Review

Skin Cancer in the Elderly

KONSTANTINOS N. SYRIGOS 1 , IFIGENIA TZANNOU 1 , NIKOLAOS KATIRTZOGLOU 1 and EVANGELLOS GEORGIOU 2

¹Oncology Unit, 3rd Department of Medicine, Sotiria General Hospital, Athens School of Medicine, Athens; ²Department of Medical Physics, Athens School of Medicine, Athens, Greece

Abstract. With the significant increase in the average lifespan in the industrial world, skin cancer has become a great health concern. There are various epidemiological, biological and molecular data suggesting that skin cancer is predominantly a disease of the elderly, since approximately 53% of skin cancer-related deaths occur in persons more than 65 years old. With regard to the management of elderly patients with skin cancer, this should be individualized depending upon the clinical performance status, and age alone should not constitute an obstruction for the administration of the optimal treatment. Since elderly patients with melanoma have a worse prognosis, emphasis should be given to primary and secondary prevention. Physicians treating elderly patients should be trained in an individualized approach to these patients and encouraged to participate in programs for the early detection of suspicious skin lesions.

The average lifespan in the industrial world has been increasing dramatically over the last three decades, and consequently the number of people over 65 years of age has risen as well. Normal aging refers to the common complex of diseases that characterize many of the elderly. However, not all individuals age in the same way. Some acquire diseases and impairments, while others experience "successful" aging, which is not accompanied by debilitating disease and disability. The percentage of the latter group is augmenting (1, 2).

Correspondence to: Konstantinos N. Syrigos, MD, PhD, Ass. Prof. of Oncology in Medicine, Athens University School of Medicine, Head, Oncology Unit, 3rd Department of Medicine, Building Z, Sotiria General Hospital, Mesogion 152, 115 27 Athens, Greece. Tel: +30 210 7475 034, Fax: +30 210 7781 035, e-mail: knsyrigos@usa.net / ksyrigos@med.uoa.gr

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The links between old age and carcinogenesis, in general, are the substantial length of time required for carcinogenesis, the occurrence of age-related molecular changes that mimic carcinogenesis and changes in the bodily environment that promote cancer progression (3). The factors that contribute to the development of skin cancer in particular are most probably reduced melanocyte density and the altered inflammatory response to dermal damage (4-7).

Therapeutic decisions for patients with skin malignancies should be made based on the estimation of life expectancy, functional status, commorbidity, nutrition, polypharmacy, social support and the potential existence of depression. Individuals who reach old age with a good functional and mental status are as likely to benefit from standard cancer treatment as younger population groups. This does not hold true for elderly patients who present with commorbid conditions or functional impairment, and who should, therefore, be identified in order for undue morbidity to be prevented (2, 3).

In an attempt to accustom physicians treating elderly individuals with skin cancer to the distinctive problems of this particular group of patients, we comprehensively reviewed the existing evidence on the links between aging and the development of skin cancer and presented the optimal clinical approach.

Epidemiology – Why do the elderly develop skin cancer?

Skin cancer is the most common malignancy known to humans and accounts for at least 40% of all human malignancies (8). The incidence of the disease is rising to endemic proportions. There are a lot of epidemiological data that demonstrate a higher incidence of skin cancer in populations living closer to the equator, and in individuals with skin types sensitive to the sun (*i.e.* skin phototypes I and II), while malignant lesions most commonly develop on sun-exposed sites of the skin (9, 10).

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Approximately 53% of skin cancer-related deaths occur in persons over 65 years of age (11). Epidemiological and experimental studies have shown that photocarcinogenesis due to sun exposure is a continuous and cumulative process, which probably justifies the enhanced risk for skin cancer in this age group (12, 13).

The carcinogenetic properties of sunlight reside in ultraviolet radiation, especially in the UVB range. UV rays can cause both direct and indirect cellular DNA damage through photo-oxidative mechanisms (14), which an aged human organism is unable to repair properly (15-18). At the same time, prostaglandins, induced by UV radiation, are also considered to play a significant part in UV-induced inflammation, photocarcinogenesis and the photoaging processes (19). The stratospheric ozone layer is responsible for the absorption of UV rays, therefore protecting the human skin from UV-generated damage. Consequently, ozone depletion may have contributed to the increased incidence of skin cancer (20, 21).

An age-related reduction of cutaneous melanocyte density results in more extensive penetration of UV light into the dermis of elderly individuals, thus causing more extensive damage (22). Furthermore, patients of this age group tend to present with decreased cell-medicated immunity as far as T-lymphocytes' number and function are concerned (23). Likewise, age has a negative effect on the number and function of Langerhans cells of the epidermis, which are also responsible for cutaneous immune function (24, 25). It is most probable that this immune deficiency is responsible for the clinical expression of malignancy (26).

Non-melanoma skin cancers

Non-melanoma skin cancers (NMSC) account for approximately 50% of all cancers reported each year in the United States (27). The most important representatives of NMSC, as far as incidence is concerned, are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). It is beyond the scope of this review to discuss other, less frequent tumors occurring in the older patient, such as Merkel cell carcinoma, atypical fibroxanthoma, sebaceous tumors, cutaneous lymphomas, angiosarcoma, Kaposi's sarcoma and cutaneous metastases.

Basal cell carcinoma (BCC). BCC remains the most common cancer seen in the United States. It accounts for 75-80% of NMSC, with more than one million cases diagnosed during the year 2000 (28). BCC is thought to arise from the pluripotential cells of the epidermis or the outer root sheath of hair follicles and is dependent on an intact connective tissue stroma for growth (29). The disease lesions have distinctive morphological features that make them readily recognizable. It is typical that older patients

consider them to be non-healing wounds at sites of repeated trauma. Various morphological types of basal cell carcinoma have been recognized. The most common is the nodular type; other clinical variants are nodulo-cystic, cystic, nodulo-ulcerative, superficial, pigmented and morpheaform (or sclerosing) (30).

The disease occurs in all races and ages; however, it is uncommon in dark-skinned people, such as Africans and Asians. Approximately 99% of patients who develop BCC are of Caucasian origin. In addition, it is rarely seen before the age of 40 and is more common in men than in women. Men have a higher incidence of BCC occurring on habitually exposed skin than women, whereas women have a three times higher incidence of developing BCC on the lower extremities (5).

It has been found that 85% of BCC occur on the head and neck, and almost 25-30% of the lesions are found on the nose (31). They frequently occur on sun-damaged skin, such as seen in many older people. Due to the fact that 20% of these cancers arise on typically non-sun-exposed sites, such as the back of the hands or the forearms, it is believed that, apart from UV radiation, other pathogenetic factors may be operative and appear to be important etiological factors in the development of BCC. It is possible, therefore, that a major effect of UV light is to increase an inherent age-related predisposition to develop skin cancer (22).

Risk factors for developing BCC include blistering sunburn, intermittent sun exposure, extensive childhood sun exposure (32), fair skin, blue eyes, blonde or red hair (33, 34), immunosuppression, a family history of skin cancer, or a history of localized irradiation or ingestion and topical application of inorganic arsenicals and other chemical carcinogens (35-37). Patients diagnosed with BCC have a nearly 50% risk of a second primary non-melanoma skin cancer developing within 5 years. Patients with a history of BCC have a three-fold higher risk of melanoma (38-40).

This malignant epithelial tumor rarely metastasizes (41). BBC may invade nerves, cartilage, bones and lungs, while it is unlikely to metastasize to regional lymph nodes or to distant organs (0.028%) (42). Given the propensity of the lesions to occur in the head and neck region, such as the ear, eyes or nasal cavity, BCC can be cosmetically disfiguring and often results in functional impairment.

The data concerning proliferation indices and their value as prognostic factors in BBC are not adequate, although Yerebakan *et al.* (43), in a study of 26 BCC cases, inferred that the expression of ki-67, CD31 and epidermal growth factor receptor differs between BCC which later recur and those that do not recur (43, 44). Before any therapy is initiated, a shave or a punch biopsy should be performed on clinically suspicious lesions. The optimal treatment approach for BCC is then based on the size and the site of the lesions as well as the patient's age and performance status.

Additionally, establishing whether the lesion is a primary cancer or a recurrence is necessary and helpful (23, 30).

Unless BCC has metastasized, it is completely curable by surgical excision. Considering that BCC rarely metastasizes, the mainstay of therapy is the complete removal or destruction of the tumor. Several types of surgical removal are in use, e.g., surgical excision, cryosurgery and Mohs micrographic chemosurgical technique for complicated and invasive lesions. Once carcinomas spread to local lymph nodes, they are notoriously resistant to standard forms of chemotherapy and are thus associated with a high mortality rate. However, there is usually an extensive time-lag – often of 15 or 20 years – between initial presentation and death from metastatic carcinoma (45). Lesions on the face, where embryologic fusion planes converge, require more aggressive treatment regimens. Vital areas and sites with emphasis on esthetic integrity, also require specialized care. Recurrence of BCC often develops within 4 to 12 months of the original treatment.

Curettage and electrodesiccation are used for all varieties of BCC except for the morpheaform type. Photodynamic therapy (PDT) is a therapeutic method used over the last 25 years in the treatment of BCC and other non-melanoma skin cancers; it involves the use of a photosensitizing agent activated by light to destroy tumor cells (46).

Radiation therapy can have a cure rate of approximately 90%. This modality is preferable for the older and infirm patient, for whom treatment would be only palliative (29). The strongest disadvantage of radiotherapy is that, in order to attain a complete response, multiple visits are usually necessary (30).

Fluorouracil remains the only proven topical agent for the treatment of BCC, at a 5% concentration for the superficial type of disease. Recently, the therapy of BCC has expanded to include retinoids, $\rm CO_2$ laser therapy and intralesional injection of chemotherapeutic agents (29, 30, 45). Nevertheless, with regards to the management of BCC, most of the trials done demonstrate that surgery and radiotherapy appear to be the most effective treatments, with surgery showing the lowest failure rates (47).

Squamous cell carcinoma (SCC). SCC is the second most common type of skin cancer; approximately 20% of all non-melanoma skin tumors are due to SCC (48). The disease is less common than BCC (ratio of 1:4) and affects men rather than women. The incidence is higher in individuals over age 55, with 60 being the average age of onset. SCC arises from keratinocytes and has a broad clinical spectrum: actinic keratosis (AK), Bowen's disease (SCC in situ), keratoacanthoma, and invasive SCC are the four main types of the disease.

The risk factors for SCC are similar to those for BCC; however, SCC tends to occur among older patients. Farmers or fishermen that work outdoors for long periods of their lives are at particularly high risk for SCC. This chronic sunexposure pattern contrasts with the intermittent sunexposure pattern characteristic of BCC and melanoma. Fair skin, blue eyes, red or blonde hair, arsenic and topical exposure to hydrocarbons, ionizing radiation, prior trauma, frostbite, chronic immunosuppression, psoralen and UVA (PUVA) therapy, and viral oncogenesis (human papilloma virus infection) are other causative agents that seem to correlate with SCC development. SCC of the lip is likely to occur as a result of sun exposure or tobacco use. The lesions of SCC may also arise from chronic inflammation, lupus vulgaris, discoid lupus erythematosus, herpes, psoriasis and chronic stasis dermatitis. Finally, patients who have undergone solid organ transplantation - especially heart transplant – as well as those with chronic lymphocytic leukemia, have a higher risk than others (32-36, 48, 49).

AK is an extremely common, premalignant lesion occurring on habitually sun-damaged skin areas (*i.e.*, face, V-area of the neck, extensor forearms and hands) of elderly individuals. If left untreated, AK has the potential of becoming invasive SCC, by extending beyond the basement membrane into the dermis. However, it has been demonstrated that SCC developing from AK lesions metastasize infrequently, with an estimated incidence of metastases ranging from 0.5 to 3% (50). On the other hand, the metastatic range of carcinomas developing *de novo* has been reported to range from 7.7 to 17.5%, while those cancers that develop from burn scars, osteomyelitis sinuses and chronic non-healing wounds have a higher metastatic rate (20-40%).

As with BCC, treatment of SCC is classified as local, regional and distant control. Simple surgical excision remains the standard treatment for SCC, particularly for difficult, recurrent, large, or aggressive tumors. In situ lesions or smaller well-differentiated tumors can also be treated with curettage and electrodesiccation, cryosurgery and Moh's surgery. Topical administration of fluorouracil is effective for SCC in situ tumors, while interferon alpha has been shown to be effective against AK, SCC and keratoacanthomas. Radiation has its own role in the removal of disease, that has neither metastasized nor spread to cartilage or bone, in the elderly population. After each treatment, patients should be monitored for recurrences and possible metastatic spread. Nearly 70% of recurrences, metastases and new primary tumors associated with SCC occur in the first two years from diagnosis (29, 30, 50).

Malignant melanoma

Malignant melanoma is a highly malignant skin cancer, which arises in any region from melanocytes, most probably as a result of over stimulation by UV light. It metastasizes *via* lymphatics to lymph nodes and *via* the circulation to the lung, brain, liver, bones and skin (1, 51). With clinicopathological criteria, the following main variants are recognized: superficial spreading, nodular, acral lentiginous and lentigo malignant melanoma.

The incidence of malignant melanoma in the European Union is 9/100,000 per year (52). The frequency of thin invasive lesions (<0.1mm), which reflects earlier and more frequent diagnosis, is relatively higher than that of thick lesions. However, the fact that the number of patients developing disseminated metastases, as well as the mortality rates, continue to rise, indicates that the increase of melanoma incidence is true and not plasmatic due to earlier detection (53).

Epidemiologically, it is known that melanoma is very rare before the age of 20, but its incidence increases thereafter (54). Current statistics have shown that the incidence of melanoma appears to be leveling off or even decreasing in younger populations, but the rates continue to rise steeply in the elderly age groups (5, 55, 56). Elderly patients may demonstrate any form of malignant melanoma, but, on the other hand, they can be affected by types of the malignancy that are less frequently seen in younger patients (56). The commonest type of melanoma in the elderly, just as in younger populations, is superficial spreading melanoma (6, 58). It accounts for about 60% of all variants in this age group and, even though its incidence peaks in middle age, it also increases through the eighth decade (52). Nodular melanoma usually appears after the age of 40. It is disproportionally more frequent in patients older than 70, and accounts for 15% of all malignant melanomas in this age group (5, 58-60). Lentigo maligna melanoma occurs only in the elderly (mean age of appearance is 65 years) (5) and accounts for 5-15% of all elderly patients with melanoma. Acral lentiginous melanoma, although rare (it accounts for 1-2% of elderly patients), is also a form which appears mainly in individuals over 65 (56, 59). Desmoplastic melanoma is rare as well, which also affects only elderly patients, while intraepithelial melanoma occurs in younger patients (1, 51). It is worth mentioning that the incidence of primary melanoma in sites other than the skin (i.e. ocular, genital and mucous membrane melanoma) is also remarkably higher in individuals over 65 years old (61-63). The most important features that indicate the presence of melanoma are those demonstrating the ABCDE rule, as described by the European Society for Medical Oncology - ESMO (52):

Asymmetry

Border irregularities

Color heterogeneity

Diameter >6cm

Evolution of color (especially darkening), elevation or size in recent months

Although melanomas are usually asymptomatic, sometimes itching, pruritus, or bleeding may occur. Older patients are more likely to report ulceration and bleeding, while itching and change in elevation and color are significantly less frequently reported (6, 51, 52, 55, 64).

The risk factors for melanoma are quite similar to those for non-melanoma skin cancers. People who belong to the Caucasian race, especially those with skin phototype I or II, seem to be more likely to develop melanoma. Likewise, people who repeatedly suffered blistering sunburn, especially during their childhood years, who practiced intense intermittent sun exposure or irregular tanning bed use before the age of 30, have a great risk of melanoma. Moreover, patients who were subjected to chronic photochemotherapy belong to the high-risk group, as do patients with immune suppression and those with genetic disorders such as xeroderma pigmentosum (4, 65-69), while a family or personal history of melanoma or other malignancy of the skin is another prognostic factor.

At high risk for melanoma in particular are persons with benign melanocytic nevi with a diameter exceeding 7mm, as well as those with an increased number of such (over 50). Another risk factor is the presence of dysplastic nevi and, even worse, the dysplastic nevus syndrome, in which case the lifetime risk of melanoma approaches 100%. Moreover, the presence of congenital nevi with a diameter greater than 20 cm (adult size) suggests a 5-15% possibility of developing melanoma. However, 60% of these melanomas happen during the first decade of life (4, 20, 65, 66).

Diagnosis and staging. Different approaches assist in the diagnosis of melanoma. In clinical practice, total body photography and dermoscopy have proven to be very helpful in melanoma diagnosis (52, 65, 69). Total body photography surveillance is used to document baseline nevi for comparison and observation of stability or instability at follow-up sessions, especially in high-risk patients. This method is less appropriate for patients with multiple or dysplastic nevi, since these people continue to develop new lesions throughout life and, in that case, unnecessary surgical removal may occur (65, 69). Dermoscopy or Epiluminescence microscopy (ELM) is a noninvasive method that helps distinguish lesions that resemble melanoma, such as dysplastic nevi, from melanoma itself. Experienced users of the dermoscope can improve the diagnostic accuracy for melanoma to 90-95% (65, 66, 69). However, the identification of a skin neoplasm as melanoma is certified by histopathological techniques (i.e. histochemistry, immunohistochemistry and microscopy). It is based on several criteria, architectural rather than cytological, and it is made on a combination basis (51, 65, 69).

Once the diagnosis has been made, it is imperative to determine the stage of the malignancy, as this is a

determinant factor both for the choice of therapy and for the prognosis. The most important criteria of all staging systems used in the past have been included in the new American Joint Committee for Cancer TNM Melanoma Staging (51, 65, 69, 70). In addition to physical examination, patients diagnosed with malignant melanoma are subjected to imaging and laboratory evaluation. The established procedures for initial staging include CT scans of the chest, abdomen and brain, bone scan and Sentinel Lymph Node Biopsy (SLNB). A new complementary technique is Positron Emission Tomography, which in the near future may prove useful in detecting small metastases (65, 71,72).

With regard to staging, it has been demonstrated that elderly patients present more often with thick melanomas and ulceration, while younger patients usually present with thin lesions (<0.1 mm). In addition, patients over 65 years of age are more often metastatic on initial diagnosis. This is probably due to negligence and delayed diagnosis, rather than a different pathophysiological mechanism linked to advanced age (58, 60, 73, 74).

There is now sufficient data to support the observation that older individuals are less capable of identifying changes on their skin: elderly people seem to lack the ability to recall the appearance of their skin. Moreover, the fact that many lesions appear on the back of elderly patients, makes their detection difficult. Finally, poor visual acuity and dysfunction of rheumatologic origin may prevent aged individuals for examining their skin frequently and correctly (5, 55, 75). On the other hand, not only the patient, but also the physician may not be alerted as far as skin cancer is concerned and may not conduct skin examination, being distracted by concurrent medical problems (such as diabetes, hypertension, arthritis, depression) (68, 76) Another factor that contributes to a more advanced stage of melanoma at initial diagnosis in patients over 65 years is that they present with nodular melanoma more frequently than younger people, a type which is invasive and has a rapid vertical and diametrical growth, making it more difficult to detect in its early stages (5, 55, 59). Likewise, acral lentigious melanoma, which is also more often found in elderly patients, is generally thicker by the time of diagnosis (59).

Prognosis. As far as disease-free and overall survival are concerned (14, 17, 36, 37), old age (>60 years) along with the male gender are considered to be among the most important negative prognostic factors, probably due to the more advanced stage of malignance at first diagnosis (5, 77). However, one study performed in the USA pointed out that elderly patients with melanoma were found to have worse prognosis, when compared with younger melanoma patients with the same tumor characteristics

(78). In terms of anatomic site, aged individuals most frequently develop melanoma on the head and neck, which has a markedly worse prognosis than melanoma on the trunk, which is most common in younger individuals. Histological features for poor prognosis, chiefly found in the elderly, are ulceration and vertical growth phase. Nodular, acral lentigious and genital melanoma, the incidence of which is also higher among people over 65, are more aggressive than the other variants. Taken together, these factors render geriatric patients more likely to have a worse outcome and to experience fast progression and death (5, 20, 61).

Treatment. The American Academy of Dermatology Guidelines/Outcomes Committee published their guidelines of care for primary cutaneous melanoma, stressing that these will not ensure successful treatment and that the ultimate judgment regarding the proper treatment must be made by the physician, taking into account all the circumstances presented by each individual patient (64). After the diagnosis has been made on the conservatively resected lesion, re-excision is required (67, 79). Cutaneous surgery is well-tolerated in even the oldest patients, including those with co-morbities and special needs that have to be accommodated by the skin surgeon (80).

Moh's Micrographic Surgery (MMS) is a surgical technique which aims at tumor removal with clear margins, while minimizing normal tissue loss. The method involves preparation of frozen sections of the removed tissue and, contrary to the conventional excision, the entire tumor margin is examined. However, the histological interpretation of melanocytes on frozen sections remains difficult. So, for the time being, MMS is not a standard treatment technique, but it is advocated for elderly patients with melanoma in surgically or cosmetically sensitive areas, such as the face, digits and genitalia, as well as for clinically vaguely defined lesions, such as lentigo maligna (5, 72, 81, 82).

Patients with clinically involved regional lymph nodes and no evidence of distant metastases might gain a survival benefit from therapeutic lymph node dissection (83). The development of SLNB helped identify patients with substantial nodal metastases and lymph nodes that need to be dissected (84). However, the practice of SLNB in elderly patients, as standard therapy, remains controversial because it is performed under general anesthesia and may cause chronic lymphedema (85, 86).

Adjuvant chemotherapy is often recommended for surgically resected high- risk melanoma, especially when lymph nodes are proven to be affected (5). Immunotherapy with interleukin-2 and interferon alpha2b has become important in the adjuvant treatment of melanoma (65). High-dose interferon alpha has been reported to increase

both median relapse-free and overall survival (87, 88). On the other hand, high-dose interferon may cause significant dose-related toxicity and thereby exacerbate or cause life-threatening auto-immune, infectious, ischaemic and neuropsychiatric disorders. This observation gives rise to scepticism about high-dose interferon with elderly patients, who are anyway prone to such disorders. However, low-dose interferon has not shown any statistically significant clinical benefit (89).

There are only a few guidelines for the treatment of individuals with metastatic melanoma. It is usually considered to be incurable and is, therefore, treated palliatively. Surgical procedures, however, should be considered for quality of life improvement. With regard to elderly patients, and especially when the performance status prohibits surgery, radiotherapy may be utilized with equally good results (72) and 90-95% of individuals over 80 seem able to complete the planned treatment (3).

With regard to chemotherapy, the current standard consists of dacarbazine (DTIC) temozolomide, or regimens based on either one of these chemotherapeutics. DTIC administration results in a response rate of 15-25%, but with a median duration of response of no more than 5-6 months, while only 1-2% of patients present a 5-year durable response (65). A lot of research into new protocols of multi-agent chemotherapy, as well as combinations of chemo- and immunotherapy is still in progress. The results are still not very encouraging (90-94). The National Cancer Network Guidelines of the USA point out, among other issues, that patients over 70 years should have some geriatric assessment, and that doses of chemotherapy should be adjusted according to the GFR, while hemopoietic growth factors should always be used prophylactically (3). The fact that temozolomide is an oral agent makes it preferable for elderly patients. In addition, the decrease of gastrointestinal absorption with age does not seem to affect the effectiveness and tolerability of chemotherapy. When the performance status of the aged patient does not permit any kind of treatment, best supportive care is the optimal choice.

With regard to newer biological treatment strategies, no therapy has yet been proved to have a definite role in the treatment of melanoma. However, new immune and gene therapies have derived from remarkable insights into the biological, immunological and molecular nature of tumor cells and the host response and several clinical trials are in progress (95, 96).

Follow-up. Currently, there is actually no consensus on the frequency of follow-up and recommendations for surveillance testing. Depending on the tumor thickness and staging, different follow-up schedules are recommended for disease-free patients of any age after surgery. According to

the ESMO Recommendations for invasive melanoma, 3-monthly follow-up for two years is recommended. After that, patients should be followed-up every 6-12 months for another three years for local melanoma (<1.5mm thickness) Otherwise, follow-up continues until ten years after primary diagnosis. However, the report of late recurrences (more than 10 years after diagnosis) emphasizes the need for self examination of the skin and regional lymph nodes. Standard follow-up examination includes: examination of the surgical scar, full-body skin examination and examination of the regional lymph nodes, liver and spleen palpation. Not many instrumental examinations are needed. Physical examinations can guide further investigations (blood counts, serum LDH, liver function tests, CTs, bone scan) (52, 66, 73, 79). The use of serological markers such as LDH, liver function tests and full blood count, as well as \$100 protein, seem to have low sensitivity and specificity (67, 97). Also PCR-based detection of circulating molecular tumor markers has been investigated (98, 99), while genetic testing for various genes has been proposed as well (100). Although, their prognostic value is still in doubt, their study could add to the knowledge of tumor biology and immunology and may promote immune and gene therapies (72, 95).

Prevention

The continuously rising incidence, as well as the high mortality (especially as far as melanoma is concerned), have made dermal cancer an important public health issue. It is of great significance that public health efforts aim both at primary and at secondary prevention (101).

Primary prevention strategies aim to prevent people from developing melanoma by increasing public awareness of the risk factors for skin cancer, such as UV-light exposure, and the presence of dysplastic or congenital nevi (20, 102). People should be educated to minimize sun exposure, especially during peak UV-B hours, and to use sunscreens with a sun protective factor ≥ 15 (even though their role is not definite) (103, 104). Sunburn and tanning should also be avoided. All this applies to children as well, as it has been proven that prolonged sun exposure and sunburn during childhood augment the life-long risk of developing melanoma (4, 20, 65, 69, 105).

Chemoprevention has also been studied as an alternative for high-risk patients in relation to non-melanoma skin malignancies. Unfortunately, none of the plentiful agents studied had any significant effect on the incidence of either BCC or SCC (106-109).

With regard to secondary prevention, educational programs are addressed to the public, as well as to clinicians, aiming to detect skin malignancies at the earliest stage possible. The public should be educated on self-

screening and the recognition of malignant and, most importantly, melanoma lesions (5, 20, 110). Moreover, individuals, especially older ones, who may not be capable of self examination, should be encouraged to visit physicians and request a skin examination (75, 102). Primary care physicians, on the other hand, should be educated with regard to skin cancer identification and high-risk patients (111-113). In order to assess an individual's risk of dermal cancer, the physician should examine various factors such as age, gender, race, skin type, family and personal history of skin cancer, exposures, occupation, geographic location and medical condition. He also has to be alert to suspicious nevi, while it would prove helpful to know the frequency of each malignancy by skin site (27). Although there is still a lot of controversy as to who should be screened by skin examination and how often, there is a general consensus that elderly patients belong in the high-risk category (112).

Conclusion

Skin cancer has become a matter of great public concern. Age-related factors as well as cumulative exposure to UV radiation contribute to the high prevalence of dermal cancer in older populations. It has been remarked that geriatric patients with melanoma have poorer prognosis than younger ones. This is a multi-factorial result that is also influenced by the fact that the elderly tend to present with a more advanced stage of this malignancy. With regard to management, advanced age should not be a barrier for an effective treatment, provided that the clinical and functional status of the elderly patient with skin cancer allow it. Otherwise, the treatment should be modified according to the patient's medical and social profile. Nevertheless, it is of vital importance to appreciate that primary prevention of skin cancer, as well as screening and early detection of malignant skin lesions, could save many lives, which would otherwise be lost to skin malignancies.

References

- Dewberry C and Norman RA: Skin cancer in elderly patients. Dermatol Clin North Am 22: 93-96, 2004.
- 2 Repetto L, Fratino L, Audusio RA et al: Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group Performance Status in elderly cancer patients: An Italian Group for Geriatric Oncology Study. JCO 20: 494-502, 2002.
- 3 Repetto L and Balducci L: A case for geriatric oncology. The Lancet 3: 289-297, 2002.
- 4 Manola J, Atkins M, Ibrahim J and Kirkwood J: Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials: JCO 18: 3782-3793, 2000.
- 5 Sachs DL, Marghoob AA and Halpern A: Skin cancer in the elderly. Clin Geriatric Dermatol 17: 238-242, 2001.

- 6 Christos PJ, Oliveria SA, Berwick M et al: Signs and symptoms of melanoma in older populations. J Clin Epidemiol 53: 1044-1053, 2000.
- 7 Gilchrest BA: In vitro assessment of keratinocyte aging. J Invest Dermatol 81: 184-189, 1983.
- 8 Miller DL and Weinstock MA: Nonmelanoma skin cancer in the United States. J Am Acad Dermatol *30*: 774-8, 1994.
- 9 Urbach F: Ultraviolet radiation and skin cancer in man. *In*: Montagna W, Dobson RL, eds: Advances in Biology of Skin. Volume 3. New York, Pergamon, pp. 310-321, 1966.
- Bliss JM, Ford D, Swerdlow AJ et al: Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. The International Melanoma Analysis Group (IMAGE). Int J Cancer 62: 367-376, 1995.
- 11 Smith JR, Venable S, Roberts TW et al: EL. Relationship between in vivo and in vitro aging: assessment of 669 cell cultures derived from members of the Baltimore Longitudinal Study of Aging. J Gerontol A Sci Med Sci 57: 239-246, 2002.
- 12 Green A, Whiteman D, Frost C and Battistutta D: Sun exposure, skin cancers and related skin conditions. J Epidemiol 9: 7S-13S, 1999.
- 13 Parrish JA, Anderson RR, Urbach F and Pitts D: Biological Effects of UV Radiation with Emphasis on Human Responses to Long-wave Ultraviolet. New York, Plenum Press, pp. 165-61, 1978.
- 14 Kondo S: The roles of cytokines in photoaging. J Derm Sci 23: 30S-36S, 2002.
- 15 Goukassian D, Gad F, Yaar M et al: Mechanisms and implications of the age-associated decrease in DNA repair capacity. FASEB J 14: 1325-1334, 2000.
- 16 Wei Q, Matanoski GM, Farmer ER et al: DNA repair capacity for ultraviolet light-induced damage is reduced in peripheral lymphocytes from patients with basal cell carcinoma. J Invest Dermatol 104: 933-936, 1995.
- 17 Moriwaki S, Ray S, Tarone RE et al: The effect on donor age on the processing of UV-damaged DNA by cultured human cells: reduced DNA repair capacity and increased DNA mutability. Mutat Res 364: 117-123, 1996.
- 18 Grossman L: Epidemiology of ultraviolet-DNA repair capacity and human cancer. Environ Health Perspect 105: 927-930, 1997.
- 19 Seo JY, Kim EK, Lee SH et al: Enhanced expression of cyclooxygenase-2 by UV in aged human skin in vivo. Mech Ageing Dev 124(8-9): 903-910, 2003.
- 20 Beddingfield FC III: The melanoma epidemic: Res Ipsa Loquitur. The Oncologist *8*: 459-465, 2003.
- 21 Godlee F: Dangers of ozone depletion. BMJ 303: 1326-1328, 1991.
- 22 Gilchrest BA: Skin and Aging Processes. Boca Raton, FL, CRC Press, Inc., pp. 67-81, 1984.
- 23 Pollack SV: Skin cancer in the elderly. Clin Geriatr Med 3: 715-728, 1987.
- 24 Smith JR, Venable S, Roberts TW et al: Relationship between in vivo and in vitro aging: assessment of 669 cell cultures derived from members of the Baltimore Longitudinal Study of Aging. J Gerontol A Sci Med Sci 57: B239-246, 2002.
- 25 Bhushan M, Cumberbatch M, Dearman RJ et al: Tumour necrosis factor-alpha-induced migration of human Langerhans cells: the influence of ageing. Br J Dermatol 146: 32-40, 2002.

- 26 Swift ME, Burns AL, Gray KL and Di Pietro LA: Age-related alterations in the inflammatory response to dermal injury. J Invest Dermatol 117: 1027-1035, 2001.
- 27 Scotto J, Fears TR and Fraumeni JF Jr: Incidence of nonmelanoma skin cancer in the United States. US Dept. of Health and Human Services Pub. No. (NIH) 1981, pp. 82-243.
- 28 Momm F, Becker G, Bartelt S and Guttenberger R: The elderly, fragile tumor patient: radiotherapy as an effective and most feasible treatment modality. J Pain Symptom Manage 27: 3-4, 2004.
- 29 Keller KL, Fenske NA and Glass LF: Cancer of the skin in the older patients. Clin Geriatr Med 13: 339-361,1997.
- 30 Proper SA, Rose PT and Fenske NA: Non-melanomatous skin cancer in the elderly: diagnosis and management. Geriatrics 45: 57-62, 1990.
- 31 Miller SJ: Biology of basal cell carcinoma. J Am Acad Dermatol 24: 1-10, 1991.
- 32 Gallagher R, Ma B, McLean D et al: Trends in basal cell carcinoma, squamous cell carcinoma, and melanoma of the skin from 1973 through 1987. J Am Acad Dermatol 23: 413-421, 1990.
- 33 Pearlman D: Weekly pulse dosing: effective and comfortable topical 5-fluorouracil treatment of multiple facial actinic keratoses. J Am Acad Dermatol 25: 665-667, 1991.
- 34 Zanetti R, Rosso S, Martinez C et al: The Multicentre South European Study 'Helios': I.Skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. Br J Cancer 73: 1440-1446, 1996.
- 35 Lin T and Huang Y: Arsenic species in drinking water, hair, fingernails, and urine of patients with blackfoot disease. J Toxicol Environ Health 53: 85-93, 1998.
- 36 Modan B, Alfondary E, Shapiro D et al: Factors affecting the development of skin cancer after scalp irradiation. Radiat Res 134: 125-128, 1993.
- 37 Shore R, Albert R, Reed M et al: Skin cancer incidence among children irradiated for ringworm of the scalp. Radiat Res 100: 192-204, 1984.
- 38 Bower C, Lear J, Bygrave S *et al*: Basal cell carcinoma and risk of subsequent malignancies: a cancer registry-based study in Southwest England. J Am Acad Dermatol 42: 988-991, 2000.
- 39 Karagas M, Stukel T, Greenberg R et al: Risk of subsequent basal cell carcinoma and squamous cell carcinoma of the skin among patients with prior skin cancer. JAMA 267: 3305-3310, 1992.
- 40 Marghoob A, Kopf A, Bart R et al: Risk of another basal cell carcinoma. J Am Acad Dermatol 28: 22-28, 1993.
- 41 Domarus HV and PJ Stevens: Metastatic basal-cell carcinoma. J Am Dermatol 10: 1043-1060, 1984.
- 42 Mikhail GR, Nims LP, Kelly AP *et al*: Metastatic basal cell carcinoma. Arch Dermatol *113*: 1261-1269, 1977.
- 43 Yerebakan O, Ciftcioglu MA, Akkaya BK and Yilmaz E: Prognostic value of ki-67, CD31 and epidermal growth factor receptor expression in basal cell carcinoma. J Dermatol 30: 33-41, 2003.
- 44 Healy E, Angus B, Lawrence CM and Rees JL: Prognostic value of ki67 antigen expression in basal cell carcinomas. Br J Dermatol 133: 737-741, 1995.
- 45 Smoller J and Smoller: BR Skin malignancies in the elderly. Diagnosable, treatable, and potentially curable. J Gerontol Nurs 18: 19-24, 1992.

- 46 Zeitouni NS, Oseroff AR and Shieh S: Photodynamic therapy for nonmelanoma skin cancers. Current review and update. Mol Immunol 39: 1133-1136, 2003.
- 47 Bath FJ, Bong J, Perkins W and Williams HC: Interventions for basal cell carcinoma of the skin. Cochrane Database Syst Rev 3: 412-416, 2003.
- 48 Euvrard S, Kanitakis J, Pouteil-Nobel C *et al*: Comparative epidemiologic study of premalignant and malignant epithelial cutaneous lesions developing after kidney and heart transplantation. J Am Acad Dermatol *33*: 222-229, 1995.
- 49 Veness M: Aggressive skin cancers in a cardiac transplant recipient. Australas Radiol 41: 363-366, 1997.
- 50 Lin AN, Carter DM and Balin AK: Nonmelanoma skin cancers in the elderly. Clin Geriatr Med 5: 161-170, 1989.
- 51 Smith KJ, Hamza S and Skelton H: Histologic features in primary cutaneous squamous cell carcinomas in immunocompromised patients focusing on organ transplant patients. Dermatol Surg 30: 634-641, 2004.
- 52 ESMO: Minimum clinical recommendations for diagnosis, treatment and follow-up of cutaneous malignant melanoma. Ann Oncol *14*: 1012-1213, 2003.
- 53 Lamberg L: "Epidemic" of malignant melanoma: true increase or better detection? JAMA 287: 2201, 2002.
- 54 Chang CK, Jacobs IA, Vizgirda VM and Salti GI: Melanoma in the elderly patient. Arch Surg *138*: 1135-1138, 2003.
- 55 Kelly JW: Melanoma in the elderly-a neglected public health challenge. MJA 169: 403-404, 1998.
- 56 WH McCarthy: The Australian experience in sun protection and screening for melanoma. J Surg Oncol 86: 236-245, 2004.
- 57 Morris BT and Sober AJ: Cutaneous malignant melanoma in the older patient. Derm Clin 4: 473-480, 1986.
- 58 McHenry PM, Hole DJ and MacKie RM: Melanoma in people aged 65 and over in Scotland,1979-89. BMJ 304: 746-749,1992.
- 59 Hanrahan PF, Hersey P and D'Este CA: Factors involved in presentation of older people with thick melanoma. MJA 169: 410-414, 1998.
- 60 Loggie B, Ronan SG, Bean J et al: Invasive cutaneous melanoma in elderly patients. Arch Derm 127: 1188-1193, 1991
- 61 Chamberlain A, Fritschi L, Graham G *et al*: Nodular type and older age as the most significant associations of thick melanoma in Victoria, Australia. Arch Derm *138*: 609-614, 2002.
- 62 Rogers RS and Gibson LE: Mucosal, genital, and unusual clinical variants of melanoma. Mayo Clin Proc 72: 362-366, 1007
- 63 Sutherland CM, Chmiel JS, Henson DE et al: Patient characteristics, methods of diagnosis, and treatment of mucous membrane melanoma in the United States of America. J Am Coll Surg 179: 561-566, 1994.
- 64 Gutman M, Inbar M, Chaitchik S *et al*: Malignant melanoma of the mucous membrane. Eur J Surg Oncol *18*: 307-312,1992.
- 65 Sober AJ, Chuang TY, Farmer ER et al: Guidelines of care for primary cutaneous melanoma. J.A.A. Dermatology 45: 579-586 2001
- 66 Zalaudek I, Ferrara G and Argenziano G: A diagnosis and treatment of cutaneous melanoma: a practical guide. Skin Med 2: 20-31, 2003.
- 67 Chamberlain AJ and Kelly JW: Nodular melanomas and older men: a major challenge for community surveillance programs. Med J Aust 180: 432-435, 2004.

- 68 Hafner J, Schmid MH, Kempf W et al: Baseline staging in cutaneous malignant melanoma. Br J Dermatol 150: 677-686, 2004.
- 69 Edman RL and Wolfe JT: Prevention and early detection of malignant melanoma. Am Fam Phys 62: 2277-2284, 2000.
- 70 Chaudry V, Chompret A, Bressac-de Paillerets B et al: Influence of genes, nevi, and sun sensitivity on melanoma risk in a family sample unselected by family history and in melanoma-prone families. J Natl Cancer Inst 96: 785-795, 2004.
- 71 Balch CM, Buzaid AC, Soong SJ et al: Final version of the AJC on cancer staging system for cutaneous melanoma. JCO 19: 3635-3648, 2001.
- 72 Consensus Development Panel on Early Melanoma: Diagnosis and treatment of early melanoma. JAMA 268: 1314-1319, 1992.
- 73 Eedy DJ: Surgical treatment of melanoma. Br J Dermatology 149: 2-12, 2003.
- 74 Demierre MF: Thin melanomas and regression, thick melanomas and older Men. Arch Derm 138: 678-682, 2002.
- 75 Goodwin JS, Samet JM, Key CR et al: Stage at diagnosis of cancer varies with the age of the patient. Am Geriatr Soc 34: 20-26, 1986.
- 76 Hanahan PF, Hersey P, Menzies SW et al: Examination of the ability of people to identify early changes of melanoma in computer-altered pigmented skin lesions. Arch Derm 133: 301-311, 1997.
- 77 Wender RC: Barriers to effective skin cancer detection. Cancer suppl 75: 691-698, 1995.
- 78 Rivers JK, Kelly MC, Kopf AW et al: Age and malignant melanoma: comparison of variables in different age groups. Am Acad Dermatol 21: 7171-722, 1989.
- 79 Austin PF, Cruse CW, Lyman G et al: Age as as prognostic factor in the malignant melanoma population. Ann Surg Onc 1: 487-494, 1994.
- 80 Carlson GW: Age and the incidence of sentinel lymph node metastases in melanoma. Ann Surg Oncol 11: 236-237, 2004.
- 81 Cascinelli N: Margin of resection in the management of primary melanoma. Semin Surg Oncol 14: 272-275, 1998.
- 82 Rhodes LM, Norman RH, Wrone DA et al: Cutaneous surgery in the elderly: ensuring comfort and safety. Derm Ther 16: 243-253, 2003.
- 83 Bialy TL, Whalen J, Veledar E *et al*: Mohs micrographic surgery *vs* traditional surgical excision: a cost comparison analysis. Arch Dermatol *140*: 736-742, 2004.
- 84 Kanzler M and Mraz-Gernhard S: Treatment of primary cutaneous melanoma. JAMA 285: 1819-1821, 2001.
- 85 Gietema HA, Vuylsteke RJ, de Jonge IA et al: Sentinel lymph node investigation in melanoma: detailed analysis of the yield from step sectioning and immunohistochemistry. J Clin Pathol 57: 618-620, 2004.
- 86 McMasters KN, Reintgen DS, Ross MI et al: Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. JCO 19: 2851-2855, 2001.
- 87 Bostick P, Morton D, Turner R et al: Prognostic significance of occult metastases detected by sentinel lymphadenectomy and reverse transcriptase-polymerase chain reaction in early stage melanoma patients. JCO 17: 3238-3244, 1999.
- 88 Cascinelli N, Belli F, MacKie R et al: Effect of long-term adjuvant therapy with Interferon alpha-2a in patients with regional node metastases from cutaneous melanoma: a randomized trial. The Lancet 358: 866-869, 2001.

- 89 Pehamberger H, Soyer HP, Steiner A et al: Adjuvant interferon alpha-2a treatment in resected primary stage II cutaneous melanoma. JCO 16: 3205-3206, 1998.
- 90 Cascinelli N, Buffalino R, Morabito A and MacKie R: Results of adjuvant interferon study in WHO Melanoma Program. The Lancet 343: 913-914, 1994.
- 91 Hwu WJ, Krown S, Panageas K *et al*: Temozolamide plus thalidomide in patients with advanced melanoma: results of a dose finding trial: JCO *20*: 2610-2615, 2002.
- 92 De Gast GD, Batchelor D, Kersten MJ *et al*: Temozolomide followed by combined immunotherapy with GM-CSF, low-dose IL2 and IFN alpha in patients with metastatic melanoma. BJC 88: 175-180, 2003.
- 93 Danson S, Lorigan P, Arance A *et al*: Randomized phase II study of temozolomide given every 8 hours daily with either interferon alpha 2a or thalidomide in metastatic malignant melanoma. JCO *21*: 2551-2557, 2003.
- 94 Creagan E, Suman V, Dalton R et al: Phase III clinical trial of the combination of cisplatin, dacarbazine, and carmustine with or without tamoxifen in patients with advanced malignant melanoma. JCO 17: 1884-1890, 1999.
- 95 Rosenberg S, Young J, Schwartzentuber D et al: Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon alpha –2b. JCO 17: 968-975, 1999.
- 96 Edelstein ML, Abedi MR, Wixon J and Edelstein RM: Gene therapy clinical trials worldwide 1989-2004 – an overview. J Gene Med 6: 597-602, 2004.
- 97 H. Lee Moffit Cancer Center and Research Institute: Advances in gene therapy for malignant melanlma. Cancer Control 9: 39-48, 2002.
- 98 Deichmann M, Benner A, Bock M et al: S100-Beta, melanoma-inhibiting activity, and lactate dehydrogenase discriminate progressive from nonprogressive melanoma. JCO 17: 1891-1896, 1999.
- 99 Wascher R, Morton D, Kuo C et al: Molecular tumor markers in the blood: early prediction of disease outcome in melanoma patients treated with a melanoma vaccine. JCO 21: 2558-2563, 2003.
- 100 Palmieri G, Strazzulo M, Ascieto PA et al: Polymerase chain reaction-based detection of circulating melanoma cells as an effective marker of tumor progression. JCO 17: 304-311, 1999.
- 101 Kefford RF, Newton Bishop JA, Bergman W et al: Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: a consensus statement of the Melanoma Genetics Consortium. JCO 17: 3245-3251, 1999.
- 102 MacKie RM: Secondary prevention of cutaneous malignant melanoma. Melanoma Res 2: 151-154, 1997.
- 103 Jerant AF, Johnson JT, Demastes-Sheridan C et al: Early detection and treatment of skin cancer. Am Fam Physician 62: 357-368, 2000.
- 104 Rigel DS and Carucci JA: Malignant melanoma: prevention, early detection and treatment in the 21st Century. CA: Cancer J Clinic 50: 215-236, 2000.
- 105 Marks R: Photoprotection and prevention of melanoma. Eur J Dermatol 9: 406-412, 1999.
- 106 Austoker J: Cancer prevenion in primary care: melanoma: prevention and early diagnosis. BMJ 308: 1682-1686, 1994.

- 107 Greenberg ER, Baron JA, Stukel TA et al: A clinical trial of beta-carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group. N Engl J Med 323: 789-795, 1990.
- 108 Clark LC, Combs Jr GF, Turnbull BW et al: Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. J Am Med Assoc 276: 1957-1963, 1996.
- 109 Hong WK and Lippman SM: Cancer chemoprevention. J Natl Cancer Inst Monogr 49-53, 1995.
- 110 Einspahr JG, Bowden GT and Alberts DS: Skin cancer chemoprevention: strategies to save our skin. Rec Res Cancer Res 163: 151-164, 2003.

- 111 Berg AO: Screening for skin cancer, recommendations and rationale. US Preventive Task Force. Am J Prev 20(supp3): 44-46, 2001.
- 112 Welsh B: The summer skin check. Aust Fam Physician 33: 37-42, 2004.
- 113 Whited JD and Grichnik JM: Does this patient have a mole or a melanoma? JAMA 279: 696-701, 1998.

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