with systemic metastases.
- Metastatic disease (stage IV) has a poor prognosis, and management (surgery, radiotherapy, chemotherapy, immunotherapy) should be individualized taking into account the age, underlying medical conditions of the patient, number and site(s) of metastasis, previous treatments and the wishes of the patient and family.

Preventing Skin Cancer

According to the Canadian National Sun Survey (2006):

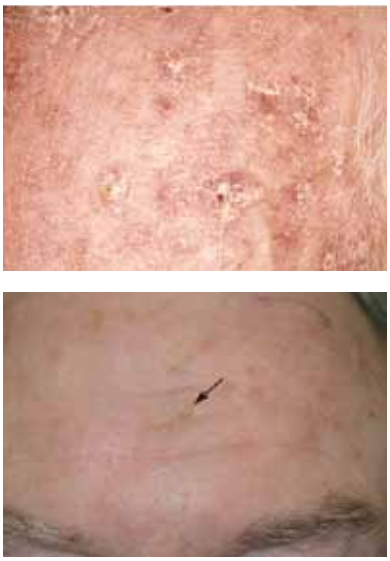
- UV exposure from the sun is greatest in older children (ages 6-12 years)
  - Over 50% of this age group spending at least two hours in the sun on a typical summer day.
- Young adults (ages 16 - 24 years) experience the second highest UV exposure.
- 29% of Atlantic Canadians aged 16 – 64 have occupations that require them to work outdoors.
  - Of these outdoor workers 41% spend four or more hours outdoors daily

To reduce your risk from overexposure to UV Rays:

- Use a broad-spectrum sunscreen with a Sun Protection Factor (SPF) of 30 or higher
  - A broad spectrum sunscreen provides protection against both UVA and UVB rays.
  - Follow sunscreen directions - apply an adequate amount and reapply as directed. Be sure to check expiry dates.
- Sunscreen should be used along with the following protective measures not instead of them:
  - Check the UV Index - this is a daily forecast widely available between April and September when the sun is strongest. It provides guidance on the level of sun protection required on a given day.
  - When possible, limit time in the sun between 11 a.m. and 4 p.m. when the UV Index is high. When this is not possible, be sure to use all other available sun safety measures.
  - Cover up with a wide-brimmed hat that shades your face, ears and neck
  - Use clothing to protect your arms and legs
  - Use shade to reduce overall UV exposure
  - Do not use a tanning bed for any reason. The evidence does not support getting a base tan to protect the skin from further sun exposure.
  - Ensure children in your care are protected from overexposure to the sun's UV rays.
  - For babies under one year:
    - Keep babies out of direct sunlight and limit time outdoors between 11 a.m. and 4 p.m.
    - Use a small amount of sunscreen on exposed areas of the skin that are not covered by clothing such as the face, neck and the backs of the hands.
      - A patch test on inner arm and surveillance for reaction over 48 hours before more general use is advised

Actinic Keratosis, a Precursor to Non-Melanoma Skin Cancer

Skin cancer is a major public health problem, as it is the most common cancer in North America.



ACTINIC KERATOSIS

Actinic keratoses (AK) arise from proliferating aberrant epidermal keratinocytes. Lesions can remit, persist, or develop into squamous cell carcinoma. Approximately 60% of squamous cell carcinomas can arise from AK. There is, in-fact, some controversy surrounding whether AKs should be classified as in-situ SCC. AK presents as single or multiple discrete, rough, scaly, erythematous lesions on chronically sun-exposed skin of adults (face, dorsa of hands, lower lip and on bald portion of scalp in males). Chronic exposure to sunlight, and inadequate protection against it, is the major predisposing factor.

AKs are clinically important because they are one of the strongest predictors that an individual may subsequently develop melanoma or non-melanoma skin cancer.

Prevention

Patients with AK should be counseled regarding sun protection (including limiting exposure to the sun, wearing protective clothing, use of sunscreen and avoidance of tanning beds). For more information on sun protection see page 3.

Management

Treatment

- Liquid nitrogen
- Topical 5% 5-fluorouracil (Efudex®) BID x 2-4 weeks, Tubes of 40 mg
- Topical 5% imiquimod cream (Aldara™) 2 times per week 3-4 days apart, up to 16 weeks, single-use packets of 250 mg
- Topical 3.75% imiquimod cream (Zyclara™) OD for two, 2-week treatment cycles separated by a 2-week no-treatment period, single-use packets of 250 mg
- Topical ingenol mebutate gel (Picato®) 0.015% to AK on face and scalp once daily for 3 consecutive days
- Topical ingenol mebutate gel (Picato®) 0.05% to AK on trunk and extemities once daily for 2 consecutive days
- Photodynamic therapy
- Chemical peels (rarely used)

Ingenol Mebutate Gel (Picato®)

A recent study in the New England Journal of Medicine (Lebwohl, M, et al, 2012) investigated the use of ingenol mebutate gel as a treatment for actinic keratosis at two different concentrations. For AK of the face and scalp, a concentration of 0.015% was used, whereas a concentration of 0.05% was useful in treating AK of the trunk and extremities. Patients applied the gel once daily for 3 consecutive days when treating lesions on the face and scalp, or for 2 consecutive days when treating the trunk and extremities.

Results indicated that the rate of complete clearance for the face and scalp was 42.2% with ingenol mebutate versus 3.7% for placebo. Local skin reactions were present in the first weeks of treatment but rapidly decreased after day 8, approaching baseline by day 29. For treatment of the trunk and extremities, a pooled analysis of the trials showed a 34.1% rate of complete clearance for ingenol mebutate versus 4.7% for placebo.

Non-Melanoma Skin Cancer (NMSC)

The Canadian Cancer Society estimates that 81,700 individuals will develop non-melanoma skin cancer in 2013. NMSC occurs in all populations, although is most common in light skinned individuals.

There are two major types of non-melanoma skin cancers: Basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC). BCC is a malignant epithelial tumor of the skin that arises from non-keratinizing cells in the basal layer of the epidermis and follicular epithelium. SCC is a malignant proliferation of suprabasal epidermal keratinocytes. BCC is thought to commonly arise de novo, while SCC most likely arises in most cases from precursor lesions such as actinic keratosis (see page 4).

Non-melanoma skin cancer (NMSC) is a major public health problem, as it is the most common skin cancer and cancer overall in Canada and the United States. BCC is the most common type of skin cancer, and represents approximately one-third of all cancers. The Canadian Cancer Society estimates that 81,700 individuals will develop non-melanoma skin cancer in 2013.

Risk Factors

Environmental Factors

- Solar Radiation (most common cause)
- Radiation therapy
- Toxins
  - Arsenic
  - Hydrocarbons
- Thermal
- Infection (Human papilloma virus for SCC)

Host Factors

- Light hair and eye colour
- Inability to tan
- Chronic wounds/scars
- Genetic disease (genodermatoses)
- Xeroderma pigmentosum
- Albinism
- Immunosuppression (SCC)

Genetics

Oncogenes (i.e., Ras) and tumor-suppresser genes (i.e., p53, Basal cell nevus gene) have been implicated in NMSC. The gene for Basal Cell Nevus Syndrome (BCNS) has been cloned on 9q-homologue to Drosophilia patched (PTCH) gene. BCNS is an autosomal dominant condition with multiple BCCs at an early age with palmar pits and skeletal abnormalities.

Defects in hedgehog (HH) signalling pathway, involved in establishing cell differentiation, growth and patterning in embryonic development, have been implicated in up to 25% of all cancers, including BCC Specifically, mutations in the PTCH1 (also known as PTCH or PTC1) and SMO genes can cause tumor formation through uncontrolled activation of this pathway.

Diagnosis

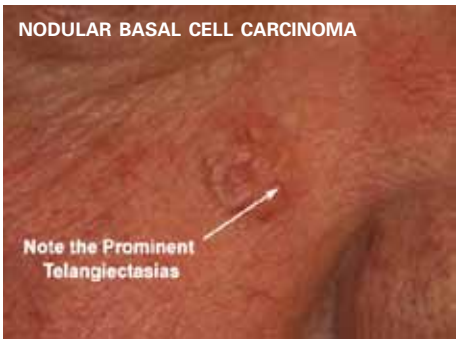
Diagnosis is made by clinical recognition of morphologic features and can be confirmed by histopathologic assessment in cases where it is difficult to discriminate benign lesions from NMSC. A table provided in Appendix I shows some benign lesions that may resemble skin cancer.

Clinical Presentation

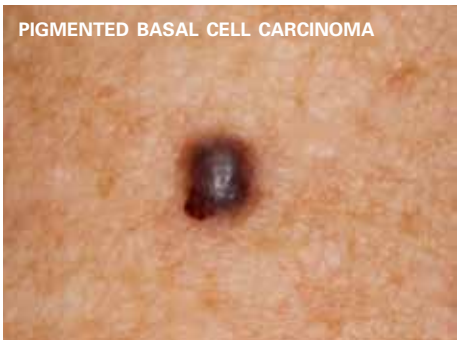
Basal Cell Carcinoma (BCC)
Approximately 70% of BCCs occur on the head and neck.

The clinical features of BCC are similar in those of African decent, Asians, Hispanics, and Caucasians.

There are four main clinical types of BCC:

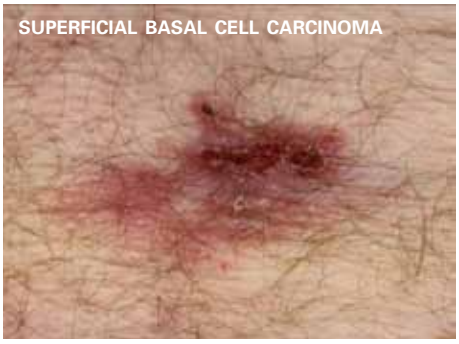


1 Nodular (noduloulcerative)
- Most common type found on sun-exposed areas of the head and neck.
- Translucent, skin colored, waxy, papule with telangiectasias on surface.
- Enlarge slowly over time, and central area becomes depressed with firm elevated, rolled border. If neglected this type can ulcerate (rodent ulcer).



2 Pigmented
- Similar to noduloulcerative except pigmented brown, blue or black.
- Can resemble melanoma.
- Pigmentation occurs more often in skin of colour (50% of BCC cases) than in Caucasians (5% of BCC cases).

3 Morphea-Form or Sclerosing
- Solitary, flat or slightly depressed, white, sclerotic plaque that is scar-like.
- Surface is smooth and shiny.
- Border is often ill-defined.

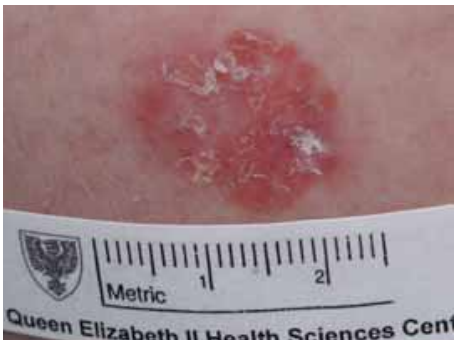


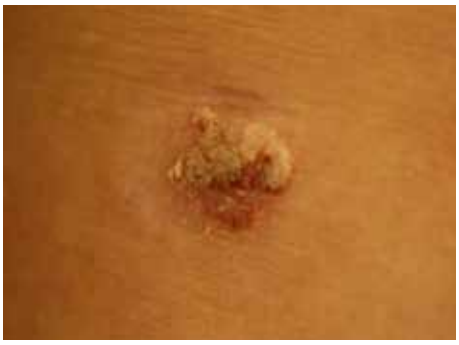
4 Superficial
- Erythematous, scaling, slightly infiltrated patch.
- Patches may be surrounded by a fine pearly border.
- Can resemble psoriasis, eczema, or tinea corporis.
- In contrast to the first three types, superficial BCCs occur most commonly on the trunk.

Squamous Cell Carcinoma (SCC)

SCC can occur anywhere on the skin or mucous membranes with squamous epithelium, but most commonly arises on sun-damaged skin of the head, neck and dorsal hands.

SCC is the most frequently diagnosed skin cancer in those of African decent and the second most common skin cancer in Caucasians, Asians, and Hispanics.





SCC *in situ* (Bowen's disease) commonly presents as a well-defined, red or pink, hyperkeratotic papule or plaque that may resemble psoriasis or nummular eczema. Invasive SCC (Bowen's carcinoma) presents as a slow-growing, keratotic or eroded papule or plaque.

Invasive SCC can be categorized as:

- Highly differentiated
  - form lesions showing signs of keratinization on the surface
- Poorly differentiated
  - soft lesions with a fleshy, granulomatous appearance.

Recurrence, Metastasis and Prognosis

Basal Cell Carcinoma (BCC)
Untreated BCCs may invade local tissue causing significant morbidity, particularly when invasion is around certain areas (eye, nose, skull). Metastasis is extremely rare, but recurrence is relatively common. The 5-year cumulative risk of developing one or more BCCs is 45% (n=260) in patients with a history of BCC. Patients with a history of BCC should receive periodic full-body skin examinations and counseling regarding sun protection and self-examination.

Squamous Cell Carcinoma (SCC)
Like BCC, SCC can be locally aggressive, but also has significant metastatic potential. Although the metastatic rate has historically been reported as between 0.5 and 6 percent, the literature also suggests that metastatic tendency may be partially site-dependent:

The metastatic rates for SCC (5 year follow-up) have been reported as follows:
- Primary SCC: 5.2% (skin) 13.7% (lip), all sites ranges from .5%-16%.
- Recurrent SCC: 25-45% (site dependent).
- 5-year survival after metastases: all sites/modalities 26%.

Metastatic rates have also been based on tumor thickness:
- 4% in tumors between 2.1 mm and 6.0 mm in thickness.
- 16% with a thickness greater than 6.0 mm.
- Local Recurrence Rate: 3%.
- Key Prognostic Factors: increased tumour thickness, immunosuppression, localization at the ear and increased horizontal size.
- Only SCC greater than 2.0 mm in thickness are associated with a significant risk of metastasis.

Management

Conventional surgical excision is generally the preferred treatment for both BCC and SCC.

Other treatments include:

- Electrodessication and Curettage (BCC)
- Radiotherapy (BCC and SCC)
- Mohs Micrographic Surgery (used mostly for BCC)
  - Used for large tumors, recurrent tumors, certain locations (periocular, perinasal, and periauricular), indistinct tumors and those with sclerosing pathology
  - Involves meticulous histologic examination of horizontal sections of removed tissue to guide the excision
  - Highest cure rate for recurrent tumors, clinically indistinct tumors, and tumors in difficult locations on the face where either tissue preservation is crucial or recurrence rates are higher with standard surgery.
  - Indications:
    - Large size (>2cm)
    - Recurrent tumor
    - Certain histologic subtypes (sclerosing)
    - Anatomic site associated with high recurrence
    - Areas where tissue sparing is important and or clinical extent is unclear

Other treatments for BCC include:

- Topical 5% imiquimod cream (Aldara™), 5 times per week for 6 weeks [for superficial BCCs with a maximum diameter of 2 cm located on the trunk of the body, neck, or extremities – excluding hands and feet], single-use packets of 250 mg
- Topical 5% 5-fluorouracil (Efudex®) BID for 2 to 4 weeks [for superficial BCCs], Tubes of 40 g
- Cryosurgery
- Photodynamic therapy

A recent study published in the *New England Journal of Medicine* (Sekulic, A, et al, 2012) examined a new form of therapy for locally advanced or metastatic basal cell carcinoma that does not involve surgical treatment. This oral medication is called Vismodegib and it is a small molecule-inhibitor that showed a 58% response rate among patients with advanced BCC. Patients received daily doses of 150 mg of oral Vismodegib. Results show that for the 33 patients with metastatic BCC, the response rate was 30%. For the 63 patients with locally advanced BCC, the response rate was 43%, with complete responses in 21%.

CAM are potential precursors of melanoma and markers for patients at risk of developing primary melanoma.

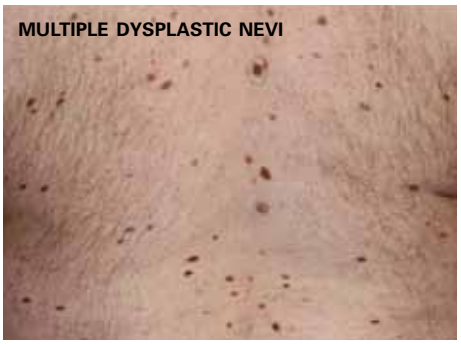
Clinically Atypical Moles (Dysplastic Nevi)

Clynically Atypical Moles (CAM) are a type of acquired melanocytic lesion that has been identified as a marker and potential precursor for cutaneous melanoma. Precise clinical and histologic definitions of CAM are controversial and continue to evolve. In general, CAM have one or several clinical features of melanoma and histologically consist of a disordered proliferation of variably atypical melanocytes often in a lentiginous epidermal pattern with dermal mesenchymal changes.

Data regarding the prevalence on CAM is limited and estimations of prevalence are frequently based on studies evaluating associated risk of melanoma. Prevalence is estimated to be between 7-24% in Caucasian adults. CAM occur in approximately 10% of adults of northern European descent based on multiple case-control studies. CAM usually appear by age 20, but new lesions can develop throughout life.

Diagnosis

Diagnosis of CAM is made by clinical recognition of morphologic features and can be confirmed by histopathologic assessment in cases where it is difficult to discriminate from melanoma. Dermoscopy (magnification with oil or polarized light) may enhance the diagnosis.



MULTIPLE DYSPLASTIC NEVI

DYSPLASTIC NEVIS *(left)*
VS. COMMON NEVIS *(right)*[1]

[1]From Langley, R.G.B., Mihm, M.,C. and Sober, A.J. (2001).

Clinical Presentation

- May be sporadic or familial
- Patients with familial dysplastic nevi can inherit this in an autosomal-dominant mode and appear to have an elevated risk for developing melanoma.
- Clinical characteristics:
  - *Anatomic distribution*: any site affected, including sun-protected sites.
  - *Number*: 1-100's.
  - *Shape*: round, oval, or may be asymmetrical.
  - *Outline*: can have an irregular or ill-defined border.
  - *Color*: irregular pigmentation within the lesion with varying shades of brown, tan, pink or red occasionally.
  - *Size*: usually greater than 5 mm in diameter.
  - *Surface*: may be flat, the surface may have "cobblestoning", or have fried-egg appearance with central raised portion.

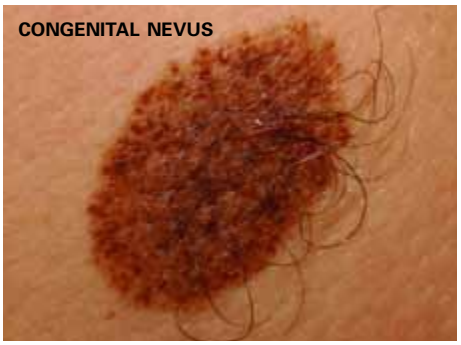
Management

CAM are potential precursors of melanoma and markers for patients at risk of developing primary melanoma. Multi-center, prospective-case, control studies have identified an increased risk of melanoma with the number of non-dysplastic and dysplastic nevi.

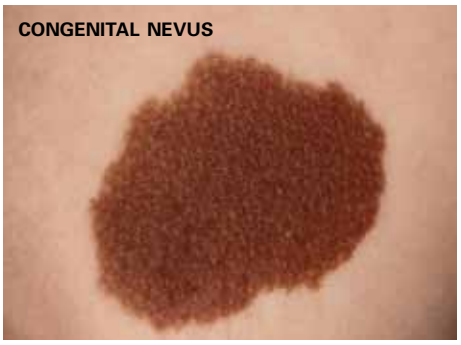
Although 20% - 50% of melanomas may arise in nevi and atypical nevi, the routine removal of CAM is neither necessary nor recommended. The lifetime risk of malignant degeneration of a nevus is low. It has been recently estimated that the risk of transformation of a nevus to melanoma in a 20 year old is 1:3,164 for males and 1:10,800 for females.

Recommendations for Management:

- Changing lesions or atypical lesions, in which the differentiation of early melanoma is not possible, should be excised.
- Patients with CAM, particularly those with multiple atypical moles, should practice self-examination.
- Patients with CAM should be assessed by a physician at regular intervals.
- Photographs may be an important tool in detecting mole changes over time.



CONGENITAL NEVUS



CONGENITAL NEVUS

Congenital Nevi

Congenital nevomelanocytic nevi (CNN) are benign neoplasms composed of cells called nevomelanocytes, which are derived from melanoblasts; rare varieties of CNN can develop and become clinically apparent during infancy. Lesions may be divided according to largest diameter as small (<1.5 cm), medium (1.5-19.9 cm) or large (≥ 20 cm).

CNN may be precursors of malignant melanoma. The risk of melanoma development appears to be proportional to the size of the congenital nevus. The cumulative 5-year risk has been calculated to be 2.3 % and 5.7% in patients with congenital nevi that involve over 5% of the body surface.

The treatment of CNNs, large and small, depends on the perceived risk of melanoma plus cosmetic and functional considerations.

Cutaneous Melanoma

The Canadian Cancer Society estimates 6000 will develop cutaneous melanoma in Canada in 2013, accounting for 3.2% of all cancers. The Maritimes have the highest rates of melanoma in Canada.

Cutaneous melanoma is an increasingly frequent and potentially lethal malignancy that results from the malignant transformation of melanocytes in the epidermis/dermis. Approximately 20 – 50% of melanomas arise within pre-existing nevi including common melanocytic nevi, dysplastic nevi, and congenital nevi.

Epidemiology

The Canadian Cancer Society estimates 6,000 Canadians will develop cutaneous melanoma in 2013, accounting for 3.2% of all cancers (excluding non-melanoma skin cancer).

The Maritimes have among the highest rates of melanoma in Canada. The Canadian Cancer Society has estimated the 2013 age-standardized incidence rate for melanoma in Nova Scotian males as 23/100,000 and 19/100,000 for females, as compared to the estimated Canadian incidence of 12/100,000 for males and 12/100,000 for females.

Risk Factors

The development of melanoma is multifactorial and appears to be related to multiple risk factors, some of which are outlined in the following table:

Risk Factors in Melanoma

Nevi	**Atypical Nevi**	■ Presence and number of atypical/ dysplastic nevi: the presence of a solitary dysplastic nevus doubled the risk of developing melanoma while having 10 or more dysplastic nevi was associated with a 12-fold elevation of risk.
	Melanocytic Nevi	■ Significant number of melanocytic nevi (more than 50) is a relative risk factor for developing melanoma of 5-fold or greater.
	Other	■ Unusual in colour or shape. ■ Large (giant) congenital nevi (>20 cm diameter in an adult). ■ Presence of a changing mole or evolving lesion on the skin.
Phenotype		■ A fair-skin phenotype (blue/green eyes, blond or red hair, light complexion, sun sensitivity (e.g. burns easily, never tans).
Personal History		■ A personal history of a previous melanoma is a relative risk of 5-fold or greater of developing another melanoma. ■ A history a of blistering or severe sunburn(s) in childhood and adolescence, and/or excessive sun exposure.
Family History of Melanoma		■ Family history of melanoma in a first-degree relative corresponds to approximately a 2-fold increase in risk for developing melanoma.
Other Risk Factors		■ Immunosupression. ■ Age (<30 or>50). ■ Sex (men>women).

Health professionals are encouraged to assess each individual's unique risk factors for all skin cancers (personal and environmental) and provide clinical advice tailored to the individual.

Those at a higher risk may benefit from monthly skin self-examinations and should be advised to become familiar with the pattern of moles, freckles, and other marks on their skin. Patients should be encouraged to report any changing lesions to their health care provider.

Genetics

Several genes have been linked to increased melanoma risk, including CDKNZA, CDK4, and MCIR.

However, likely the most important gene associated with melanoma is BRAF, which regulates several signaling pathways involved in cell division, differentiation, and secretion reported a mutation in BRAF in 66% of malignant melanomas. This oncogene may play a critical role in our understanding of malignant melanoma and has been the focus of most new research into melanoma treatments (see systemic therapy, pages 24 and 27). Recently a prospective observational study involving BRAF-tested patients with metastatic melanoma identified BRAF mutations in 48% of patients, of which 74% had V600E, 20% had V600K, and 6% had other genotypes. While BRAF mutations may be associated with poorer survival, it seems the presence of mutant BRAF had no impact on the interval from diagnosis of primary melanoma to first distant metastasis.

CDKN2A/p16, cyclin-dependent kinase inhibitor 2A, has been intensively studied in multiple-case families and in population-based series of melanoma cases. This gene is commonly called p16 and is also referred to as MTS1, INK4, and MLM. This tumor suppressor gene controls the passage of cells through the cell cycle and provides a mechanism for holding damaged cells at the G1/S checkpoint to permit repair of DNA damage prior to cellular replication. Loss of function of CDKN2A is a critical step in carcinogenesis.

Melanoma in Pregnancy

The overall incidence of melanoma in pregnancy is estimated to be 0.14 to 0.28 cases per 1000 births. Although it is rare to see melanoma in pregnant women, melanoma is one of the most common tumors known to metastasize to the placenta and fetus. Despite the fact that melanocytic nevi commonly become larger and darker under the hormonal influence of pregnancy presumably due to increased levels of estrogen and melanocyte stimulating hormone, there exists no conclusive evidence that pregnancy significantly affects the biologic aggressiveness of a melanoma in terms of increasing the incidence of metastasis or lowering overall survival. Moreover, pregnancy occurring either before or after the diagnosis and treatment of melanoma similarly seems to have no significant effect on the clinical course of the disease. Because the overwhelming (75% - 90%) majority of melanoma recurrences happen within 2 to 3 years after treatment of the primary lesion, women of child-bearing age should be encouraged to avoid becoming pregnant for that period of time postoperatively.

Diagnosis

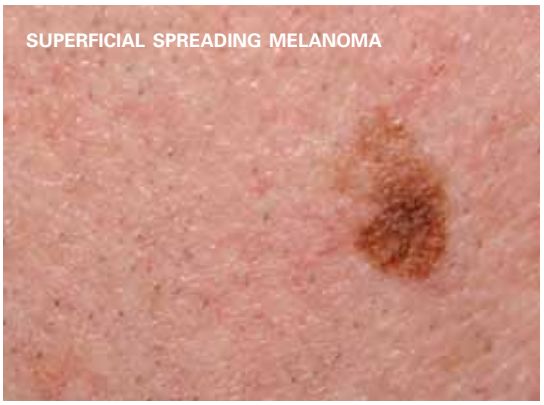
Four clinical and pathologic subtypes of melanoma have been identified. The most salient features of each are outlined below:

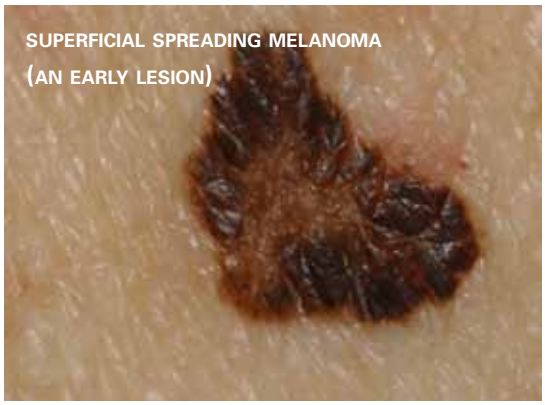
Comparisons of Clinical Features of Cutaneous Melanoma

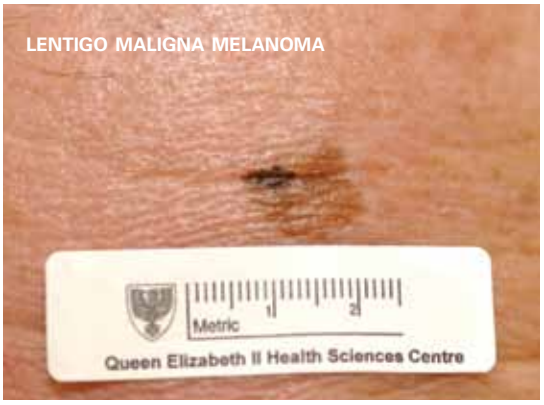
Type of Melanoma	Frequency	Duration of radial growth phase (years)	Median Age at Diagnosis (years)	Site	Clinical Features
Superficial spreading melanoma	70%	1 -7	44	Any site; lower legs in females, back in both sexes	Various shades: often, brown, black, white, gray
Acral lentiginous melanoma (including subungal melanoma)	5 - 10%	1- 3	65	Sole, palms, subungal	Flat irregular border; various shades of dark brown, black
Lentigo maligna melanoma	5%	3 - 15+	65	Sun-exposed sites including nose, cheeks, temples	Highly irregular border with areas of regression; brown-tan macular lesion with variation in pigment pattern; may be amelanotic
Nodular Melanoma	15%	Theoretically no radial growth phase	53	Any site	Nodule arises in apparently normal skin or in a nevus; brown to brown-black; may have bluish hues; may be amelanotic

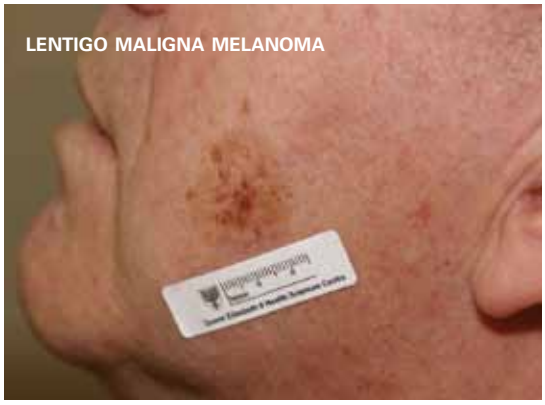
Adapted from Langley, R.G.B., Barnhill, R.L., Sober, A.J., Mihm, M.C. Jr., Fitzpatrick, T.B.F. (2003). Neoplasms: Cutaneous melanoma. In Fitzpatrick, T.B., Eisen, A.Z, Wolff, K. and Freedberg, I.M., eds, *Fitzpatrick's Dermatology in General Medicine, 6th Edition*.pp 917-947. Toronto: McGraw Hill Ryerson.

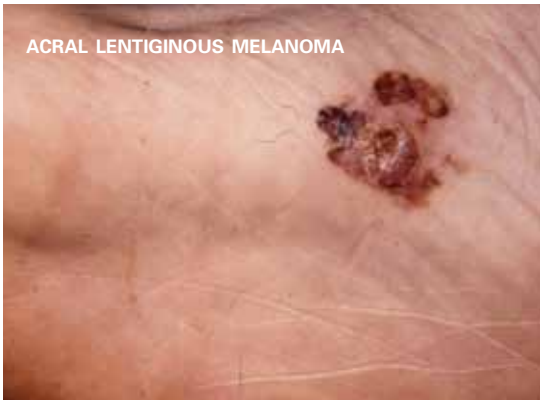
Cutaneous Melanoma *(continued)*

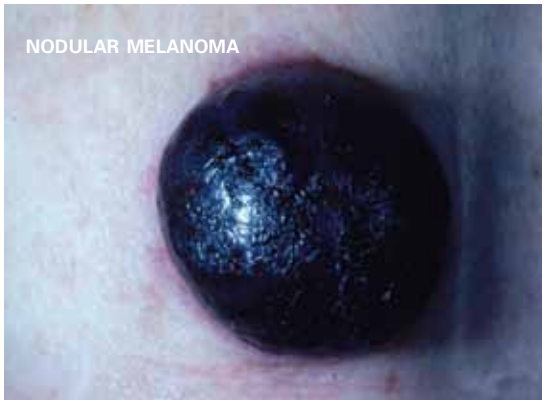












Adapted from Langley RG, Mihm MC and Sober AJ. (2001).

The most common change noted initially in early melanoma is increased size (diameter) and color change.

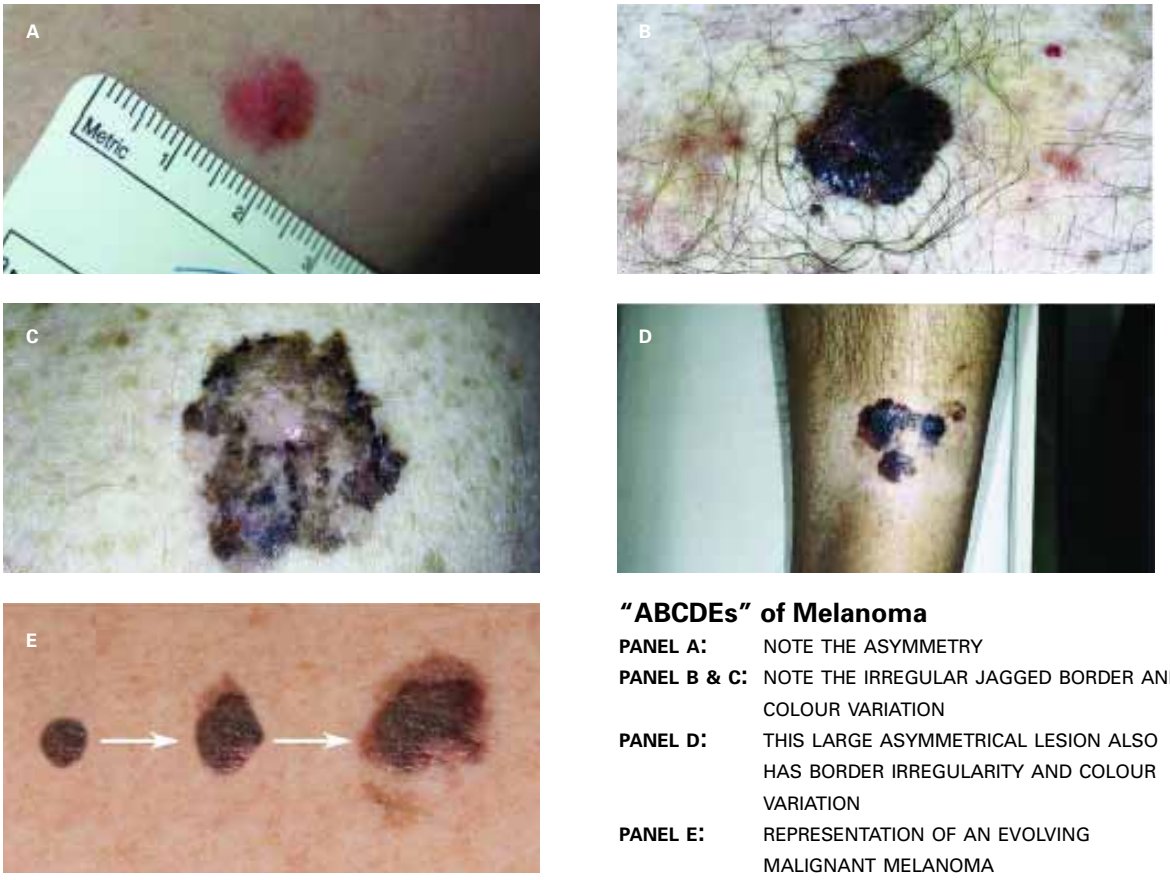
ABCDE Rule

A key feature of a skin lesion that proves to be a melanoma is a change observed over a period of months. A change in a pre-existing nevus, a new, pigmented lesion appearing in an adult, or the development of any symptoms (itching) or signs (enlargement, asymmetry, darkening, bleeding, ulceration) should prompt referral for assessment of a pigmented lesion.

The **ABCDE** rule can be used to facilitate early diagnosis in a patient with a pigmented lesion:

Asymmetry
Border irregularity
Color variation
Diameter greater than 6 mm and
Evolving - change in size, shape, symptoms (itch, tenderness), surface change (e.g. bleeding), or color shade change

Small superficial spreading and nodular melanomas may lack some or all of these clinical criteria.



"ABCDEs" of Melanoma

PANEL A: NOTE THE ASYMMETRY
PANEL B & C: NOTE THE IRREGULAR JAGGED BORDER AND COLOUR VARIATION
PANEL D: THIS LARGE ASYMMETRICAL LESION ALSO HAS BORDER IRREGULARITY AND COLOUR VARIATION
PANEL E: REPRESENTATION OF AN EVOLVING MALIGNANT MELANOMA

Adapted from Langley, R.G.B., Mihm, M.,C. and Sober, A.J. (2001).

The ABCDE's should be emphasized to any patient with moles, and in particular with specific risk factors for melanoma, to facilitate self-examination.

The **seven point checklist** has also been validated as a screening tool for early melanoma. (Haenssle, H.A., et al, 2010).

Major features *include:*

1. Change in size.
2. Change in color.
3. Change in shape.

The presence of any major feature should prompt consideration for removal of lesion or referral.

Minor features *that may increase suspicion of melanoma include:*

4. Diameter >6 mm.
5. Sensory change(itch, altered sensation).
6. Inflammation (red tinge in lesion).
7. Oozing, crusting or bleeding.

It is essential to augment the checklist with a complete history of the evolution of the lesion, sun exposure history, family history and previous skin cancer history.

Establishing a Histological Diagnosis

Lesions suspicious for malignant melanoma must be biopsied to confirm the diagnosis in a timely fashion.

- A complete excision with narrow margins is recommended, where practical.
- An incisional biopsy or punch biopsy may be performed when the lesion is large and complete excision cannot be easily performed. Shave biosies may transect the lesion and should be avoided
- A biopsy of the lesion should remove the most raised area, if raised, and remove the darkest area, if flat.

Excisional margins will be determined based on thickness (i.e. Breslow depth), after the entire lesion is excised.

For detailed information concerning biopsy, please refer to the *CCNS* Guidelines for the Management of Malignant Melanoma.

Pathology and Staging

The goals of histopathological assessment are to establish a diagnosis and to examine relevant prognostic factors.

Most important among these are:

- thickness of the lesion.
- presence or absence of ulceration.
- mitotic rate in thin (≤1mm in thickness) melanomas.
- presence or absence of microsatellites.
- status (involved or uninvolved) of the surgical margins.

The 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual (Edge, et al., 2010) was released in 2010. Staging recommendations are outlined in the table below:

The 2010 American Joint Committee on Cancer (AJCC) staging system

Stage	Primary tumour (T)	Lymph nodes (N)	Metastases (M)
IA	< 1 mm, no ulceration, mitoses < 1 mm^2		
IB	< 1 mm, with ulceration or mitoses ≥1 mm^2 1.01–2 mm, no ulceration		
IIA	1.01–2 mm, with ulceration 2.01–4 mm, no ulceration		
IIB	2.01–4 mm, with ulceration > 4 mm, no ulceration		
IIC	> 4 mm, with ulceration		
IIIA	Any Breslow thickness, no ulceration	Micrometastases, 1-3 nodes	
IIIB	Any Breslow thickness, with ulceration	Micrometastases 1–3 nodes	
	Any Breslow thickness, no ulceration	1–3 palpable metastatic nodes	
	Any Breslow thickness, no ulceration	No nodes, but in-transit or satellite metastasis/es	
IIIC	Any Breslow thickness, with ulceration	Up to three palpable lymph nodes	
	Any Breslow thickness, with or without ulceration	Four or more nodes or matted nodes or in-transit disease + lymph nodes	
	Any Breslow thickness, with ulceration	No nodes, but in-transit or satellite metastasis/es	
IV, M1a			Skin, subcutaneous or distant nodal disease
IV, M1b			Lung metastases
IV, M1c			All other sites or any other sites of metastases with raised lactate dehydrogenase

Updates on the Pathologic Staging of Melanoma – AJCC 7th Edition (2010)

i For patients with localized (stage I or II) melanoma, tumor thickness, mitotic rate and ulceration are considered the most powerful prognostic indicators.

ii Clark's level of invasion was replaced by Mitotic Index; Mitotic Index for T1: <1/mm$^{2;}$ Mitotic Index for T2: ≥1/mm$^{2.}$

iii All patients with microscopic nodal melanoma metastases (including those with only 1 cell identified) are classified as stage III.

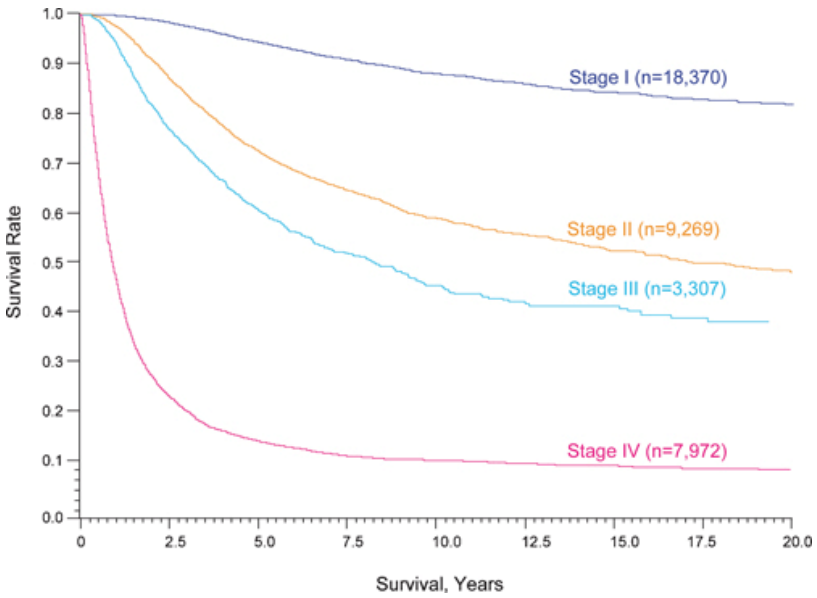
iv For patients with regional lymph node metastases, the number of lymph nodes involved, metastatic tumor burden, and ulceration and thickness of the primary tumor were the most predictive independent factors of survival.

v For patients with distant metastases, the site (non-visceral vs lung vs other visceral) and serum LDH elevation continue to define the M category.

For detailed information concerning staging, please refer to the *CCNS* Guidelines for the Management of Malignant Melanoma.

Prognostic Factors

Health professionals should help patients and families understand the prognosis of melanoma so that they can make appropriate informed decisions about their treatment. In general, melanoma stage is correlated with survival. Early stage disease, as calculated by TNM, has better prognosis than late stage disease.



Twenty-year survival curves for patients with localized melanoma (Stages I and II), regional metastases (Stage III), and distant metastases (Stage IV). The numbers in parentheses are the numbers of patients from the AJCC Melanoma Staging Database used to calculate the survival rates. The differences between the curves are highly significant (p = 0.0001). (Edge, et al., 2010)

In addition to stage, certain clinical and histological prognostic factors have been identified:

Clinical Features

- Sex: Female sex confers a better prognosis.
- Age: Older patients have a poorer prognosis.
- Anatomic location: Extremity melanomas have a better outcome than truncal or scalp melanomas.
- Distant metastases usually indicate a poor prognosis.

Histologic Features

- Thickness: The vertical thickness of the primary tumor as measured by Breslow is the most important histologic factor in determining prognosis of primary (non-metastatic) melanoma; increasing thickness of melanoma portends a progressively worse prognosis.
- Nodes involved: The number of nodal metastases is also a prognostic indicator. With only 1 node involved, the prognosis is comparatively better than when more than 2 nodes are involved.
- Ulceration: The presence of ulceration confers a poorer outcome.
- Mitoses: The greater the number of mitoses, the poorer the prognosis.
- Other: Tumor-infiltrating lymphocytes are believed to be a favorable prognostic feature, whereas regression may be indicative of a poorer prognosis.
- Elevated serum LDH at the time of initial Stage IV diagnosis is an independent and highly significant predictor of poorer survival outcome among patients who present with or develop Stage IV.

Practical Notes on Diagnosing Skin Cancer

Many benign skin conditions resemble skin cancers and may be difficult to distinguish clinically. A table provided in Appendix I outlines some of the most commonly encountered benign lesions that resemble cancers and provides some insight regarding distinguishing benign and malignant lesions.

A basic triage algorithm (Weinstock et al., 1996) is included in Appendix II and can serve as a general guideline for clinical decision making when faced with a lesion that could possibly be skin cancer.

Referral

Patients who present with suspicious new lesions or changes in existing lesions should be biopsied or referred to a dermatologist or surgeon with experience in melanoma management for biopsy and definitive care. Delay, misdiagnosis or mismanagement of malignant melanoma can have a serious effect on patients' chances of survival.

Primary Melanoma

Primary wide excision of the melanoma is the standard of care in the majority of newly diagnosed melanoma. Management recommendations for primary melanoma are outlined in the table below:

Management of Primary Cutaneous Melanoma

Breslow Thickness	In situ	<1 mm	1.01 - 2mm	>2 mm	>4 mm
Surgical Margin	0.5 cm	1.0 cm	1.0 - 2.0 cm	2.0 cm	2.0 cm
Sentinel Node Biopsy[22]	No	Only with Ulceration or mitosis (stage T1b)	May be recommended for staging	May be recommended for staging	May be recommended for staging

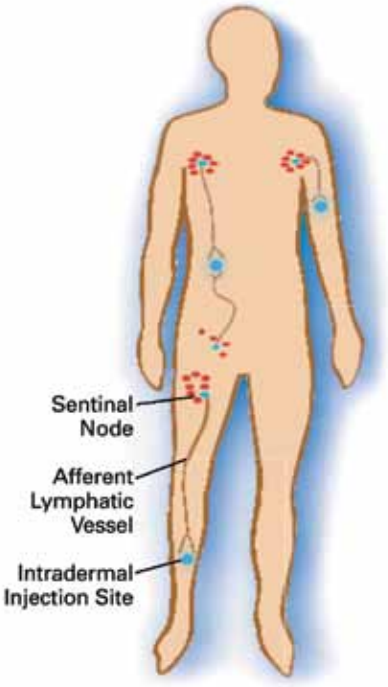
Lentigo maligna histologic subtype may require greater than 0.5 cm margins as these lesions may have a broad subclinical extension.

For **satellite lesions** (within 2 to 5 cm of the primary lesion): there is little evidence to guide management. Excision should be incorporated into the excision of the primary lesion maintaining the 2 cm margin beyond the radial edge of satellite lesion.

For **in-transit lesions** (beyond 5 cm of the primary lesion but between the primary lesion and draining nodal basin) complete excision with clear margins and primary closure where possible is recommended.

Sentinel Lymph Node Biopsy (SLNBx)

There is a large body of evidence supporting the SLNBx as the most sensitive staging tool and, furthermore, that SLN status is the most important factor for prognosis and survival. The Multi-centre Selective Lymphadenectomy Trial (MSLT) was the first large randomized trial to demonstrate the accuracy of lymphatic mapping/ SLNB technique. The results of this study suggest that disease-free and melanoma-specific survival is higher for patients who have a positive sentinel node biopsy and complete node dissection. Despite these findings, there is still considerable controversy regarding whether SLN status can accurately predict prognosis. Specifically, there is evidence to suggest that not all positive SLNs, especially ones with micrometastatic disease, will progress to clinically relevant disease, resulting in "prognostic false positive". Currently, it is recommended that SLNB be considered for stage T1b (0.76 – 1.00 mm in thickness) and upward.



Completion lymph node dissection (CLND) is recommended for all patients with a positive SLNBx. CLND achieves regional disease control. Whether or not CLND following a positive SLN biopsy improves survival is the subject of the ongoing Multi-centre Selective Lymphadenectomy Trial II.

Elective Lymph Node Dissection

In the past, considerable controversy has surrounded the choice of resection margins in melanoma. Recent prospective, randomized surgical trials are now providing evidence to guide surgical management of melanoma.

Patients with intermediate-thickness lesions (1 to 4 mm) have a 10% to 45% incidence of microscopic regional disease and a 3% to 25% risk of distant metastases and should theoretically derive the greatest therapeutic benefit from elective lymph node dissection. Prospectively randomized studies, however, have consistently failed to demonstrate a significant survival advantage with elective lymph node dissection. Nevertheless, the excision of clinically negative, microscopically positive lymph nodes in patients with melanoma may provide valuable staging information and serves to identify those patients at high risk for systemic disease who may be candidates for additional surgical or adjuvant treatment.

Cutaneous melanoma >1mm thick and clinically positive lymph node metastases
Patients presenting with, or subsequently developing, regional lymph node metastases are at high risk for distant metastases. These patients should undergo advanced scanning with intravenous contrast of the chest, abdomen, and pelvis and CT or MRI scanning of the brain. PET/CT is the most accurate tool for evaluating potential disease recurrence, distant metastasis or extent of metastatic disease.

In patients with cytologically or histologically proved regional nodal metastases, formal (complete) lymph node dissection is performed. The development of palpable lymph node metastases is correlated significantly with substantially diminished survival (10% to 50%). Survival is influenced strongly by the number of and the extent to which the lymph nodes are involved and the primary melanoma thickness.

Current recommendations for resection margins are:

a) Malignant melanoma *in situ* is excised with 0.5 cm margins. Lentigo maligna histologic subtype may require greater than 0.5 cm margins as these lesions may have a broad subclinical extension.
b) Thin (< 1 mm) melanomas have an extremely low rate of local recurrence (< 2%) and are excised with 1 cm margins.
c) For intermediate-thickness (1 to 4 mm) lesions, the safety of 2 cm excision margins has been confirmed in prospectively randomized studies.
d) For thick melanomas (>4mm), 2.0 cm margin.

Advanced Melanoma

The management of regional metastatic disease is dependent on the number and location of metastatic lesions. Generally, isolated lesions may be surgically excised. Patients with regional lymph node involvement may consider therapeutic lymph node dissection or adjuvant therapy. Patients with extensive metastases (Stage IV) may undergo chemotherapy, radiation therapy, biologic therapy or combination therapy.

Adjuvant Therapy
Until recently, there has been no standard therapy for patients with resected melanoma who are at high risk for recurrence (adjuvant therapy). Currently the only adjuvant chemotherapy approved for the treatment of resected malignant melanoma is Interferon.

High-dose Interferon alpha therapy:
Course
- Four weeks IV therapy
- Patient self-administration subcutaneously three times weekly for 48 weeks(acquired by the patient through their retail pharmacy)

Risks
- Severe toxicity, 67%
- Life-threatening toxicity, 9%

(Toxicities included grade 3 flu-like symptoms, elevated liver enzyme levels with lethal hepatotoxicities, neurologic and neuropsychiatric symptoms, and a rare lethal rhabdomyolysis)

The results of the Eastern Cooperative Oncology Group trials (Kirkwood et al, 1996, 2000, 2001) demonstrated an improvement in relapse-free survival but not overall survival for high-risk melanoma patients given high-dose interferon.

A more recent study evaluated different dosing regimes for Interferon and found no difference in survival benefit between patients given a high dose of Interferon for one month and then a low dose for one year versus those who were only given a high dose of Interferon for one month.

A very recent randomized, open-label, phase 3, parallel-group trial investigated whether adjuvant therapy with intermediate-dose Interferon alfa-2b for 1 or 2 years would improve outcomes in patients with stage IIB-IIC or III resected cutaneous melanoma. Results of this study showed that adjuvant therapy with an intermediate dose of Interferon alfa-2b did not significantly improve overall survival.

Current treatment recommendations are as follows:
Stage IA,IB,IIA, IIB (T3bN0): no adjuvant therapy
Stage IIB, IIC (T4a or b, N0): observation or Interferon alfa 2b
Stage III: observation or Interferon alfa 2b

Because of the significant cost and toxicity associated with the use of Interferon alfa 2b, patients who are candidates for consideration should be referred to medical oncology for review and discussion of the risks and benefits.

Radiotherapy

The use of radiotherapy in the postoperative setting has been shown to improve local control but there is no evidence for survival benefit.

Post-operative radiotherapy could be considered in the following circumstances:

- Positive or close resection margin when re-excision is not possible
- Gross residual disease
- Multiple positive lymph nodes or single node 2.5 cm in size or greater
- Extra nodal or soft tissue extension

Monitoring Response to Therapy and Reassessment of Disease

FDG PET/CT is the most accurate method of assessing treatment response.

Local Recurrence

Local recurrence in a patient with malignant melanoma is almost always associated with the development of systemic metastases. The survival of these patients is extremely poor averaging approximately 10% at 5 years. Diagnosis is made by fine needle aspiration biopsy. Following confirmation of recurrence, a complete metastatic survey (CT and/or MRI and/or PET/CT) should be performed, as most of these patients will have evidence of systemic metastases. Referral to the palliative care team should also be considered and advanced care planning discussed with the patient and family.

Complete surgical resection is the standard treatment for both solitary recurrences and multiple, local subcutaneous metastases (wide excisions may require grafting). Despite complete surgical resection, further local and regional recurrence occurs in approximately two-thirds of patients.

Isolated hyperthermic limb perfusion may be used in cases of non-resectable in-transit metastases or inoperable primary tumours confined to an extremity. Patients who might benefit should be referred to the Melanoma Cancer Site Team at the QEII.

For more detailed information on the management of local recurrence, please refer to the *CCNS* Guidelines for the Management of Malignant Melanoma.

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Metastatic Disease

Melanoma is the third most common cause of metastases to the central nervous system. About 2/3 of these are multiple; the other third are solitary metastases.

The aims of therapy in stage IV melanoma generally include one or more of the following:
1. To relieve symptoms of a life-threatening problem.
2. To increase length of survival.
3. To evaluate new therapies.

Therapy should be individualized and consider the age, underlying medical condition of the patient, number and site(s) of metastasis, previous treatments, and the wishes of the patient and family.

Surgical excision of isolated metastases in the skin and subcutaneous tissue, lymph nodes, lung, brain and gastrointestinal tract may improve survival. Prognosis is dependent on the number and location of the metastases. These patients should be referred to a surgical oncologist.

Radiotherapy should be considered for patients with unresectable metastatic melanoma and is most commonly used for patients with advanced axillary or groin disease, brain metastasis and extensive cutaneous lesions not amenable to surgery. Radiation remains the primary treatment modality for symptomatic bone metastases.

Chemotherapy with Dacarbazine may be offered. Other therapies including combination chemotherapy with Decarbazine and chemotherapy with immuno-therapies have not been shown to provide advantage over single agent Dacarbazine.

Interleukin 2 is associated with prolonged complete remission in approximately 5% of patients. This therapy is not available in Nova Scotia.

Temozolomide, the oral pro drug of Dacarbazine, offers similar response rates to Dacarbazine (i.e. 15-20% and no improvement in overall survival) but offers the convenience of an oral medication. It is not approved in Nova Scotia for treatment for metastatic melanoma. Some third party payers will finance the drug.

Patients who have unresectable metastic disease should be considered for any clinical trials which are open.

For more detailed information on the treatment of advanced melanoma, please refer to the *CCNS* Guidelines for the Management of Malignant Melanoma.

New Therapies for Non-resectable Melanoma

In recent trials, two systemic therapies, Ipilimumab and Vemurafenib have shown promise in improving survival for these patients. (Robert, C., et al, 2011; Kirkwood, J.M., et al, 2011; Chapman, P.B., et al, 2011).

Ipilimumab (a fully human, IgG1 monoclonal antibody) blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) (a negative regulator of T cells) thereby augmenting T-cell activation and proliferation. Ipilimumab was approved by the US Food and Drug Administration for the treatment of unresectable or metastatic melanoma. In a very recent phase III study of 502 patients with previously un-treated metastatic melanoma, Ipilimumab (at a dose of 10 mg per kilogram) in combination with Dacarbazine (850mg M^2), as compared with Dacarbazine plus placebo, improved overall survival (11.2 months vs. 9.1 months) with higher survival rates in the Ipilimumab plus Dacarbazine group, after 3 years (20.8% vs. 12.2%).

Vemurafenib (PLX4032) is a potent inhibitor of mutated BRAF with antitumor effects against melanoma cell lines with the BRAF V600E mutation. In a multicenter, phase 1, dose-escalation trial involving 49 patients with primary melanoma tumors carrying the BRAF V600E gene, it was found that treatment resulted in partial or complete tumor regression in the majority of patients. A very recent phase III randomized clinical trial comparing Vemurafenib with Dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation found that overall survival was improved in the Vemurafenib group (84%) compared with the Dacarbazine group (64%) at 6 months. This unprecedented finding in the interim analysis prompted an independent data and safety monitoring board to permit patients who were treated with Dacarbazine to cross over to receive Vemurafenib. Although the immediate results appear promising, responses may be short-lived due to acquired drug resistance, possibly as a result of secondary mutations in B-RAF(V600E), MAPK reactivation, and activation of alternative survival pathways.

While these new therapies represent hope for patients with metastatic disease, long-term efficacy and safety remain to be proven and further study is needed.

Follow-up

- Frequency of follow up visits is determined by risk of recurrent disease and presence of other risk factors including: history of multiple melanomas, presence of atypical nevi, family history, patient anxiety and patient's ability to reliably perform self examination
- Routine surveillance blood work or imaging is not justified for asymptomatic patients and investigations should be guided by findings on history and physical examination.
- Patients with thin, primary melanomas may be followed by dermatologist, surgeon and/or family physician.
- Patients with more advanced melanomas, recurrent or node positive disease, distant metastases or other high risk factors may benefit from a multidisciplinary approach (dermatologist, surgeon, oncologist and family physician).

The chart below suggests intervals for follow up:

Stage	Frequency of Follow up Assessments
Stage 1	Every 3-6 months for first 3 years Every 6 months until year 5 Consider annual follow up thereafter
Stage 2	Every 3 months for first 3 years Every 6 months until year 5 Consider annual follow up thereafter
Stage 3	Every 3 months for first 3 years Every 6 months until year 5 Consider annual follow up thereafter
Stage 4	Every 3 months or at discretion of treating physician

Psychosocial Support

The needs and concerns of individual melanoma patients varies depending on the stage of disease at diagnosis, whether it is a new diagnosis or a recurrence, the difficulty in resection or treatment and risk of disfigurement as a result of treatment. Their needs include physical, emotional, psychological, practical, informational, social, and spiritual issues, and all are important in the provision of person-centred care.

The majority of melanoma patients will not have life-threatening disease. Survivors of cancer who are treated with less aggressive therapies, have relatively good survival rates and have a high number of years lived without disability. They may be more concerned about fear of recurrence and less troubled by physical impairments resulting from the cancer itself or its treatment. Not all patients with melanoma exhibit clinical levels of psychological distress or need intensive psychosocial support. Many melanoma patients adjust and cope well. However, it is important that those who require psychosocial health services and palliative care are identified and provided with necessary supports. It is important to remember that family members may also experience clinically significant distress, at levels equivalent to or greater than patients.

Distress is now recognized as the 6th Vital Sign of cancer care. In Nova Scotia, identification of patient distress through screening and management of the cancer-related distress is a standard of care.

It is the responsibility of the health care team to provide basic support through the continuum of disease. Regular patient assessment (including screening the patient for distress) should be conducted and the goals of care changed as appropriate. Patients and families will benefit from supportive communication (e.g., clear communication, provision of relevant information, active listening, empathy), supportive counseling (e.g., provision of support, minimizing symptoms, making patients and families aware of resources) and symptom management (supportive care), as appropriate. Patients at higher risk of emotional distress include those with poor overall health status, those with certain personality types (e.g. maladaptive coping styles), and those without a social network. For those patients and families referral for specialized psychosocial care (psychosocial oncology), is recommended.

The Inventory of Psychosocial Resources in Nova Scotia was developed by *Cancer Care Nova Scotia's* Supportive Care Cancer Site Team, in partnership with the Canadian Cancer Society – Nova Scotia Division. The Inventory is intended to assist health care professionals who care for cancer patients and individuals affected by cancer, in more readily accessing psychosocial services. The inventory includes a list of both public and private psychosocial resources, available in each of the nine health districts. The focus is on licensed health care professionals, such as psychologists, psychiatrists, social workers, nurses, spiritual care providers, as well as others who provide psychosocial and supportive care to patients.

For further information and guidance concerning the management of cancer-related distress, refer to the Standards of Psychosocial Health Services for Persons with Cancer and their Families (CAPO, 2010) and the *CCNS* Best Practice Guideline for the Management of Cancer-Related Distress in Adults.

UV Exposure and Preventing Skin Cancer

Understanding the Risks

Ultraviolet (UV) radiation from the sun is classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen and cause of melanoma and other skin cancers. The sun is the main source of exposure to UV radiation. Additionally, radiation from UV emitting tanning devices was reclassified by the International Agency for research on Cancer in 2009 to a Group 1 carcinogen.

The literature demonstrates an increased melanoma risk in indoor tanners. And, even more alarming, an escalating risk with total hours, sessions or years of tanning bed use.

- First exposure to sunbeds before 35 years of age significantly increases the risk of melanoma skin cancer (summary relative risk, 1.75; 95% CI, 1.35-2.26).
- Use of sunbeds to provide protection from subsequent sun exposure is not supported by the evidence.
- UV radiation exposure from tanning beds is associated with increased risk of early-onset melanoma. Risk increases with greater use and earlier age at first use.

Canadians at Risk

According to the Canadian National Sun Survey (2006), UV exposure from the sun is greatest in older children (ages 6-12 years) with over 50% of this age group spending at least two hours in the sun on a typical summer day. This is followed by young adults (ages 16 - 24 years) with 47% of males and 32% of females similarly exposed to at least 2 hours on a typical summer day.

- Younger adults and older children, the age groups experiencing the greatest sun exposure and the least protection, are the most likely to get a sunburn.
- Most adults get their worst sunburn while taking part in outdoor recreational activities. Over 50% of children also get their worst sunburn while watching or participating in outdoor recreational activities.
- While 49% of outdoor workers in Atlantic Canada spend four or more hours outdoors daily, this group does not practice optimal sun safety. Just over half of outdoor workers report that they wear a hat, protective clothing or protective eyewear. Only 29% use sunscreen.
- 49% percent of young women (ages 16-24) and 28% of young men actively try to get a tan from the sun.
- Use of tanning equipment is more common among young women than among young men or older adults.
  - 27% of young women use tanning equipment.
  - 15% of women aged 25-44 use tanning equipment.
  - Only 8% of women aged 45-64 use tannning equipment.

Tanning Bed Legislation in Nova Scotia

The Nova Scotia Tanning Beds Act was proclaimed into law on May 31st, 2011. The purpose of this Act is to protect the health of Nova Scotians, and in particular young persons, by restricting their access to tanning equipment in tanning facilities in light of the risks associated with the use of tanning equipment.

The Tanning Beds Act bans access to commercial tanning equipment for anyone under the age of 19 years in Nova Scotia. Regulations governing the legislation require vendors to post signage that speaks to the age restriction and to the health risks associated with use. Compliance is supported through education packages for vendors, the role of enforcement officers, incremental fines up to a maximum of $10,000 and potential for business closure for up to two years for repeated violations of the law. A 1-800 number for reporting violations of the law further supports compliance.

While focused on protecting youth, the legislation also serves to raise awareness and inform the broader Nova Scotia public of the health risks associated with tanning bed use.

Sharing the Prevention Message with Patients

Given the number of factors that can contribute to a person's risk of developing skin cancer, health professionals are encouraged to assess each individuals' unique risk factors for skin cancer (personal and environmental) and provide clinical advice tailored to the individual.

When assessing risk factors, health professionals should be mindful of the potential of high UV exposure amongst three particular groups: older children and young adults (the most active tanners and the least compliant with sun protection practices) and outdoor workers (highly exposed to natural UV).

Patients whose skin tans poorly and those who have a large number of abnormal moles, and/or a family history of melanoma in two first-degree relatives, may have an increased risk of developing melanoma skin cancer. These patients may benefit from monthly skin self-examinations. Patients should know the pattern of moles, freckles, and other marks on their skin so that they can recognize changes and report these to their health care provider.

A recent study (Green et al, 2011) found that long-term, regular use of sunscreen significantly reduced the rate of melanoma in adults.

To reduce your risk from overexposure to UV Rays:

- Use a broad-spectrum sunscreen with a Sun Protection Factor (SPF) of 30 or higher
  - A broad spectrum sunscreen provides protection against both UVA and UBV rays.
  - Follow sunscreen directions - apply an adequate amount and reapply as directed. Be sure to check expiry dates.
- Sunscreen should be used along with the following protective measures not instead of them:
  - Check the UV Index - this is a daily forecast widely available between April and September when the sun is strongest. It provides guidance on the level of sun protection required on a given day.
  - When possible, limit time in the sun between 11 a.m. and 4 p.m. when the UV Index is high. When this is not possible, be sure to use all other available sun safety measures.
  - Cover up with a wide-brimmed hat that shades your face, ears and neck.
  - Use clothing to protect your arms and legs.
  - Use shade to reduce overall UV exposure.
  - Do not use a tanning bed for any reason. The evidence does not support getting a base tan to protect the skin from further sun exposure.
  - Ensure children in your care are protected from overexposure to the sun's UV rays.
  - For babies under one year:
    - Keep babies out of direct sunlight and limit time outdoors between 11 a.m. and 4 p.m.
    - Use a small amount of sunscreen on exposed areas of the skin that are not covered by clothing such as the face, neck and the backs of the hands.
      - A patch test on inner arm and surveillance for reaction over 48 hours before more general use is advised.

For more information on the UV Index, sunscreen, shade or covering up, refer patients to the Canadian Dermatology Association (www.dermatology.ca), Health Canada (www.hc-sc.gc.ca) and the Canadian Cancer Society (www.cancer.ca).

Phototoxicity

Several medications and over-the-counter products can increase the sensitivity of the skin to burn (phototoxicity). These photosensitizing agents include:

- Commonly-used antibiotics (eg. Quinolones such as Ciprofloxacin and Norfloxacin, sulfonamides such as Co-trimoxazole, and Tetracyclines).
- Non-steroidal, anti-inflammatory drugs (eg. Ibuprofen, including over-the counter products, Diclofenac, Indomethacin and Naproxen).
- Quinine, Quinidine, and some anti-cancer drugs (such as 5-fluorouracil and Vinblastine).
- Diuretics or antihypertensives such as Furosemide and Hydrochlorothiazide.
- Dyes such as acriflavin, eosin, methylene blue and toluene blue (may be found in medications and food products).
- Foods and herbs such as: figs, lemon, lime, anise, celery, dill, fennel, and some herbs found in natural health products.

Patients who are taking any phototoxic product or food, are at increased risk of sunburn and other harm to the skin and must take particular care to keep sun exposure to a minimum as long as the products are in their system. With some agents, such as the retinoid drugs (e.g. tretinoin, isotretinoin), even a small exposure to the sun can cause skin reactions. Avoiding sun exposure (with protective clothing, hats, etc.) is advised; use of sunscreens may provide less protection than expected when taking any photosensitizing agent or food.

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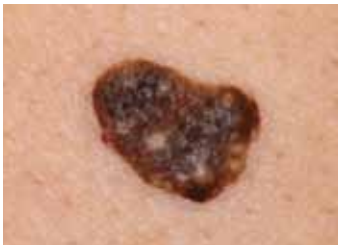
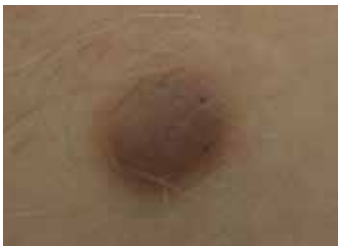
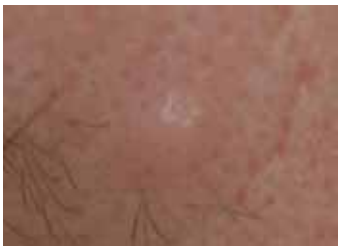
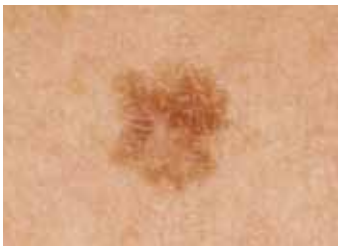
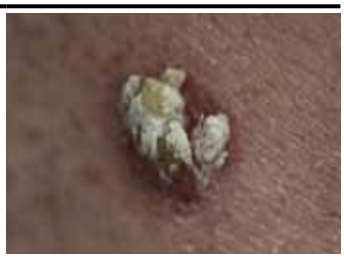
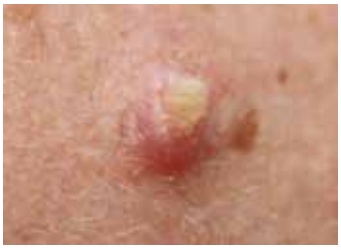
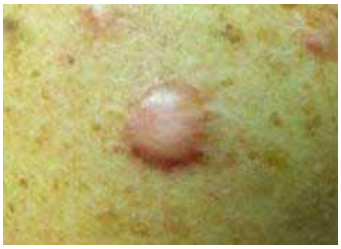
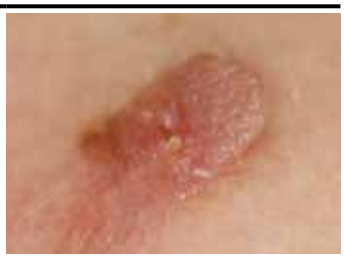
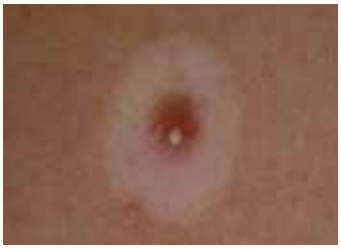
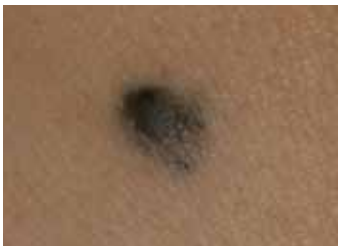
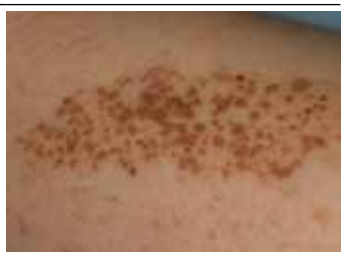
Appendix I. Benign Lesions that May Mimic Skin Cancer

	Clinical Characteristics	How to Differentiate from Skin Cancer	Example
Seborrheic Keratosis	Papules or plaques, with or without pigment, that may have a "stuck-on" or greasy appearance or feel; Small, white keratin cysts (horn cysts) may be visible with close examination or dermoscopy	■ Presence of horn-cysts ■ May be easily removed from the underlying skin by shave biopsy	
Dermatofibroma	Solitary, firm, well-defined papular or nodular lesions usually found on the trunk or extremities, brown/ red in color	■ Presence of "retraction sign" or dimpling when surrounding skin is compressed	
Sebaceous Hyperplasia	Small, soft, skin-colored papules (1-3 mm in diameter) with central umbilication *** May have telangiectasia and are often mistaken for basal cell carcinomas*	■ Central punctum ■ Sebum may be released on compression	
Solar Lentigo	Well-defined tan to brown macule, commonly 1-3cm in diameter; variable in color and shape and appear exclusively on sun-exposed areas More common in individuals over 40 years of age with skin phototype I or II	■ Can be differentiated from lentigo maligna based on evaluation of the "ABCDEs" or dermoscopy ■ Suspicious lesions should be biopsied to confirm the diagnosis	

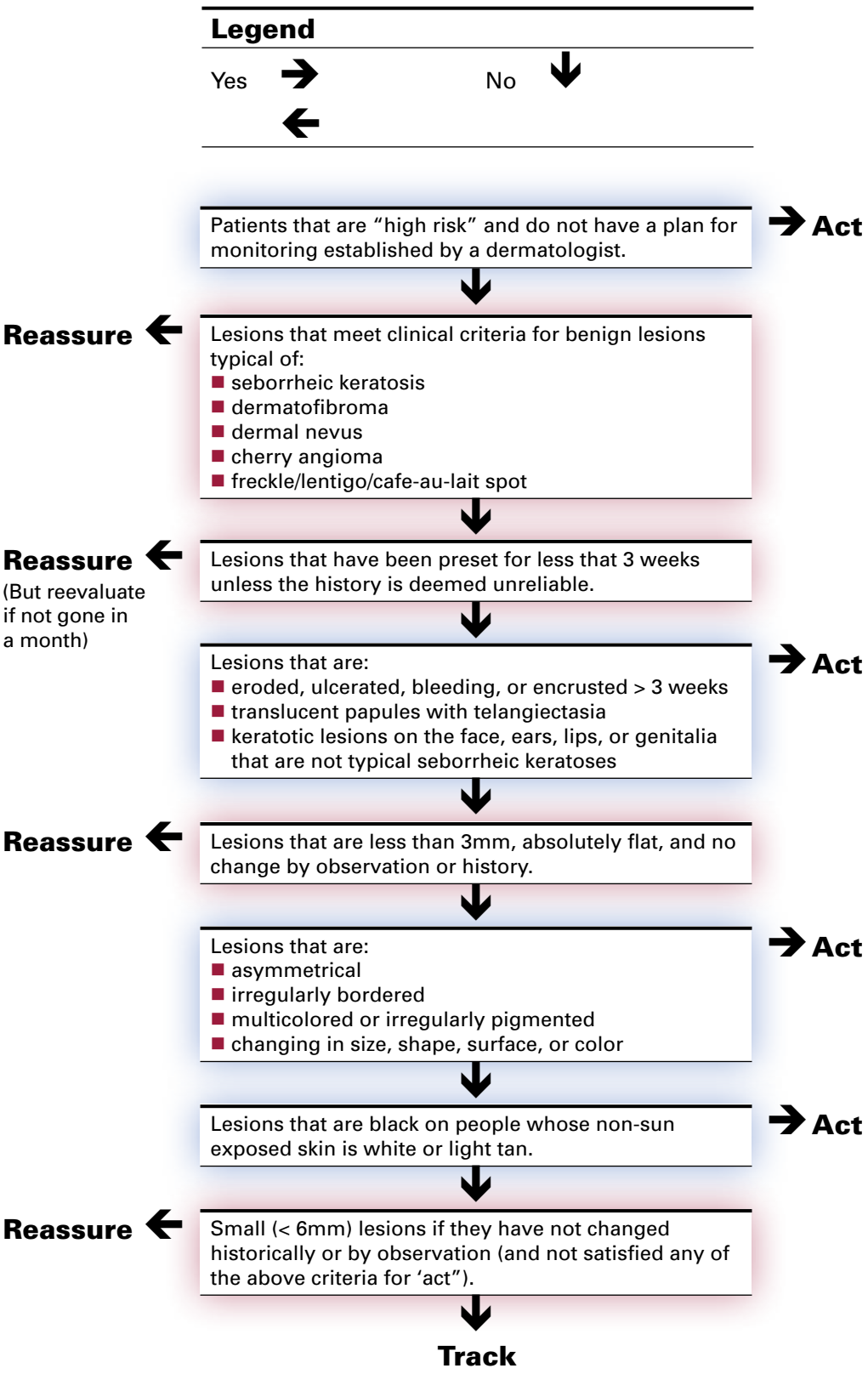
Appendix I. Benign Lesions that May Mimic Skin Cancer *(continued)*

	Clinical Characteristics	How to Differentiate from Skin Cancer	Example
Verruca Vulgaris (Common Wart)	Firm papules, 1-10 mm in diameter with a hyperkeratotic or clefted surface	■ Presence of black "dots" – thrombosed vessels within the lesion	
Keratoacanthoma	Smooth, red papule that grows rapidly over a number of weeks, after which the tumor resembles a crater filled with keratin; often found in conjunction with actinic keratosis. More common in light-skinned individuals and on sun-exposed areas of the skin.	■ Can be differentiated based on characteristic clinical appearance ■ Suspicious lesions should be biopsied to confirm the diagnosis	
Pyogenic Granuloma	Smooth, bright red, violaceous or brown-black papule caused by overgrowth of capillaries Usually develops rapidly following minor trauma	■ Can be differentiated based on characteristic clinical appearance	
Keloid	Firm, tender, well-defined nodule or plaque; atypically large scar resulting from the abnormal growth of fibrous tissue Common in young adults and in dark skinned individuals	■ Can be differentiated based on characteristic clinical appearance	

Appendix I. Benign Lesions that May Mimic Skin Cancer *(continued)*

	Clinical Characteristics	How to Differentiate from Skin Cancer	Example
Skin Tag (acrochordon)	Soft, skin-colored papule or flap, typically occurring on the axillae or neck; may appear smooth and flat, folded or pedunculated.	■ Can be differentiated based on characteristic clinical appearance	
Halo Nevus	Brown, papular, junctional, compound, or dermal nevus encircled by an area of depigmentation.	■ Can be differentiated from melanoma based on evaluation of the "ABCDEs" ■ Suspicious lesions should be biopsied to confirm the diagnosis, particularly in patients over 40 years of age	
Blue Nevus	Firm, well-defined, dark-blue to gray-black papules or nodules; usually < 10 mm in diameter and round to oval in shape	■ Stable lesions with no history of change ■ Suspicious lesions should be biopsied to confirm the diagnosis	
Nevus Spilus	Oval or irregularly-shaped, lightly-pigmented flat lesion containing focal areas of dark brown hyperpigmented macules or papules	■ Can be differentiated based on characteristic clinical appearance ■ Rate of malignant transformation is very low	

Appendix II. Basic Skin Cancer Treatment Algorithm[1]



[1] Reprinted with Permission. Weinstock MA, Goldstein MG, Dubé CE, Rhodes AR, Sober AJ. Basic skin cancer triage for teaching melanoma detection. J Am Acad Dermatol. 1996 Jun;34(6):1063-6. PubMed PMID: 8647972.

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