

SKIN CANCER

Introduction

Skin cancer is the most common form of cancer in the United States. It is estimated that there will be more than 1 million new cases of non-melanoma skin cancers in 2008,¹ 62,480 new cases of melanoma,² and the incidence of this disease has been growing 4% to 8% a year since the '60s.³ It is estimated that there will be 8420 deaths from melanoma in 2008. However, the risk of death from non-melanoma cancer is small: out of the 1 million new cases, it is estimated that there will be fewer than 1000 deaths, and most skin cancers are detected before they metastasize and cause serious harm.

There are three forms of skin cancer: squamous cell carcinoma, basal cell carcinoma (these are commonly called non-melanoma skin cancers), and melanoma. The non-melanoma skin cancers are, for the most part, benign, although there is a risk of metastasis and morbidity and mortality: this risk is greater for basal cell carcinoma.⁴ Melanoma is much more serious. Although it only accounts for 4% of all skin cancers, it causes 74% of all the deaths from skin cancer.⁵

Squamous Cell Carcinoma

Pathogenesis/Causes

Squamous cell carcinoma (SCC) is the second most common form of skin cancer.⁶ It is a malignant cancer that forms in the keratinocytes of the epidermis,⁷ and like most cancers it is the result of damage to DNA that results in abnormal growth of nonfunctional cells.

There are many factors involved in the development of SCC, and it is triggered by exposure to causative agents and a host response. The most common cause is exposure to ultraviolet B (UV-B) radiation from sunshine.⁸ The UV-B causes direct damage to the DNA of the keratinocytes, and it also causes local and systemic immunosuppression which leads to tumor growth.⁹ Other risk factors for the development of SCC are:

- Fair skin/complexion.
- Scottish or Irish descent.
- Outdoor occupation.
- Male sex (2:1 male:female ratio).
- Age (most patients with SCC are in their 80s).
- Exposure to arsenic in drinking water or from industrial sources.
- Immunosuppression from disease (e.g., HIV) or drugs (transplant patients that are receiving immunosuppressive drugs).
- Thermal burn scars and chronic ulcers.
- Actinic keratoses
- Radiation therapy sites.
- Treatment with psoralen or UV-A treatment.

- Chronic use of tanning beds.
- Infection with human papillomaviruses.
- Chronic inflammatory conditions, e.g., venous ulcer, lymphedema, etc.
- Chronic infectious conditions, e.g., osteomyelitis, deep fungal infections, etc.
- Exposure to polycyclic aromatic hydrocarbons found in coal tar and soot.
- Xeroderma pigmentosum.
- Cigarette smoking.

Diagnosis/Complications/Prognosis

SCC vary widely in appearance and clinical presentation. They often appear as an ulcerated erythematous nodule that does not heal and most SCC are located on the head and/or neck.¹⁰ The borders of the lesion are irregular, it may bleed easily and be painful, but many are asymptomatic. SCC is diagnosed through the appearance of the lesion and by biopsy. SCC are staged according to tumor size, tumor depth, lymph node involvement, and distant metastases.

Complications can occur with SCC, and the incidence of these complications and the incidence of metastasis depends, in part, on the depth and width of the lesion and its location. Lesions of the ear, lips, and eyelids are particularly prone to metastasize.¹¹ Complications include tumor recurrence, metastasis to the lymph nodes, development of cutaneous melanoma (the most common secondary malignancy), malignancies of the lungs, breast, pharynx, larynx, and salivary glands, and non-Hodgkins lymphoma.¹² The exact incidence of these cancers is not known, but one study noted that patients with non-melanoma skin cancers had a 2.30 greater risk for developing a secondary cancer.¹³ As well, patients who develop these cancers subsequent to having SCC have an increased chance of dying compared to people who have these cancers as their primary diagnosis.¹⁴

The prognosis for SCC is generally good, and surgical excision often cures the disease.¹⁵ Indicators of a poor prognosis are:^{16,17}

- Recurrence, particularly with lesions of the head and neck.
- Lower lip lesions (16% metastatic rate) and ear lesions (11% metastatic rate).
- Association with a scar (metastatic rate 8 times that of a lesion caused by sun exposure).
- Large size (recurrence rates are double and metastatic rates are triple for lesions > 2 cm).
- Greater depth (> 4 mm in depth).
- Infiltrative growth pattern.
- Perineural (surrounding a nerve or nerves) invasion.
- A patient who is immunosuppressed.
- High cytologic grade.
- Adenosquamous, spindle cell, and acantholytic histologic types.
- Lymph node metastasis.

Basal Cell Carcinoma

Pathogenesis/Causes

Basal cell carcinoma (BCC) is the most common cancer among Caucasians, and approximately 75% of all skin cancers are basal cell carcinoma.¹⁸ This cancer has a low mortality rate and the rate of metastasis is very low, <0.1%.¹⁹ The male to female ratio is approximately 3:2 and among Caucasians, the lifetime risk of developing BCC is 33-39% in men and 23-28% in women.²⁰ UV radiation causes damage to DNA, and it is believed that BCC develops in the pluripotential cells of the basal layer of the epidermis or follicle structures,²¹ and is the result of an alteration in an intracellular signaling pathway that is involved in cell multiplication.

The exact cause(s) of BCC are not known, but exposure to UV radiation is thought to be a significant risk factor.²² However, the precise relationship of exposure to UV radiation and BCC is still not clear.²³ There are many cases of BCC that develop on the trunk, and although sun exposure during childhood and frequent sunburns appear to increase the risk of developing BCC, occupational exposure to the sun and sunburn as an adult do not.²⁴ As well, there is not a definite relationship between the amount/time of UV exposure and the development of BCC. Other factors that contribute to the development of BCC and/or predispose the individual to this disease are:

- Immunosuppression.
- Treatment with psoralen and UV-A treatment.
- Therapeutic ionizing radiation.
- Exposure to arsenic.
- Cigarette smoking (possible, but unlikely).
- Blue or green eyes.
- Fitzpatrick skin type I (Always burn, never tan).
- Low vitamin intake, high fat intake.
- Family history.
- Human papilloma virus.
- Increasing age.

Diagnosis/Complications/Prognosis

Basal cell carcinoma is diagnosed with biopsy and physical exam. BCC lesions vary in appearance, but often have a waxy, translucent, or pearly appearance.²⁵ They may also be eroded, bleed, or have telangiectases on the surface. Approximately 86% of BCC are found on the face.²⁶

Complications of BCC are unusual. As mentioned previously, BCC rarely metastasizes, but it can be serious when it does: there is less than 20% survival at 1 year and 10% survival at 5 years in these cases.²⁷ Metastatic lesions are usually large (> 20 cm), located on the head or neck, and occur mainly in men. BCC is associated with an increased risk of developing SCC and melanoma, and it is possible that BCC is associated with an increased risk of developing cancer of the lung, thyroid, mouth, breast, and cervix, and non-Hodgkin's lymphoma.²⁸

The prognosis for uncomplicated BCC is good: surgical treatment is often a complete cure. The prognosis worsens if the BCC metastasizes. Other bad prognostic factors are:²⁹

- Tumor site: Tumors of the eyes, nose, naso-labial folds, lips and ears.
- Tumor size: Recurrence rate increases as the size of the tumor increases.
- Treatment failures/recurrence.

Malignant Melanoma

Pathogenesis/Causes

Malignant melanoma is a malignant growth that arises from cutaneous melanocytes, the skin cells that synthesize the skin pigment melanin, and although the pathogenesis is not completely understood, it is most likely caused by genetic mutations that affect cell proliferation, and individual susceptibility to ultraviolet radiation.³⁰

Exposure to the sun appears to be the major etiologic factor for the development of malignant melanoma.³¹ Individual risk/causative factors for the development of this disease are:³²

- Age: Increasing age increases the risk of developing malignant melanoma: the average age for diagnosis is 53 years.
- Gender: Women are more likely to develop malignant melanoma. It is the most common cancer in women aged 25-29. However, this association appears to reverse after the age of 40: after that, the disease is more common – and more dangerous – for men.
- Fair complexion
- Caucasian race.
- Excessive childhood sun exposure.
- Family history of melanoma: 5-10% of all melanomas occur in people with melanoma-prone families.
- Increased number of nevi.
- Intense and *intermittent* sun exposure.
- Green eye color.
- Freckling.
- Prior non-melanoma skin cancer.
- Xeroderma pigmentosum
- Familial atypical mole melanoma syndrome.
- Transplant patients.

The incidence rate of malignant melanoma have been rising in the past 25 years.³³ In the United States, from 1973 to 2002, the incidence increased from 7.5 cases per 100,000 to 21.9 cases per 100,000, an increase of almost 200%.; this increase has been especially notable among men.³⁴ During that period, the mortality rate increased from 2.1 cases per 100,000 to 2.9 cases per 100,000. The mortality rate for women aged 20 to 54 years decreased, but it increased for women aged 55 to 64 years, and this trend was also true for men.

Diagnosis/Complications/Prognosis

There are four *common* types of malignant melanoma; it is not clear if subtype is associated with a better or worse prognosis. The subtypes are classified according to clinical appearance, history, and histological characteristics.^{35,36}

- Superficial spreading melanoma: Irregular borders, usually > 6 mm in diameter, the lesions are flat or slightly raised plaques and are often pigmented (blue, black, white, or pink). It is most common on the trunk in men and women and the legs in women.
- Nodular melanoma: These are nodular lesions, usually brown or black, they can often be eroded and bleeding, and they account for approximately 15-30% of all cases. They are most commonly seen on the legs and trunk. These lesions often cannot be found using the classic ABCDE detection criteria (This will be explained in the next section)
- Lentigo maligna melanoma: The lentigo maligna subtype grows slowly, it is usually found on patients with fair skin and an average age of 65 years, and it is found on the face, neck, or arms.
- Acral lentiginous melanoma: This subtype only accounts for 2-8% of all cases. It is found on the palms, the soles, or the nail plates.

In general, diagnosis of malignant melanoma is made using the **ABCDE** detection criteria, although there is some controversy over the accuracy of this method.^{37,38}

- **A**symmetry: The two halves of the lesion do not match.
- **B**order: The edges are ragged, irregular, etc.
- **C**olor variegation: the color of the lesion is not uniform.
- **D**iameter: A lesion > 6 mm is of concern.
- **E**volving: the size, appearance, etc., of the lesion change over time.

Biopsy and histopathological examination are diagnostic, and when a diagnosis is made, the lesion can be staged. The staging system is fairly complex. It takes into account the size of the lesion, the presence of ulceration, and regional or distal metastasis,³⁹ and provides the clinician with a reasonably accurate idea of the prognosis/survival rate. Survival rates for malignant melanoma are good if it is detected early, but very poor when it reaches the advanced stage: median survival in many such cases is 6-9 months.

Treatment

Squamous Cell Carcinoma

Most SCC are easily recognized, and there are many treatment options.

- Simple excision: Although this is effective and well tolerated, it has the disadvantages of unwanted tissue destruction and the possibility that parts of the lesion will be left behind.⁴⁰
- Mohs micrographic surgery: Mohs micrographic surgery (MMS) is the treatment of choice for SCC lesions that are high risk or ill-defined, or when tissue preservation is important.⁴¹ It has an excellent cure rate - 94-99% - and recurrences are unusual. The procedure is done in the outpatient setting using local anesthesia and sedation. The advantages of MMS is that as opposed to normal surgical excision, a much smaller area of tissue with more precise margins is removed; this allows for less peripheral damage. As well, the particular method of examining the excised lesion reduces the chance of missing pieces of tumor that were not removed.
- Cryotherapy: Liquid nitrogen can be used to remove SCC lesions. It is safe and has a high 5-year cure rate. The disadvantages include scarring, hypopigmentation and alopecia.⁴²
- Electrodesiccation and curettage: The removal technique involves removing the tumor with a curette and cauterizing the wound. Although the cure rate has been reported to be very high, success depends on the skill and experience of the practitioner and if the margins of the lesion are not precisely identified, recurrence is possible.⁴³
- Topical chemotherapy: SCC can be treated with application of 5-fluorouracil (5-FU).
- Immune response modifying: Imiquimod is a topical cream that is applied to SCC. It acts to increase the patient's immune response by enhancing the activity of pro-inflammatory cytokines. It appears to be safe, there are few side effects, and it appears to be effective in destroying lesions and preventing recurrences.^{43,44}
- Photodynamic therapy: The patient is given a photosensitizer which makes the SCC lesion vulnerable and then a light source is applied. This causes inflammation and destruction of the lesion. This therapy has been associated with a high recurrence rate.⁴⁵
- Radiation therapy: Radiation therapy has a high cure rate (although not as high as surgery) and is not associated with the trauma of surgery. However, the therapy is time consuming, and the long-term cosmetic effects are often not good: there can be dyspigmentation, atrophy, and telangiectasia at the treatment site. However, it appears to be a good treatment option for patients with early stage SCC of the head and neck.⁴⁶
- Chemotherapy: Chemotherapy has been used for treating SCC, and some authors have reported a good success rate.⁴⁷

Basal Cell Carcinoma

As with SCC, there are many treatment options for BCC, and overall, the cure rates are good. Surgical treatments vary in their recurrence rates, complications, and clinical applications; there is no one *best* treatment.

- One of the most common surgical methods of treatment of BCC is surgical excision. This is often curative (3-8% 5-year recurrence rate) , but it is always possible that the margins of the tumor may not be clearly identified and cancerous tissue will be left behind: one author reports an incidence of incomplete surgical excision of BCC of 4.7-10.8%.⁴⁸
- Curettage and electrodesiccation: This method may be used to remove BCC tumors, but scarring can be a problem.
- Mohs micrographic surgery: This technique is useful for patients with recurrent tumors, high-risk tumors, tumors > 2 cm, or tumors in areas that are cosmetically important. It appears that the recurrence rate is very low, as is the rate of unwanted tissue destruction.⁴⁹
- Cryotherapy: Cryotherapy treatment for BCC is quick and cost-effective, but complete tumor removal may not be possible.⁵⁰ It is most appropriate for tumors with well defined borders, and there are many possible adverse effects.⁵¹

There are also many non-surgical treatments available for BCC.

- Radiation therapy: Radiation therapy can be useful, but there is a relatively high risk of cosmetic complications and the development on non-melanoma skin cancers in the treated area.⁵²
- Photodynamic therapy: Photodynamic therapy has been shown to be useful for certain types of BCC, and it is particularly useful (because of the absence of scarring) for treating BCC in children and adolescents.⁵³

Pharmacological treatments for BCC include:

- Topical 5-fluorouracil: Topical fluorouacil can be an effective treatment for superficial BCC lesions in low risk areas, but recurrence rates are high for other BCC lesions. Also hyper-pigmentation and ulceration at the treatment sites can be distressing.⁵⁴
- Imiquimod: As with fluorouacil, imiquimod appears to be most successful when treating low-risk, superficial BCC lesions.⁵⁵
- Interferon: Interferon stimulates macrophage and natural killer cell activity and other cellular processes that interfere with tumor growth. It has been shown to be useful for treating BCC, but good clinical experience is lacking, and there is a high incidence of systemic side effects.⁵⁶

Malignant Melanoma

Treatments for malignant melanoma are limited to surgical removal and drug therapy. Unfortunately, passive immunotherapy, radiation therapy, retinoid therapy, vitamin therapy, biologic therapy, and adjuvant chemotherapy do not increase survival rates.⁵⁷ Surgery is indicated for small (< 2 cm) lesions. High-dose interferon can be used for larger tumors with local lymph node involvement. Melanoma vaccines have been investigated, but it is unclear at this point how effective they are.⁵⁸

Successful management for metastatic melanoma depends on the stage of the disease, and at this point, there does not appear to be any therapy that prolongs survival. Dacarbazine is a chemotherapeutic drug that has been used for many years, but it is < 10% effective.⁵⁹

Screening/Prevention

Patients who are at high risk should be taught how to perform skin self-examination (there is some information that suggests this could reduce mortality) and should have yearly exams by their physician.⁶⁰ Patients should also be taught to avoid UV radiation, use protective clothing, wear a broad-brimmed hat, and apply sunscreen (SPF 15 or more) daily.

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