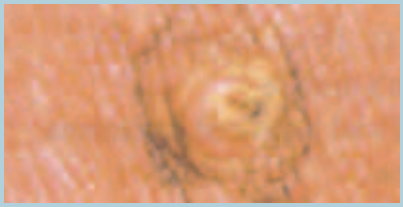
abstract



Skin neoplasias are more commonly seen in older patients. These skin diseases can frequently be more severe, particularly in long-term care residents. Common nonmelanoma skin cancers seen in these individuals include actinic keratoses, squamous cell carcinomas, and basal cell carcinomas. Benign neoplasias that are seen in older patients include seborrheic keratoses, skin tags, and classical Kaposi's sarcoma. Treatment for neoplasias in the older adult are often not as aggressive as in younger patients.

Key words: *actinic keratosis, squamous cell carcinoma, basal cell carcinoma, seborrheic keratosis, skin tag, classical Kaposi's sarcoma*

Skin Neoplasias in Older Adults

John Kraft, HBSc, *Medical Student, University of Toronto, ON.*

Carrie Lynde, HBSc, *Medical Student, University of Toronto, ON.*

Charles Lynde, MD, FRCPC, *Assistant Professor, Dermatology, University of Toronto, Toronto; Dermatology Consultant for Metropolitan Homes for the Aged in Toronto, Markham-Stouffville Hospital, and Scarborough Grace Hospital; Dermatologist, Dermatology Practice, Markham; Former President, Canadian Dermatology Association.*

Introduction

Primary neoplastic disease of the skin is common in older patients and can be severe, particularly among residents of long-term care. Early recognition and therapy can prevent potentially fatal complications of nonmelanoma skin cancers from developing. A number of such lesions, particularly actinic keratoses, seborrheic keratoses, and skin tags can be treated in the primary care setting, whereas malignant and extensive lesions are likely to require referral to a specialist.

Actinic Keratosis

Actinic keratosis (AK), also known as solar keratosis, is a consequence of skin damage caused by the sun and is considered a premalignant neoplasm. They are more common in men than women and tend to occur in individuals with fair skin, light hair and eyes, a poor ability to tan, and who burn easily. AK is found in a high proportion of pale-skinned individuals around the world and its incidence increases with age.[1]

AK lesions are often small, discrete, yellow-brown, scaling pink, round/oval areas less than 1 cm in diameter. These scaly patches are frequently found on a background of sun-damaged skin (bearing pigmentary changes and elastosis) and may feel like sandpaper on palpation. AK may also take the form of cutaneous horns.

AK lesions are found on areas of maximum sun exposure: forehead, bald scalp, ears, temples, nose, cheeks, lips, neck, forearms, hands, and shins. The differential diagnosis includes seborrheic keratosis, viral warts, Bowen's disease (squamous cell carcinoma in situ), superficial basal cell carcinoma (BCC), and chronic cutaneous lupus erythematosus.

Many lesions are easily identified and treated without further investigation. A biopsy can be performed to confirm diagnosis or exclude malignancy. This is particularly important for lesions not responding to conventional therapy, suggesting squamous cell carcinoma (SCC). If ever the diagnosis is in question, or if the lesion may be malignant, patients should be referred to a dermatologist.

Prompt treatment of lesions is very important even though some lesions regress spontaneously. One percent of AK lesions per year transform into malignancies (mainly SCC) and there may be occult foci of SCC within clinically benign–appearing lesions (especially in the hyperkeratotic variety).[2,3] Avoiding UVR exposure is the key to any AK treatment regime. Advise patients to avoid sunlight and wear appropriate sunscreen.

Field therapy is perhaps the most promising approach for treating AKs, as this approach treats lesions that are not clinically apparent. Topical fluorouracil or 5-FU is for more serious cases and is especially useful if there are large numbers of lesions on the face. Normally, a 5% 5-FU cream is applied to lesions once daily for 2–4 weeks.[4]

Topical imiquimod is another field therapy for treating AKs.[5] Imiquimod

acts by stimulating Toll-like receptors found on antigen presenting cells, stimulating the release of inflammatory cytokines.[6] The induction of inflammatory cytokines promotes an immune-mediated destruction of atypical keratinocytes and resolution of the lesion. Patients are typically instructed to apply the creams to affected areas, even where lesions may not be clinically detectable, once daily, two days per week, for 16 weeks. They should be advised that there will be significant inflammation and that cream should be applied in spite of this. Only if there is severe inflammation should the dosing regime be decreased or stopped.

Photodynamic therapy is a field therapy that may be equivalent to 5-FU cream.[7] In PDT, a photosensitizer such as aminolevulinic acid hydrochloride (ALA) is applied to the affected area for up to eighteen hours.[8] With an appropriate light source such as blue light, ALA triggers a cytotoxic reaction that kills the atypical cells in the treated area. Different formulations of ALA and light sources are currently being studied and compared to other therapies for AK. It may not be as effective as other therapies, such as cryotherapy, and is not regularly used in Canada.

Cryosurgery (liquid nitrogen) is the mainstay of local treatment for AK. Curettage and excision may also be performed, and these methods are particularly useful for hyperkeratotic lesions. Dermabrasion and laser resurfacing may be tried if extensive coexistent photodamage is present.

Although AKs themselves may be safe, they are associated with SCCs and other nonmelanoma skin cancers, and referral to a dermatologist for complete skin care may be advised. This recommendation particularly applies to younger patients and those with extensive lesions, and for lesions not responding to a given treatment.

Squamous Cell Carcinoma

A squamous cell carcinoma (SCC) is a malignant neoplasm of keratinocytes in skin epithelium and some mucous membranes. SCCs represent 10% of skin cancers.[9] Its incidence is strongly influenced by environmental factors (Table 1). Due to its ability to invade and metastasize, any lesion suspected of being an SCC should prompt immediate referral to a dermatologist.

The lesions themselves are firm, red-brown, keratotic papules or nodules that may be ulcerated and crusted (Figure 1). Eroded nodules suggest aggressiveness. The course of an SCC is more rapid than that of a basal cell carcinoma. From 2–6% of cases will metastasize, although this tends to occur later on.[10] Tumours in the oral cavity are more likely to spread, and the most common site of distant spread is the lung.[11]

SCC also includes Bowen's disease and keratoacanthoma. Bowen's disease is the clinical descriptor given to an SCC in situ. These scaling, plaque-like lesions are often found on the lower legs where they may resemble plaques of psoriasis or eczema. These lesions can progress to invasive or metastatic SCC and should be treated promptly.[12]

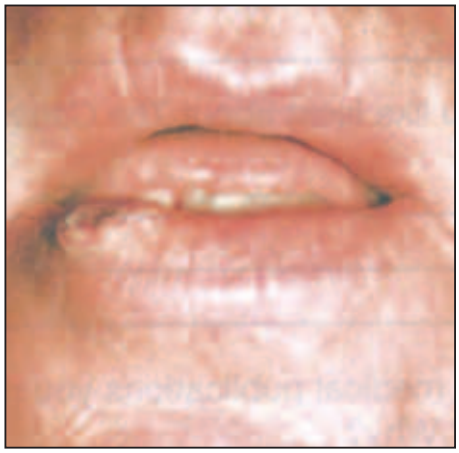


Figure 1: Squamous Cell Carcinoma
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Keratoacanthoma is an SCC variant on sun-exposed skin that often regresses without treatment.[13] The lesion has steep sides that may be red/skin-coloured with a central plug of keratinization (Figure 2). It erupts suddenly (2.5 cm in 6 weeks), takes on the characteristics of an SCC, and then may disappear 2–6 months later. A disfiguring scar may follow regression. Although it may resolve on its own, the lesion must be carefully treated as it is an example of squamous cell carcinoma.[14] Management of keratoacanthoma involves surgical excision, curettage, and electrocautery.

SCCs are distributed similarly to AKs but may also occur on mucous membranes and on sites of exposure to

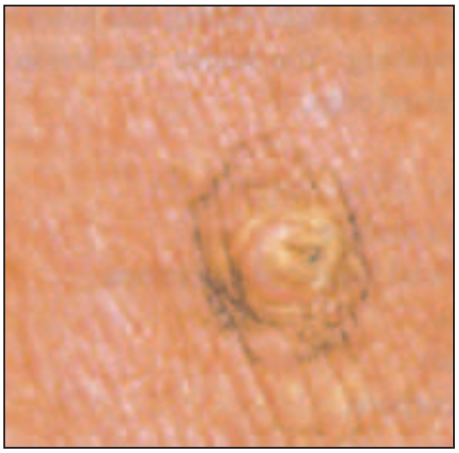

Figure 2: Keratoacanthoma
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Table 1: Environmental Factors Affecting the Incidence of Squamous Cell Carcinoma

chronic sun exposure in light-skinned individuals
immunosuppression (disease or drug therapy)
persistent inflammatory and destructive skin conditions (lichen planus)
scarring processes (chronic ulcers, burns)
chemical carcinogens (cigarette smoking, hydrocarbons, arsenic)
human papilloma virus (e.g., types 16, 18, 35)
ionizing radiation exposure (x-rays, gamma rays, radium)

other SCC risk factors (Table 1). The differential diagnosis includes actinic keratosis, SCC *in situ* (Bowen's disease), verruca vulgaris, BCC, melanoma, numular eczema, psoriasis, and Paget's disease.

An accurate histopathological diagnosis is critical. Biopsies must include epidermis and dermis. Scoop shave or deep curette biopsy are generally sufficient. If there is concern about obtaining adequate tissue, an incisional or excisional biopsy may be useful.

Regional lymph node palpation is critical to assess tumour stage.[15] If deep invasion (cartilage, bone, or parotid gland) or perineural spread is suspected, further radiological and surgical investigations are performed.

Management of SCC depends on the tumour grade and stage, as well as individual patient characteristics. The risk of local recurrence and metastases after treatment depends on certain characteristics (Table 2).

Although management is mainly surgical, radiation and pharmacological tools are also available. Cryosurgery is used if the SCC is small and superficial. It involves freezing the tumour to between –40°C and –70°C (two cycles of at least 60-second thaw time).[16]

Curettage and electrodesiccation usually involves three cycles of curette scrapings and subsequent electrodessications. For both methods, the treatment margin must extend 3–4 mm around the tumour. Treated areas require several weeks to heal and may leave hypertrophic or atrophic hypopigmented scars.

Standard surgical excision is more commonly done. A 4–6 mm margin is left around the tumour.[17] Light curettage may help define extent of the SCC. Intraoperative frozen sections are typically done to confirm that the margins are clear of tumour.

For SCC in cosmetically sensitive areas, with high recurrence rates, indistinct margins, a history of recurrence, in younger patients, and with an SCC that is aggressive, Mohs micrographic surgery is the gold standard.[11] The tumour is removed in a series of thin layers that are precisely oriented and is immediately processed for evaluation. This is continued until all margins are clear, ensuring complete removal of the tumour and tissue conservation. Adjuvant radiotherapy may be necessary in some cases.

Radiotherapy is often used for uncomplicated tumours on the head and neck, in patients with advanced age, and when surgery presents many risks.[10] 500cGy may be given 3–5 times per week over 2–6 weeks. Patients should be warned about hypopigmentation, telangiectasia, loss of adnexa, late (10–20 years) tumour recurrence, and radiation dermatitis.

Basal Cell Carcinoma

Basal cell carcinomas (BCCs) are the most frequently diagnosed skin cancers.[18] BCC most commonly presents in the 7th and 8th decades. The risk factors for BCC are similar to the other types of nonmelanocytic skin cancer. A previous history of BCC is a strong risk factor; there is a 40% chance of developing another BCC within 10 years. Less commonly, BCCs may arise following burns and other inflammatory processes.[19] Due to the likelihood of recurrence and local invasion, patients with suspected basal cell carcinomas should be referred to a dermatologist.

BCCs usually present on chronically sun-exposed areas, especially on the head and neck (80% of cases), and nose.[18] They are slow-growing malignancies arising from the basal cells of the epidermis. Due to their tendency to grow larger and deeper, destroying local tissue, they are sometimes referred to as rodent ulcers. A BCC on the face may destroy the eyes and nose, and may invade the skull and the dura mater, resulting in death. Although they are locally destructive, metastasis is very rare, with only a handful of cases reported in the literature.[20]

The pattern of growth is variable and may be circumscribed or diffuse. Circumscribed is the most common form of

Table 2: Factors Associated with Increasing Risk of Local Recurrence and Metastases of Squamous Cell Carcinoma

tumour size >2 cm
tumour depth >4 mm
perineural invasion
poor histologic differentiation
tumour location (ear, temple, lip, genitalia)
treatment modality
recurrence history
host immunosuppression
regional lymphadenopathy

Key Points

- Consider field therapy (i.e., imiquimod, topical 5-FU) for extensive actinic keratoses.
- Treat actinic keratoses to prevent development of squamous cell carcinomas.
- Squamous cell carcinomas should be diagnosed and treated early to prevent metastasis.
- Although basal cell carcinomas rarely metastasize, they should be treated to prevent local complications.
- Seborrheic keratoses can be mistaken for more serious lesions and should be biopsied if there is any doubt as to the diagnosis (especially irritated SKs and Bowen's disease).
- Skin tags are extremely common and should be removed when irritating.
- Classical Kaposi's sarcoma is one of four subtypes of Kaposi's sarcoma and often found in older men of Mediterranean descent; treatment is challenging.

BCC. This form includes "nodular" and "pigmented" BCCs. They are found on sun-exposed areas. Clinically, they appear as well-demarcated, pearly papules with telangiectasias and waxy borders, and may have central ulceration. The rolled border, when the skin is stretched, may look as though a string is outlining the lesion. A pigmented BCC only differs from the nodular type by the presence of brown pigmentation.

Diffuse forms include morpheiform and superficial spreading BCCs. Morpheiform (fibrosing or sclerosing) BCC is often found on the head and neck. Lesions are solitary, indurated, flat, or slightly depressed yellowish plaques. They have an ill-defined border that makes treatment difficult. Superficially spreading BCCs are found mainly on areas not exposed to the sun, predominantly on the trunk.[21] There may be one or several erythematous, scaling, and slightly infiltrated patches that slowly increase in size by peripheral extension. Superficial spreading BCCs are often surrounded, at least in part, by a fine, thread-like, pearly border (Figure 3). They may also show small areas of ulceration and crusting and a centre with smooth, atrophic scarring.

All potential BCCs should be confirmed with biopsy; based on site and size, a technique is chosen that will provide an adequate dermal component for histological examination. These include incisional or excisional, punch or deep shave biopsies. An adequate dermal component is essential to determine the tumour growth pattern.

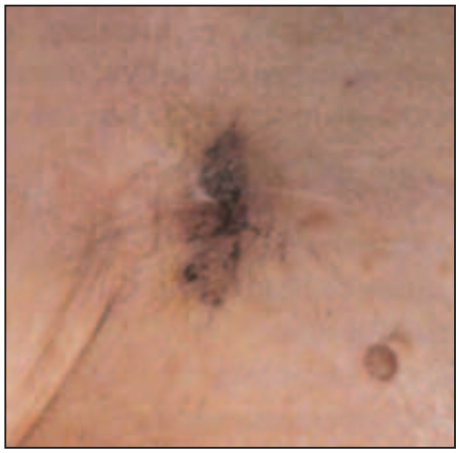

Figure 3: Superficial Basal Cell Carcinoma
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As with other nonmelanoma skin cancers, a lymph node examination should be performed.

The aim of therapy is the complete eradication of malignant cells. Inadequate therapy results in local recurrences that are often larger and more aggressive than the initial tumour. Recurrences are most likely to occur during the first five years after therapy.[22] Tumours found on the centre of the face and around the ears have the highest recurrence rates. BCCs near the ear canal are especially dangerous and require aggressive therapy as extension down the canal provides them with easy access to the brain and other intracranial structures.

When deciding on an optimal method to eradicate the tumour, the preservation of function and the cosmetic outcome should be taken into account. Unfortunately, most BCCs occur in areas that are particularly vulnerable to the destructive effects of both the tumour and the treatment (i.e., central face and the eyes, nose, and mouth). The patient's medical history, current health, and age should also be considered when deciding on a treatment strategy. Watchful waiting may even be the best option for some older patients.

Most treatment strategies are surgical. Curettage and electrodesiccation and cryotherapy, when performed with two freeze-thaw cycles, have a cure rate of more than 95%.[18]

Topical imiquimod is a promising topical treatment for small nodular and superficial BCCs in low-risk locations.[23,24] Imiquimod 5% cream is applied to lesions seven times per week for six weeks (superficial BCCs), or once daily for seven days per week for either six or twelve weeks (nodular BCCs).

Excisional surgery can give a cure rate of 99% for low-risk BCCs <1 cm in diameter.[25] Lesions that are incompletely excised should either be re-excised or referred for Mohs surgery.[26] A 4 mm resection margin is used for nodular BCCs < 1 cm in diameter. This margin is not adequate for morpheiform BCCs and larger or recurrent tumours. These require larger resection margins and intraoperative histologic control. Mohs micrographic surgery is used for higher-risk tumours in areas where maximum tissue conservation is essential. The five-year recurrence rates for BCCs following Mohs surgery range from <1% (primary tumours) to 6% (recurrent tumours).[22]

Radiation therapy may be an option for patients unable or unwilling to undergo surgery.[18] This is especially true for those with BCCs around the nose where surgery may be difficult and disfiguring. A practical drawback, however, is that radiation requires a significant commitment by the patient who should be prepared for several weeks of daily visits to the radiation oncology clinic.

Benign Skin Neoplasias in the Older Adult

Seborrheic keratoses

A seborrheic keratosis is a benign neoplasm of epidermal cells. It is very common among older adults and is unusual in patients younger than 30. From 80–100% of patients with SKs are over 50 years.[27,28] There is evidence of autosomal dominant inheritance in patients with a large number of lesions.[29] These patients can have hundreds of lesions. There is an increased prevalence in Caucasians, and they are less commonly found in dark-skinned individuals.[30] Males and females are equally affected.[27] Although there is still some debate concerning their etiology, exposure to sunlight has been suggested to be a risk factor for SKs.[28,29]

SKs are found in hair-bearing skin, particularly on the trunk, extremities, neck, and face. Lesions are round/oval, sharply demarcated macules, papules, or plaques (Figure 4). They can range in colour from waxy yellow to light brown to black-brown. As they mature, lesions develop a "warty" surface and may become pedunculated. Follicular plugging gives a velvety surface that lends to a "stuck-on" appearance. Most are 0.5–1 cm in diameter but can grow upwards of 6 cm. SKs can become inflamed following trauma. Irritated SKs

Figure 4: Seborrheic Keratosis
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are erythematous, crusting, painful, and/or pruritic.

Although SKs rarely resolve on their own, the majority are asymptomatic. Some conditions such as erythroderma, malignancy, and pregnancy cause new lesions to appear followed by resolution. With psoriasis and pregnancy, lesions may increase in size and number.

A striking increase in the number of SKs may represent a paraneoplastic syndrome (Leser-Trélat sign) that is associated with a visceral malignancy (breast, colon, gastric adenocarcinoma, lymphoma).[31] Consider investigating a Leser-Trélat sign with a CBC, CXR, mammogram, and gastrointestinal endoscopy.

The differential diagnosis of an SK includes a pigmented BCC, Bowen's disease, squamous cell carcinoma, skin tags, condyloma acuminatum, spreading pigmented actinic keratosis, solar lentigo, melanocytic nevi, malignant melanoma, and verruca vulgaris. SKs can be identified clinically, but when in doubt consider a biopsy or consider referral to a dermatologist. It is particularly challenging to differentiate an irritated SK from Bowen's disease, or from an invasive SCC. Sometimes a nonmelanoma skin cancer can develop within an SK; thus, it is important to monitor for these changes.

Treatment of SKs is mainly done for cosmetic reasons. In some cases, lesions may be considered a nuisance, especially where they interfere with undergarments and around the belt line. Treatment can be by destructive methods (cryotherapy, electrodessication, CO2 laser) or by surgical excision (shave excision).

Skin Tags

Skin tags (acrochordons or fibroepithelial polyps) are the commonest fibrous lesions of the skin. Their incidence increases with age. Nearly half of all males and females have at least one skin tag.[32]

Clinically, skin tags are single or multiple, skin-coloured to hyperpigmented soft, pedunculated papules ranging from 0.1 to 2 cm in size. They are commonly found on the neck, axillae, and groin. Skin tags are asymptomatic unless injured by torsion or infarction. The differential diagnosis includes seborrheic keratosis, intradermal melanocytic nevus, and a pedunculated neurofibroma.

Treatment is often demanded when lesions become infarcted or irritated, or if the skin tag is a cosmetic concern. Skin tags are easily removed by scissor excision, cryotherapy, and electrodessication. If confident in the diagnosis, treatment can be performed in a well-equiped primary care office, or a referral can be made to a dermatologist.

Classic Kaposi's Sarcoma

Kaposi's sarcoma (KS) is an indolent neoplasm found mainly on the skin.[33] There are four types of Kaposi's sarcoma: Classic KS, AIDS-related epidemic KS, KS in iatrogenically suppressed patients, and African Endemic KS.[34] In the long-term care setting, a physician is most likely to encounter Kaposi's sarcoma in the classical form. A dermatology consult should be arranged for the diagnosis and management of suspected KS lesions.

Human herpes virus 8 (HHV-8) is the causative agent.[35] HHV-8 stimulates cell proliferation, angiogenesis, and inflammation.

Classical Kaposi's sarcoma is typically found in older men with a male:female ratio ranging from 15:1 to 3:1. The majority of cases occur in individuals over age 50, especially in those of Mediterranean, Jewish Ashkenazi, or Eastern European descent.

Clinically, classic KS lesions are slow-growing, red-blue, purple macules or papules that may coalesce into plaques or nodules (Figure 5).[36] Lesions are often found on the distal lower extremities and may become disseminated. KS lesions are in fluctuation, with some resolving and others just beginning. Although primarily a neoplasia found on the skin, lesions can often be found in the mouth and GI tract.[37] The differential diagnosis of Kaposi's sarcoma includes angiosarcomas, hemangiomas, acroangiodermatitis or chronic venous insufficiency, cutaneous lymphoma/leukemia, venous and lymphatic malformations, polyarteritis nodosa, tufted angioma, and melanoma.[34]

Treatment of classical Kaposi's sarcoma is challenging and there are high recurrence rates. For some patients, watchful waiting may be the best option. Destructive therapies (vigorous cryotherapy, laser) can be tried, particularly for superficial macules and plaques. Solitary lesions can be surgically excised for biopsy and removal. New topical retinoids may prove beneficial. Alitretinoin gel has been shown to be successful in treating AIDS-related KS.[38]

Radiation and chemotherapy can be used for more extensive cases. Classic KS can respond well to radiation once a week for 6–8 weeks. Chemotherapy is only indicated when there are more than

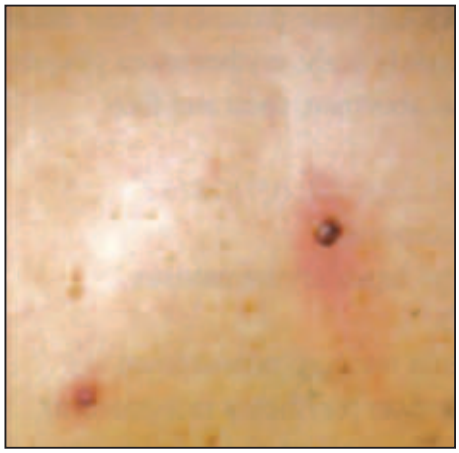

Figure 5: Kaposi's Sarcoma
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ten new skin lesions per month, or if there is symptomatic visceral involvement or lymphedema.

Conclusion

Skin neoplasias are common in the older population. Early therapy can prevent worsening and deadly complications of nonmelanoma skin cancers. Many of these lesions, especially AKs, SKs, and skin tags can be managed in the primary care setting. Malignant or extensive lesions, those that are challenging to diagnose, and those without proven treatments such as KS tend to require referral to a dermatologist.

John Kraft and Carrie Lynde have no competing financial interests declared.
Dr. Charles Lynde has been an investigator for 3M Pharmaceuticals.

References

1. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 1992;26:1–26.
2. Lebwohl M. Actinic keratosis: epidemiology and progression to squamous cell carcinoma. Br J Dermatol 2003;149(Suppl 66):S31–3.
3. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. Lancet 1988;1:795–7.
4. Weiss J, Menter A, Hevia O, et al. Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2, or 4 weeks. Cutis 2002;70:22–9.
5. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. J Am Acad Dermatol 2004;50:714–21.
6. Miller RL, Gerster JF, Owens ML, et al. Imiquimod applied topically: a novel immune response modifier and new class of drug. Int J Immunopharmacol 1999;21:1–14.
7. Kurwa HA, Yong-Gee SA, Seed PT, et al. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. J Am Acad Dermatol 1999;41:414–8.
8. Jorizzo JL. Current and novel treatment options for actinic keratosis. J Cutaneous Med Surg 2004;8 (3 Suppl):S13–21.
9. Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42(Suppl):S4–7.
10. Goldman GD. Squamous cell cancer: a practical approach. Semin Cutan Med Surg 1998;17:80.
11. Rowe DE, Carroll RJ, Day CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. J Am Acad Dermatol 1992;26:976.
12. Kao GF. Carcinoma arising in Bowen's disease. Arch Dermatol 1986;122:1124.
13. Schwartz RA. Keratoacanthoma. J Am Acad Dermatol 1994;30:1.
14. Bernstein SC, Lim KK, Brodland DG, et al. The many faces of squamous cell carcinoma. Dermatol Surg 1996;22:243.
15. Rudolph R, Zelac DE. Squamous cell carcinoma of the skin. Plast Reconstr Surg 2004;114:82–94.
16. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Dermatol 2002;146:18.
17. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol 1992;27:241.
18. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. NEJM 2005;353:2262–9.
19. Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns 2005;31:403–13.
20. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. J Cutaneous Med Surg 2005;9:10–5.
21. McCormack CJ, Kelly JW, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. A possible indicator of differing causes. Arch Dermatol 1997;133:593–6.
22. Rowe DE. Comparison of treatment modalities for basal cell carcinoma. Clin Dermatol 1995;13:617–20.
23. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. Brit J Dermatol 2005;152:939–47.
24. Shumack S, Robinson J, Kossard S, et al. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma: comparison of dosing regimens. Arch Dermatol 2002;138:1165–71.
25. Silverman MK, Kopf AW, Bart RS, et al. Recurrence rates of treated basal cell carcinomas; part 3: surgical excision. J Dermatol Surg Oncol 1992;18:471–6.
26. Robinson JK, Fisher SG. Recurrent basal cell carcinoma after incomplete resection. Arch Dermatol 2000;136:1318–24.
27. Mackie RM. Epidermal skin tumours. In: Champion RH, Burton JL, Burns DA, et al., editors. Textbook of dermatology, 6th Edition. Oxford: Blackwell Science Ltd, 1998: 1658–60.
28. Yeatman JM, Kilkenny M, Marks R. The prevalence of Seborrheic keratoses in Australian population: does exposure to sunlight play a part in their frequency? Br J Dermatol 1997;137:411–14.
29. Engel A, Johnson ML, Haynes SG. Health effects of sunlight exposure in the United States. Results from the first national health and nutritional examination survey, 1971–74. Arch Dermatol 1988;124:72–9.
30. Memon AA, Bothwell J, Tomenson J, et al. Prevalence of solar damage, keratosis and skin cancer in an English population. Br J Dermatol 1995;132:642.
31. Schwartz RA. Sign of Leser-Trelat. J Amer Acad Dermatol 1996;35:88–95.
32. Banik R, Lubach D. Skin tags: localization and frequencies according to sex and age. Dermatologica 1987;174:180–3.
33. Hengge UR, Ruzicka T, Tyring SK. Update on Kaposi's sarcoma and other HHV8 associated diseases; part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy. Lancet Infect Dis 2002;281–92.
34. North PE, Hull C, Kincannon J. Vascular neoplasms and neoplastic-like proliferations. In: Bolognia JL, Jorizzo JL, Rapini RP, editors. Dermatology. Toronto: Mosby, 2003: 1830–3.
35. Chang Y, Cesarman E, Pessin MS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994;1865–9.
36. Schwartz RA. Kaposi's sarcoma: advances and perspectives. J Am Acad Dermatol 1996;804–14.
37. Kolios G, Kaloterakis A, Filiotou A. Gastroscopic findings in Mediterranean Kaposi's sarcoma (non-AIDS). Gastrointest Endosc 1995;336–9.
38. Bodsworth NJ, Bloch M, Bower M, et al. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Amer J Clin Dermatol 2001:2:77–87.