REVIEW ARTICLE

Diagnosis and Management of Nonmelanoma Skin Cancer

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KEYWORDS:

Basal Cell Carcinoma

Dermatofibrosarcoma Protuberans

Keratinocyte Carcinoma

Merkel Cell Carcinoma

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Squamous Cell Carcinoma

ABSTRACT: Nonmelanoma skin cancer (NMSC) is the most common cancer in the world. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common types. SCC lesions are more likely to metastasize when compared to BCC, but due to low risk for metastasis, prognosis for NMSC is excellent. Ultraviolet radiation exposure is the main risk factor for developing NMSC. Merkel cell carcinoma and dermatofibrosarcoma protuberans are rare forms of NMSC. The most common BCC lesions types are nodular, superficial, and sclerosing. Nodular BCC typically consists of papular lesions with a pearly border. Superficial BCC lesions are flat or slightly raised, often red to brown. Sclerosing BCC lesions usually have nondiscrete margins. The gross appearance of SCC is that of an erythematous plaque with scale and/or ulceration. The diagnosis of NMSC starts with gross examination, followed by biopsy. Recommended biopsy techniques include punch, shave, and excisional biopsy. Dermatoscopy should also be used to aid in the evaluation of suspected NMSC and other skin cancers, as it greatly enhances the point-of-care diagnosis of skin malignancies. For low-risk lesions, surgical excision is the cornerstone of treatment, although depending on the clinical situation, curettage and electrodessication or non-surgical modalities may be used. Cryotherapy, topical treatments, photodynamic therapy, or radiation treatment can be used to treat BCC and SCC, but cure rates are lower than with surgical excision. High-risk lesions require specialist referral. All patients treated for NMSC should undergo regular complete skin exams, and counseling on the use of sun protection and avoidance.

INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common cancer in the world. In the US, 97% of all skin cancers diagnosed are NMSCs. Of these, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common.[1,2] BCC and SCC lesions arise from keratinocytes, so these lesions are typically grouped under a subtype of NMSC called keratinocyte carcinomas. This is to differentiate them from other types of NMSC such as Merkel cell carcinoma or dermatofibrosarcoma protuberans, which are not of keratinocyte origin.

It is imperative that family physicians feel comfortable with the diagnosis and treatment of these common skin malignancies. Although significant morbidity and mortality are rare with keratinocyte carcinomas, the early identification of these cancers is important given their rising incidence and the cost of late treatment.[3]

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Epidemiology

BCC affects more than three million persons annually in the US and comprises more than half of all NMSC diagnoses. It is estimated that BCC affects more than 3.3 million people annually.[4] SCC is the second most common form of NMSC after BCC. In the US, the lifetime risk for developing SCC is estimated at 9-14% for men and 4-9% for women with approximately 300,000 new cases of SCC yearly.[5] Lifetime risk for developing BCC is estimated at 30%.[6]

Prognosis for keratinocyte carcinomas is excellent, due to low risk for metastasis. SCC lesions are more likely to metastasize when compared to BCC – 4% annual incidence of metastasis for SCC versus 0.55% or less for all cases of BCC.[3,7] Risk factors for NMSC metastasis are lesions >2cm in diameter, poorly-defined lesions, recurrent disease, immunosuppression, and high risk anatomic areas such as the central face, lips, ears, hands/feet, and genitalia.[5]

Risk Factors

Ultraviolet (UV) radiation exposure is the main risk factor for developing NMSC. This includes UV exposure from tanning beds. Intense intermittent exposure increases the risk for BCC, whereas cumulative UV exposure, especially in childhood and youth, increases the risk for SCC.[5]

Other significant risk factors for developing NMSC are fair skin, exposure to radiation such as X-rays, cigarette smoking, and immunosuppression.[8]

BASA CELL CARCINOMA

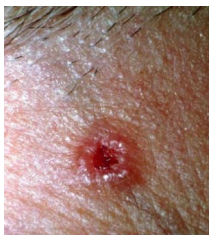
Diagnosis

The diagnosis of BCC or any NMSC starts with the gross examination of the lesion. The most common BCC lesions types are nodular, superficial, and sclerosing. Nodular BCC is the most prevalent type, comprising about 70% of all diagnosed BCC. It's usually found in the head and face. Superficial BCC is usually found on the trunk and extremities.[9]

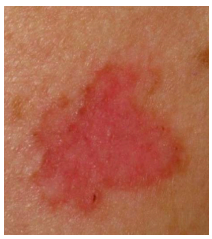
Nodular BCC typically consists of papular or raised lesions with a translucent, or pearly border. Central erosion, telangectasias, and bleeding are common. These lesions may be pigmented which make them look like a melanoma. Superficial BCC lesions are flat or slightly raised, often red to brown. Sclerosing BCC lesions usually have nondiscrete margins.[9,10] *See Table 1*.

TABLE 1:

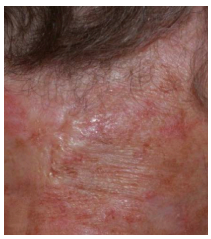
Common types of Basal Cell Carcinoma



Nodular



Superficial



Slerosing

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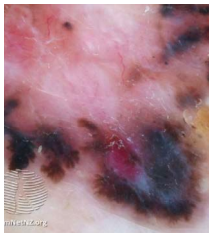
Dermatoscopy should be used to aid in the diagnosis of BCC and other skin cancers, as it greatly enhances the point-of-care diagnosis of skin malignancies. Classic dermatoscopic features of BCC include leaf-like structures, spoke wheel-like structures, and more commonly, arborizing vessels. *See Table 2*.

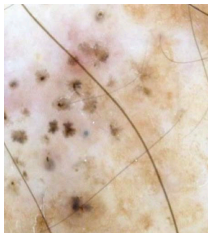
TABLE 2:

Common dermatoscopic features of Basal Cell Carcinoma

Arborizing vessels



Leaf-like structures and dark blotches



Spoke wheel-like structures

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Biopsy

Once a lesion is suspected to be BCC by gross and dermatoscopic examination, a biopsy is needed to confirm the diagnosis. Recommended biopsy techniques include punch, shave, and excisional biopsy. There is no evidence that proves any particular biopsy technique superior or preferred for the biopsy of suspected BCC lesions. The choice of biopsy technique depends on the physician's experience, comfort level, and the lesion's size and location. If the biopsy specimen proves to be inadequate for accurate histologic diagnosis of the lesion, a repeat biopsy may be considered. There are no specific margin recommendations for the biopsy of suspected BCC. Enough tissue should be removed to ensure accurate histologic diagnosis.[11]

Treatment

The treatment of a confirmed localized BCC lesion is guided not by a staging system but by determining whether the lesion is at low versus high risk for recurrence. Currently, there is no formal staging system specific to BCC.[11]

Low-risk lesions are primary lesions that are <20mm and located on the trunk and extremities, or <10mm and located in the cheeks, forehead, scalp, neck or shins. They also have well-defined borders, are not located in areas of prior radiation therapy, and are present in a patient who's not immunosuppressed. Histologically, low-risk lesions have no perineural involvement.[12]

High-risk lesions are those that are recurrent, >20mm in the trunk and extremities, >10mm in the cheeks, forehead, scalp, neck or shins, or lesions of any size located in the central face, nose, eyelids, periorbital skin, ears, lips, chin, hands, feet, or genitalia. They may be poorly-defined and of an aggressive histological subtype and may have perineural involvement.[12]

For low-risk lesions, surgical excision is the cornerstone of treatment, although depending on the clinical situation, curettage and electrodessication (C&E) or non-surgical modalities may be used. Cryotherapy, topical treatments, photodynamic therapy (PDT), or radiation treatment can be used to treat BCC, but cure rates are lower when compared with surgical excision.[11]

The goal of cryosurgery for keratinocyte carcinomas such as BCC is to destroy the same amount of tissue as that which would have been removed with standard surgical excision.[11]

Topical therapies for BCC include imiquimod and 5-FU. Imiquimod can be applied once or twice daily, for six to 16 weeks. Local reactions are common and include skin redness and swelling, vesicles, and itching. 5-FU is typically applied twice daily for three to six weeks and causes skin reactions similar to those with imiquimod. Topical therapies should be reserved for the treatment of small primary lesions in low-risk areas, when surgical excision of the lesion is not feasible or declined by the patient.[11]

For low-risk primary BCC lesions, the American Academy of Dermatology (AAD) and the National Comprehensive Cancer Network (NCCN) recommend standard excision with a 4mm margin of uninvolved skin around the tumor and/or biopsy site to a depth of the mid-subcutaneous adipose tissue with histologic

margin assessment. If margins are positive after excision, re-excision is recommended, or the patient may be referred for Mohs micrographic surgery (MMS).[11,12]

A study showed that local recurrence rates after an excision with positive histologic margins was 27% compared with 6% following excision with histologically negative margins.[13] Research studies, however, consistently report low recurrence rates after standard excision of BCC with predominantly nonaggressive histologic growth patterns.[12]

For high-risk lesions, the AAD recommends MMS, so referral to a dermatologist is recommended for these types of lesions.

Follow-up

For patients treated for BCC, the NCCN recommends a complete skin exam every six to 12 months for five years, and then annually for life.[12] Any local recurrence with nodal or distant metastases requires referral to a multidisciplinary team for treatment, although as mentioned previously metastases are very rare with BCC.

All patients should also be counseled on the use of sun protection and avoidance.

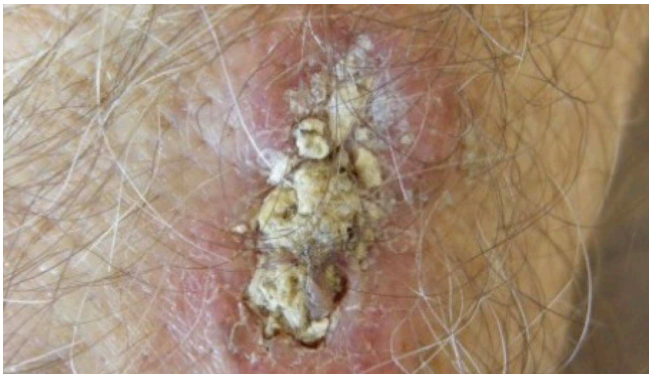
SQUAMOUS CELL CARCINOMA

Diagnosis

The gross appearance of SCC is that of an erythematous plaque with scale and/or ulceration. Keratoacanthomas, considered by some to be a variant of SCC, present as rapidly-enlarging, dome-shaped lesions, with a central keratin plug.[9,10] *See Figure 1*.

FIGURE 1:

Squamous Cell Carcinoma



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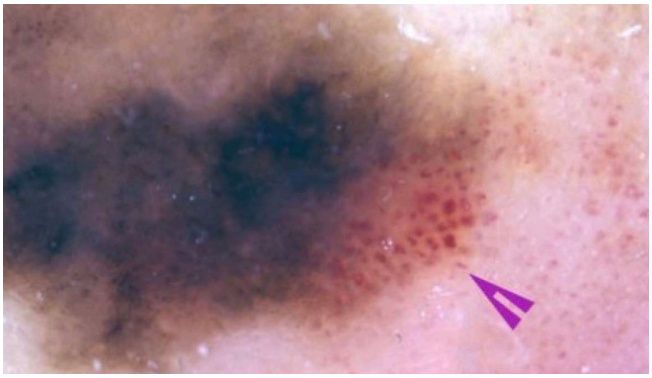
Dermatoscopy of SCC lesions may reveal focal glomerular vessels, rosettes, and peripheral brown dots and globules. *See Figure 2*.

FIGURE 2:

Glomerular vessels sometimes seen in dermatoscopy of Squamous Cell Carcinoma



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Biopsy

As with BCC, no biopsy method for SCC has been shown superior, and biopsy method selection is based on lesion size, location, and the physician's experience and comfort level. Recommended biopsy techniques include punch, shave, and excisional biopsy, and a repeat biopsy should be considered if the specimen is inadequate for an adequate histologic analysis.[5]

Treatment

There's no universally accepted staging system for risk stratification of SCC. A stratification system developed at the Brigham and Women's Hospital that classifies SCC tumors according to the presence of several clinical and pathologic risk factors does show some promise, but at this time no system is universally accepted.[5,14]

An approach to stratifying low- and high-risk tumors, similar to that used for BCC, has been provided by the NCCN, and is primarily intended to provide guidance on treatment of SCC rather than in prognosis and outcomes.[5]

Low-risk SCC lesions are primary lesions are <20mm and located on the trunk and extremities, or <10mm and located in the cheeks, forehead, scalp, neck or shins. They also have well-defined borders, are not located in areas of prior radiation therapy, and are present in a patient who's not immunosuppressed. Histologically, low-risk lesions have no perineural, lymphatic, or vascular involvement, are moderately or well-differentiated, and have a depth <=6mm and don't invade beyond subcutaneous fat. Low-risk SCC lesions also exhibit no rapid growth.[15]

High-risk SCC lesions are those that are rapid-growing or recurrent, >20mm in the trunk and extremities, >10mm in the cheeks, forehead, scalp, neck or shins, or lesions of any size located in the central face, nose, eyelids, periorbital skin, ears, lips, chin, hands, feet, or genitalia. They may have ill-defined borders or be found

on an immunocompromised patient or be found in an area of prior radiation treatment. Histologically, high-risk lesions have poorly-differentiated features, or have perineural, lymphatic, or vascular involvement. These lesions may also go deeper than 6mm or invade beyond subcutaneous fat.[15]

For low-risk primary SCC lesions, the AAD and the NCCN recommend standard excision with a 4 to 6mm margin of uninvolved skin to a depth of the mid-subcutaneous adipose tissue with histologic margin assessment.[5,15] C&E may be considered for low-risk lesions, but there's no data to compare the efficacy of C&E with other treatment methods.[15] Non-surgical methods such as topical therapies, cryosurgery, and radiation therapy may be used to treat low-risk superficial lesions, but these methods achieve lower cure rates than surgical excision.[15]

High-risk SCC lesions should be referred to dermatology for MMS.

Follow-up

For patients treated for SCC, the NCCN recommends a complete skin exam every three to twelve months for two years, then every six to twelve months for three years, then annually for life. The ADD recommends skin exams at least annually but does not specify intervals as the NCCN does.[5,15] All patients should also be counseled on the use of sun protection and avoidance and performing a self-examination of the skin.

OTHER TYPES OF NMSC

MERKEL CELL CARCINOMA

Merkel cell carcinoma (MCC), a rare form of skin cancer, is an aggressive malignancy mainly seen in older adults. It primarily affects people with light skin and has a tendency for local recurrence.[16] Affected individuals tend to be in their 70s when they present with this form of skin malignancy and the risk of MCC is greatly increased in people that have had other malignancies.[17]

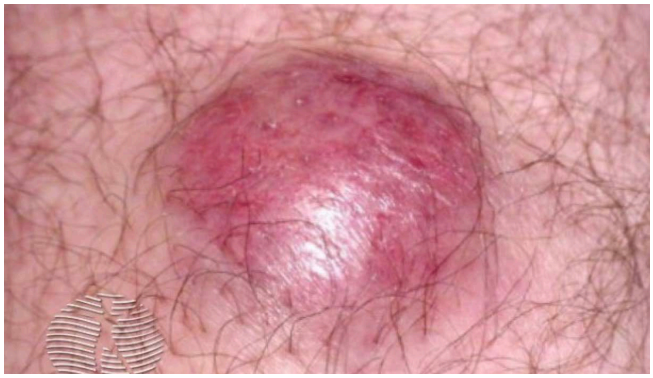
Skin mechanoreceptors, located in the basal layer of the epidermis as well as in hair follicles, contain Merkel cells. MCC is believed to arise from these cells. Malignant transformation of Merkel cells into MCC has been associated with sun exposure, immunosuppression, and the so-called Merkel cell polyomavirus, a virus thought to be part of the normal skin microbiome.[18]

MCC typically presents as a rapidly growing, painless, and firm skin nodule, usually in sun-exposed areas. Metastases are uncommon. *See Figure 3*.

Diagnosis is confirmed by histopathologic analysis of a biopsy sample. Immunoreactivity to CK20 is a fairly specific and sensitive marker for MCC. Once the diagnosis is confirmed by histopathology, and the primary tumor is removed by wide local excision, further treatment depends on results of sentinel lymph node (SLN) biopsy or the presence of metastatic disease.[19] If SLN biopsy is negative, radiation therapy to the tumor site is recommended. If SLN biopsy is positive and there are no metastases, lymph node dissection or nodal radiation therapy is indicated. If there are metastases then systemic therapy is the treatment of choice. Frequent follow-up is needed after treatment due to the high rate of recurrence of MCC.

FIGURE 3:

Merkel Cell Carcinoma



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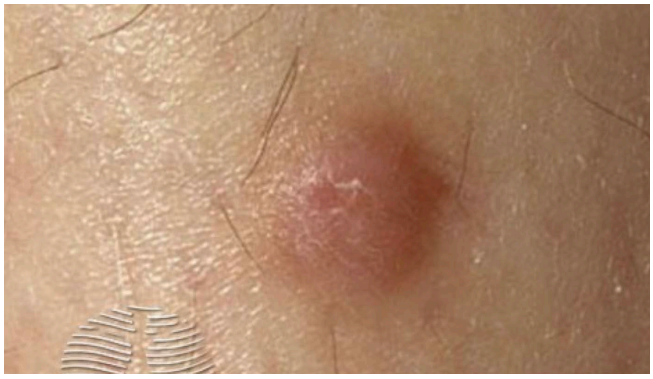
DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans (DP) is rare soft-tissue sarcoma of fibroblast origin. Its incidence in the US is approximately 4.5 cases per million persons per year.[20] DP rarely metastasizes. Given their similar gross clinical appearance, differentiation of DP from dermatofibroma can be difficult, and a deep subcutaneous punch or incisional biopsy are recommended for initial diagnosis of these lesions. *See Figure 4*.

FIGURE 4:

Dermatofibrosarcoma Protuberans



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Histologically, the vast majority of DP cases are CD34 positive and factor XIIIa negative.[21]

The treatment of DP is surgical, with repeat excision if histologic margins are positive. MMS or wide excision with 2-4 cm margins are recommended treatment strategies for this type of NMSC.[22]

Follow-up of patients after treatment of DP consist of office visits every six to twelve months.[23]

CONCLUSION

NMSC can be very effectively treated if diagnosed early. Primary care physicians are typically the first point of contact when a patient notices a "bump" on the skin they want evaluated. By becoming comfortable with the classic gross and dermatoscopic features of NMSC and the different available treatment modalities, Osteopathic family physicians can competently diagnose and treat NMSC and avoid unnecessary referrals.

AUTHOR DISCLOSURES:
No relevant financial affiliations or conflicts of interest.

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