Advances in Skin Cancer Treatment with Updates in Immunotherapy, photo-allergy, and Radiation Therapy

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Skin cancer


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Many Americans Wrong About Sun's Skin Cancer Dangers: Poll

By

Cancer Nursing Today Featured Reading-

May 5, 2021

A new survey reveals that one-third of Americans lack a basic understanding of sun safety and skin cancer. That is the surprising takeaway from an American Academy of Dermatology survey of 1,000 U.S. adults.

Fifty-three percent of respondents did not realize shade offers protection from the sun's ultraviolet (UV) rays, and 47 percent incorrectly said a base tan would prevent sunburns or were unsure. Thirty-five percent said tanning is safe as long as you do not burn or were unsure, and 31 percent were unaware that tanning causes skin cancer.

Nonmelanoma Skin Cancers: Basal Cell and Squamous Cell Carcinomas

Incidence

- **1 million new cases occur annually including 80% basal cell carcinomas (BCCs) and 20% squamous cell carcinomas (SCCs)**
- **Incidence is increasing 2% to 3% per year.**
- **SCC incidence is increased 18- to 36-fold in organ transplant recipients.**

Pathology and Biology

- **Several histopathologic subtypes exist.**
- **The more infiltrative or poorly differentiated variants are more clinically aggressive (e.g., morpheaform BCC and spindle cell SCC).**

Differential Diagnosis and Staging

- **Amelanotic melanoma, keratoacanthoma, cutaneous metastasis, cutaneous lymphoma, cutaneous lymphoid hyperplasia, adnexal tumor, Merkel cell carcinoma, and sebaceous gland carcinoma are included in the differential diagnosis.**

- **BCCs that are large, deep, or infiltrative may be locally aggressive and recurrent but metastasize only rarely (<0.05%).**

- **SCCs have a greater metaststic rate, especially those that are large, deep, have perineural invasion, or are located on the dorsal hands, lips, ears, penis, or sites of chronic infection, ulceration, or radiation.**

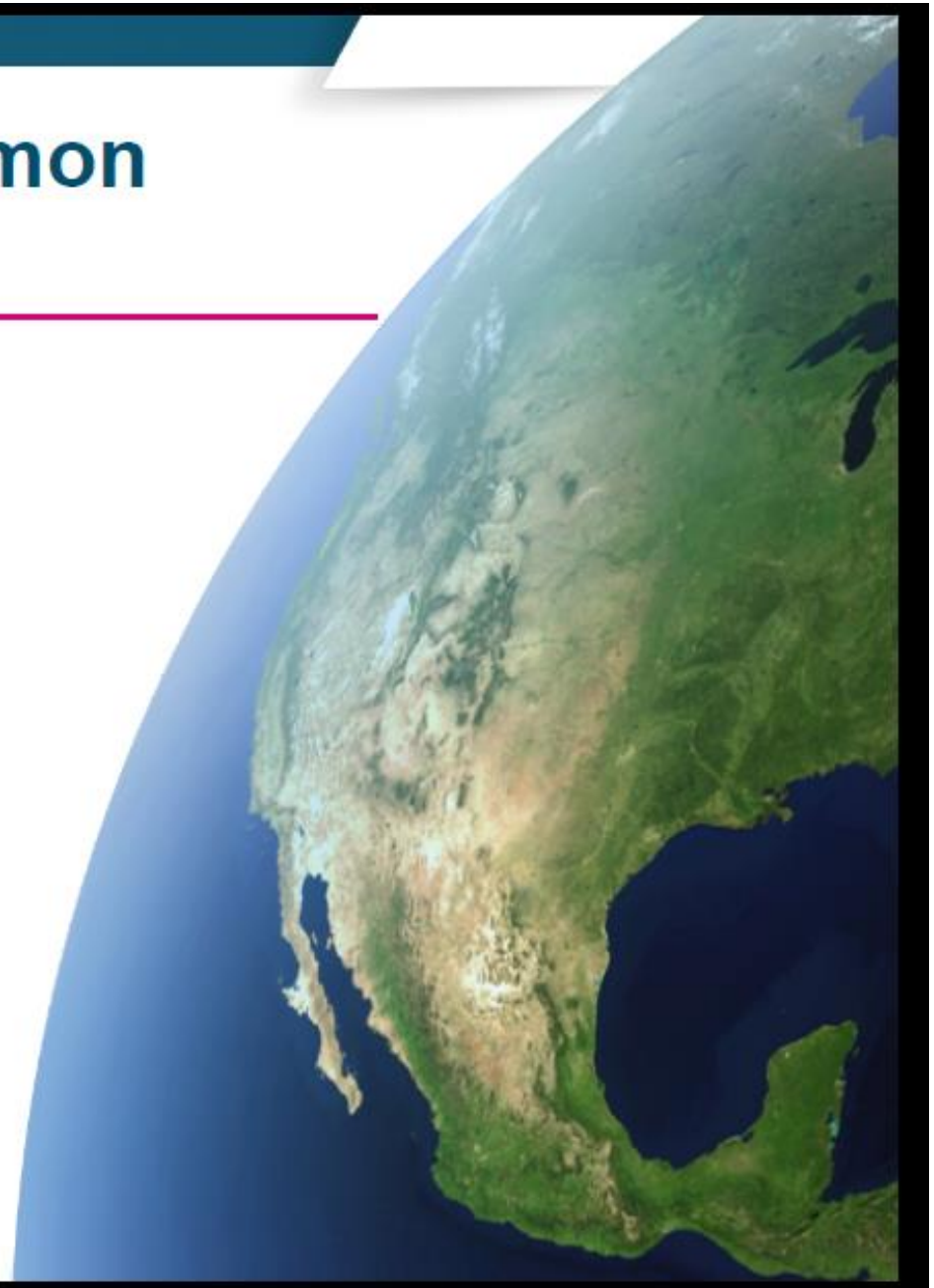
CSCC Is the Second Most **Common** Form of Skin Cancer[1,*]

CSCC incidence

Expected to increase **2%** to **4%** each year[2]

US incidence

Has increased substantially, by **50%** to **200%**, over the past 3 decades[3]



*In the United States.
CSCC, cutaneous squamous cell carcinoma.

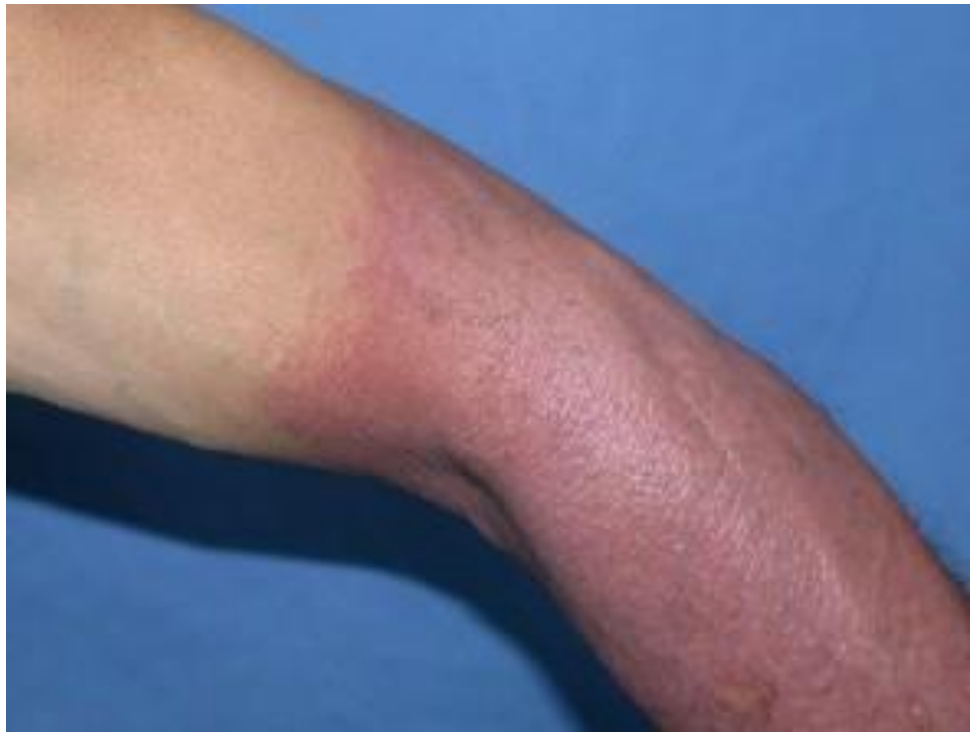
References: 1. Gurudutt VV, et al. *J Skin Cancer*. 2011;2011:502723. 2. Burton KA, et al. *Am J Clin Dermatol*. 2016;17(5):491-508. 3. Karia PS, et al. *J Am Acad Dermatol*. 2013;68(6):957-966.

RISK FACTORS FOR NMSC

Photosensitizing drugs

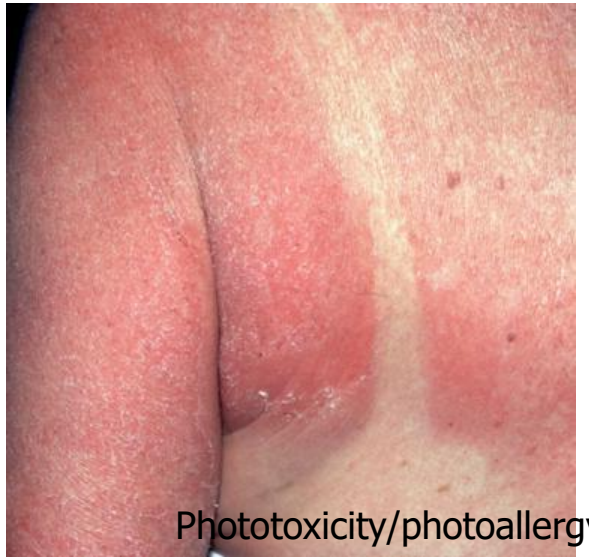
- Alpha-hydroxy acids in cosmetics
- Antibiotics (ciprofloxacin, doxycycline, levofloxacin, ofloxacin, tetracycline, trimethoprim)
- Antifungals (flucytosine, griseofulvin, voricanozole)
- Antihistamines (cetirizine, diphenhydramine, loratadine, promethazine, cyproheptadine)
- Cholesterol lowering drugs (simvastatin, atorvastatin, lovastatin, pravastatin)
- Diuretics (thiazide diuretics: hydrochlorothiazide, chlorthalidone, chlorothiazide.; other diuretics: furosemide and triamterene)
- Non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, celecoxib, piroxicam, ketoprofen)
- Oral contraceptives and estrogens
- Phenothiazines (tranquilizers, anti-emetics: examples, chlorpromazine, fluphenazine, promethazine, thioridazine, prochloroperazine)
- Psoralens (methoxsalen, trioxsalen)
- Retinoids (acitretin, isotretinoin)
- Sulfonamides (acetazolamide, sulfadiazine, sulfamethizole, sulfamethoxazole, sulfapyridine, sulfasalazine, sulfasoxazole)
- Sulfonylureas for type 2 diabetes (glipizide, glyburide)

phenothiazine



Phototoxic reactions occur because of the damaging effects of light-activated compounds on cell membranes and, in some instances, DNA.

By contrast, photoallergic reactions are cell-mediated immune responses to a light-activated compound. Phototoxic reactions develop in most individuals if they are exposed to sufficient amounts of light and drug. Typically, they appear as an exaggerated sunburn response, as shown in the image below.



Phototoxicity/photoallergy

Background

- **Drug-induced photosensitivity** refers to the development of cutaneous disease as a result of the combined effects of a chemical and light.
- Exposure to either the chemical or the light alone is not sufficient to induce the disease;
- however, when photoactivation of the chemical occurs, one or more cutaneous manifestations may arise.
- These include phototoxic and photoallergic reactions, a planus lichenoides reaction, pseudoporphyria, and subacute cutaneous lupus erythematosus.
- Photosensitivity reactions may result from systemic medications and topically applied compounds

BCCs and increased disposition to other internal cancers was explored, individuals with 6 or more BCCs had a greater risk of other malignancies, with a 3.5-fold increase in the frequent BCC cohort. High frequency BCC patients were also more likely to have a:

- 5-fold increase in leukemia and lymphoma (P=.004)
- 5-fold increase in colon cancer (P=.030)
- 6-fold increase in breast cancer (P=.009)
- 7-fold increase in prostate cancer (P<.001)
- Bogdony, J, 2020

Genomics of Basal Cell Ca

The average number of BCCs in high-frequency patients (n=61) was 11, the average age at first skin cancer diagnosis was 44 years, and 10 (16.4%) of these patients developed their first skin cancer before age 30. Among these 61 patients, 12 (19.7%) had pathogenic mutations in DNA repair genes. More specifically, they harbored 13 pathogenic mutations in 12 different genes: *APC*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, and *PALB2*.

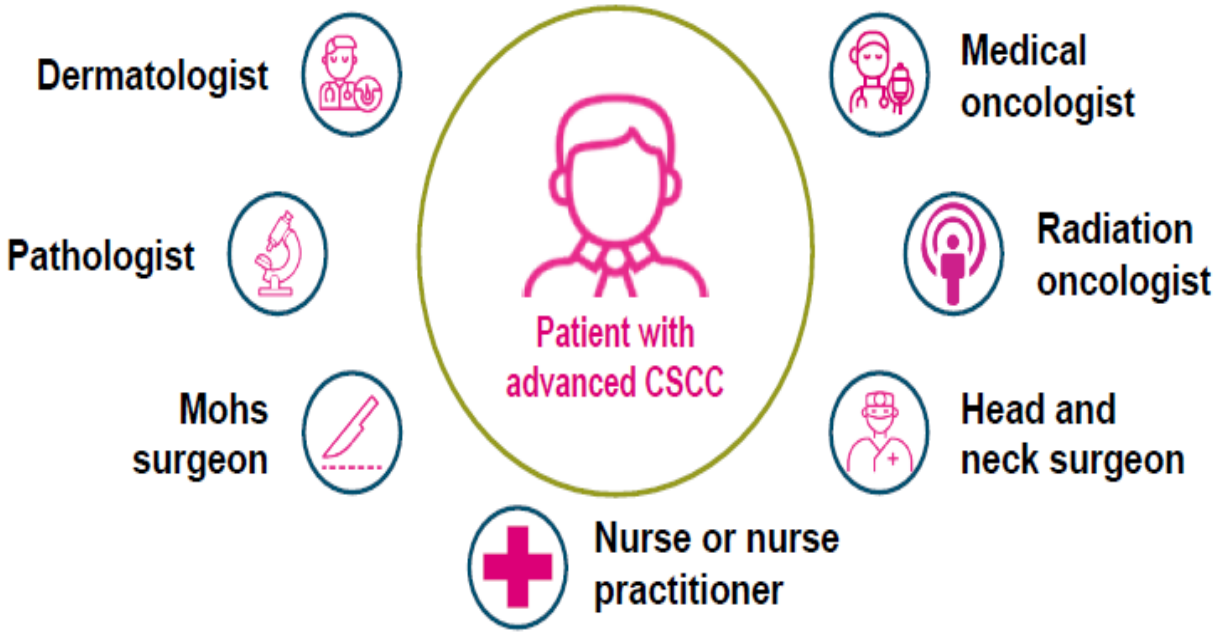
Genomics of Squamous Cell Skin Cancer

Comparison of miR-181a levels in human CSCCs to normal skin shows that miR-181a has a significantly higher expression (~8.4 folds) in CSCCs. Their results show that miR-181a overexpression (OE) and TGFBR3 knockdown (KD) significantly suppresses UV-induced apoptosis in HaCaT keratinocytes and in primary normal human epidermal keratinocytes (NHEKs). In addition, OE of miR-181a or direct KD of TGFBR3 by shRNA is sufficient for enhanced anchorage-independent survival of HaCaTs. Moreover, miR-181a OE or TGFBR3 KD enhances cellular motility through increase of migration and invasion and upregulation of EMT markers, such as *snail*, *slug*, and *vimentin*. Luciferase assay results demonstrate that miR-181a directly and specifically targets the 3'UTR of TGFBR3. Rescue experiments show that miR-181a phenotype can be partially rescued by TGFBR3 overexpression. In summary, they show that miR-181a regulates susceptibility to apoptosis as well as cellular adhesion and motility at least in part through TGFBR3.
Han, J, 2020

Research Program

A Comprehensive Retrospective Electronic Medical Record Review of Cutaneous Squamous Cell Cancer (CSCC) in a High-Risk Sunbelt Population. Epidemiological Evaluation of Patient Risk Factors, Co-morbidities, Phototoxic Drug Utilization and Gross and Pathological Tumor Characteristics to Facilitate Targeted Diagnostics and Patient Care.

A Multidisciplinary Approach Is Key to Assessing Treatment Options for Advanced CSCC*



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Squamous Cell Skin Cancer recommend multidisciplinary tumor board consultation in the management of patients with complicated high-risk tumors, regional recurrence, or development of distant metastases[1]

*The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) do not specify a specific list of disciplines that must be included in a multidisciplinary tumor board.

Reference: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Squamous Cell Skin Cancer V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed June 3, 2019. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org.

Etiology and Epidemiology

- **Ultraviolet radiation from sun exposure is a major risk factor and causes mutations in key genes.**
- **Hedgehog signaling pathway mutations are involved in BCC pathogenesis.**
- **p53 mutations are involved in both SCC and BCC pathogenesis, as well as in the development of actinic keratoses, which are the precursors of SCCs.**

STOPPING CSCC:
Risk Factors for CSCC Recurrence or Metastasis[1,2]*

- **S**ize ≥10 mm on cheeks, forehead, scalp, neck, and pretibial; ≥20 mm on trunk and extremities†
- **T**hickness >6 mm or invasion beyond subcutaneous fat
- **O**rigin of lesion on "mask areas" of the face‡, scars§, hands, and feet
- **P**oorly differentiated
- **P**erineural, lymphatic, or vascular involvement
- **I**mmunosuppression
- **N**eurological symptoms
- **G**rowth in desmoplastic or infiltrative pattern¶

Patients with even a single risk factor are deemed high risk and should be managed more aggressively than those at low risk for recurrence or metastasis[1,3,4]

*Additional risk factors are included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Squamous Cell Skin Cancer.[1] †Excluding pretibial, hands, feet, nail units, and ankles. ‡Central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear §Described as "site of prior RT or chronic inflammatory process" in NCCN Guidelines®.[1] ¶The NCCN Guidelines® include acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarcomatous) subtypes as risk factors. The NCCNGuidelines® do not list "infiltrative pattern" as a risk factor.[1]

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Squamous Cell Skin Cancer V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed June 3, 2019. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. 2. Califano JA, et al. In: Amin MB, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:171-181. 3. Stratigos A, et al. *Eur J Cancer*. 2015;51(14):1989-2007. 4. Baum CL, et al. *J Am Acad Dermatol*. 2018;78(1):141-147.

Most Early-Stage CSCC May Be Curable with Complete Surgical Excision and/or Radiation[1-4]

Common Treatment Options for Early-Stage CSCC[1-3]

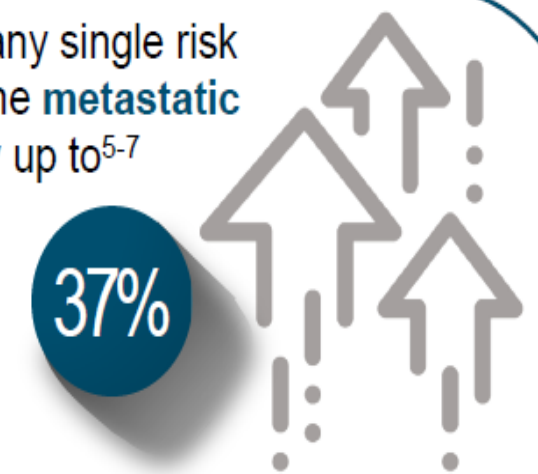
Surgery

- Surgical excision with clear margins
- Curettage and electrodessication
- Cryosurgery
- Mohs micrographic surgery
  (usually for more complicated cases, such as a difficult location)

Radiation Therapy

However, certain risk factors increase the likelihood of recurrence and metastasis[5-8]

The presence of any single risk factor increases the **metastatic potential** by up to[5-7]



and increasing numbers of coincident risk factors correlate with **worse prognosis**[8]

References: 1. Skin cancer treatment (PDQ®). National Cancer Institute website. https://www.cancer.gov/types/skin/hp/skin-treatment-pdq. Updated April 26, 2018. Accessed March 19, 2019. 2. Jennings L, et al. *J Clin Aesthet Dermatol*. 2010;3(4):39-48. 3. Stratigos A, et al. *Eur J Cancer*. 2015;51(14):1989-2007. 4. Califano JA, et al. In: Amin MB, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:171-181. 5. Burton KA, et al. *Am J Clin Dermatol*. 2016;17:491-508. 6. Karia PS, et al. *J Am Acad Dermatol*. 2013;68(6):957-966. 7. Rowe DE, et al. *J Am Acad Dermatol*. 1992;26(6):976-990. 8. Karia PS, et al. *J Clin Oncol*. 2014;32(4):327-334.

Cemiplimab study results

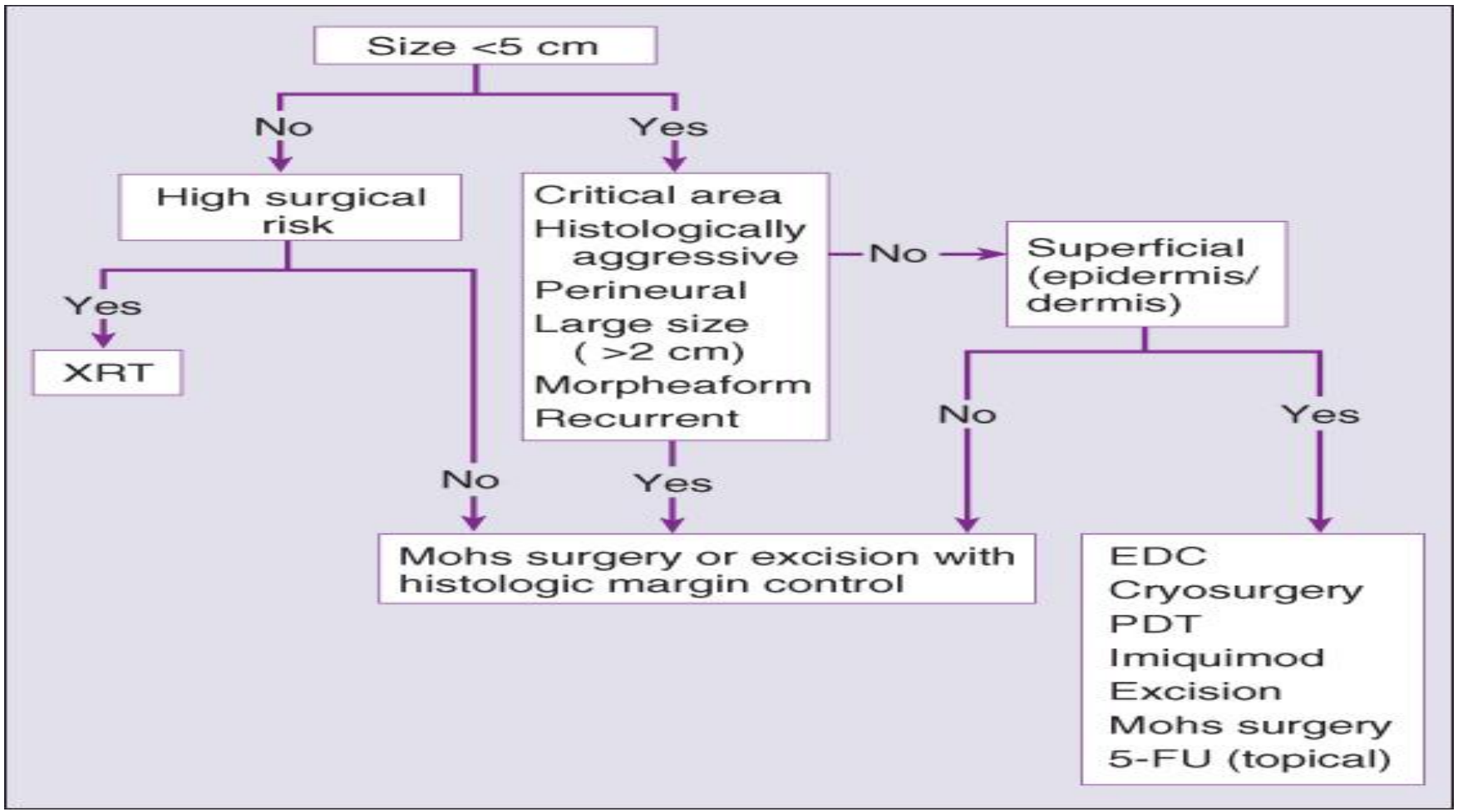
Cemiplimab helped shrink tumors in some clinical trial patients.

In 1 clinical trial of 137 patients with CSCC that had spread or could not be cured by surgery or radiation treated with Cemiplimab*:

63 out of 137 patients (46%)

saw an improvement in their advanced CSCC with Cemiplimab

Treatment for basal cell carcinoma.



Non Melanoma Skin Cancer in the Elderly: A Changing Paradigm?

P048

Gerald Sokol,[1,2] Loretta Loftus ,[3] Jorge Ayub,[2] Thomas Oliver[1]

[1]Uniformed Services University of the Health Sciences, Bethesda, MD, [2]Florida Cancer Specialists & Research Institute, Hudson, FL, [3]Moffitt Cancer Center & Research Institute, Tampa, FL.

Introduction

- The diagnosis and treatment of non melanoma skin cancer (NMSC) in the United States increased by 77% from 1994-2014.[1,2]
- Approximately 90% of NMSCs are associated with exposure to ultraviolet (UV) radiation from the sun.[1,3]
- Basal cell carcinoma (BCC) is the most common type of skin cancer, with an estimated 4.3 million cases of BCC diagnosed in the U.S. each year.[1,4]
- More than 1 million cases of squamous cell carcinoma (SCC), the second most common form of skin cancer, are diagnosed in the U.S. each year.[1,4]
- As population demographics change, the prevalence of certain age-related conditions might be expected to reflect those changes.
- Organ transplant patients are approximately 100 times more likely than the general public to develop SCC.[1,5]
- Regular daily use of sunscreen with SPF 15 or > may reduce the risk of developing SCC by approximately 40%.[1,6]
- The purpose of this study was to determine the change in incidence of SCC and BCC skin cancers in elderly patients and to explore the incidence of other conditions that may be associated with skin cancer in the elderly.

Methods

- 218 Caucasian patients randomly selected from a university affiliated practice from 2016-2018 who received radiation therapy for BCC and SCC skin cancers were evaluated.
- Observational statistics were applied.
- Data were collected for age, gender, frequency of histologic type of skin cancer, and other co-morbid conditions, including but not limited to other cancers, hematologic disorders, and immunologic conditions.

Results

Number of Patients		
	Female	91 (42%)
	Male	127 (58%)
	Total	218 (100%)
Age		
	Mean Age	74.9 Years
	Median Age	76.0 Years
Skin Cancer Type		
	SCC Alone	99 (45%)
	BCC Alone	43 (20%)
	Both SCC & BCC	76 (35%)
Skin Cancer Type by Gender		
	SCC Alone F	41 (52%)
	BCC Alone F	20 (22%)
	Both SCC & BCC F	24 (26%)
	SCC Alone M	52 (41%)
	BCC Alone M	23 (18%)
	Both SCC & BCC M	52 (41%)
Other Associated Conditions		116 (53%) of Patients
	Prostate Cancer	25
	Hematologic Cancer	21
	Head & Neck Cancer	17
	Breast Cancer	15
	Melanoma	14
	Lung Cancer	9
	Renal Transplant	5
	Miscellaneous (HIV, Autoimmune, Other Cancers)	39

Basal Cell Carcinoma

Squamous Cell Carcinoma

Discussion

- The worldwide surge in the incidence of skin cancer during the last two decades has reached “epidemic” proportions, resulting from long, lifetime sun exposure in an increasingly aging population.[7]
- Skin cancer significantly contributes to the overall burden of other comorbid conditions in the elderly population that impacts morbidity, mortality and health-related costs.[8]
- NMSC accounts for at least 80% of all skin cancers, with a prevalence of BCC (70%) over SCC (20%) in the general U.S. population.[9] However, we determined that SCC was significantly more common in the elderly population of our study.
- In addition to intermittent exposure to UV-radiation, other risk factors for development of NMSC include male sex, old age, ionizing radiation, immunosuppression, fair skin phototype (Fitzpatrick I or II), chronic arsenic ingestion, old burn, scar, and family history.[8,10] Our investigation also found that NMSC was more common in males. The majority, 53%, of the patients also had significant co-existing conditions that affect immunity such as cancer patients who receive chemotherapy, radiation and immune therapy, renal transplant patients on immunosuppressive therapy, HIV infection, and autoimmune disorders.
- BCC arises from hair follicle stem cells or from progenitor cells in the inter-follicular epidermis. BCC carcinogenesis is characterized by aberrant activation of the Hedgehog(Hh) signaling pathway involved in cell proliferation, resulting from either genetic inactivation of a transmembrane protein (Patched (PTCH) that keeps proliferation in check or by activating mutations in Smoothened (SMO) proliferation receptor protein.[8,11]
- Cutaneous SCC results from the malignant transformation of keratinocytes of the epidermis and its appendages.[8] Unlike BCC, SCC can spread to loco-regional lymph nodes and to distant metastatic disease sites.[8]
- Immunosuppression as a result of a particular disease or secondary to its treatment is the greatest host risk factor for poor outcomes in patients with cutaneous SCC. Immunosuppressed organ transplant recipients are especially high risk for development of frequent and aggressive tumors.[12] The majority of our patients had at least one other significant disease that was associated with an effect on the immune system either by the disease itself or the treatment. This may partially explain the increased incidence of SCC in both M and F patients in our investigation.

Conclusions

- Skin cancer in the elderly in our population was most frequently squamous cell carcinoma, not basal cell carcinoma.
- M patients tended to have both SCC and BCC more often than F patients.
- Alternately, the use of skin care products by F may have provided a protective effect.
- The majority of patients, 53%, had at least one other significant medical condition which, owing to disease process, aging, and/or therapies affecting immunity, may have impacted on the susceptibility to develop the dermatologic malignancy.
- Elderly patients commonly have “field” cancerization, i.e. wide confluent fields of cancer that make border control for surgery problematic, but lends itself to electron beam radiotherapy that can easily and safely treat wide areas.
- Radiation oncologists should play a leading role in the management of geriatric skin cancer.
- Intensive skin cancer screening in this patient population is warranted.
- Further research with increased numbers and diversity of races will be performed to determine if this trend continues and to further explore an underlying etiology.

References

1. Skin Cancer Foundation. Skin cancer facts & statistics. https://www.skincancer.org/skin-cancer-information/skin-cancer-facts. Accessed 06/06/2018.
2. Mohan SV, Chang AL. Advanced basal cell carcinoma: epidemiology and therapeutic innovations. *Curr Dermatol Rep* 2014;3(1):40-45.
3. Koh HK, Geller AC, Miller DR, et al. Prevention and early detection strategies for melanoma and skin cancer. Current status. *Arch Dermatol* 1996;132(4):436-442.
4. What are basal and squamous cell skin cancers? American Cancer Society. http://www.cancer.org/cancer/skincancer-basalandsquamouscell/detailedguide/skin-cancer-basal-and-squamous-cell-what-is-basal-and-squamous-cell. Accessed 01/31/2018.
5. Lindelof B, Sigurgeirsson B, Gabel H, et al. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol* 2000;143(3):513-519.
6. Green A, Williams G, Neale R, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial. *The Lancet* 1999;354(9180):723-729.
7. Donaldson MR, Coldiron BM. No end in sight: the skin cancer epidemic continues. *Semin Cutan Med Surg* 2011;30(1):3-5.
8. Garcovich S, Colloca G, Sollena P, et al. Skin cancer epidemics in the elderly as an emerging issue in geriatric oncology. *Aging Dis* 2017;8(5):643-661.
9. Rogers HW, Weinstock MA, Feldman, SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population. *JAMA Dermatol* 2012;151:1081-1086.
10. De Vries E, Trakatelli M, Kalabalikis D, et al. Known and potential new risk factors for skin cancer in European populations: a multicenter case-control study. *Br J Dermatol* 2012;167(Suppl 2):1-13.
11. Bonilla X, Parmentier L, King B, et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. *Nat Genet* 2016;48:398-406.
12. Zwald FO, Brown M. Skin cancer in solid organ transplant recipients: advances in therapy and management: part 1. Epidemiology of skin cancer in solid organ transplant recipients. *J Am Acad Dermatol* 2011;65:253.

FULL TEXT ARTICLE

Safety and efficacy of electron beam radiation therapy for epithelial skin cancer in geriatric patients

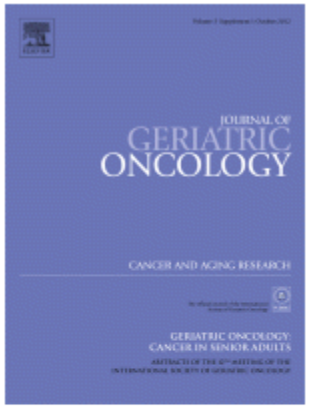
G. Sokol, S. McIntyre, L. Loftus and G. Wright

Journal of Geriatric Oncology, 2012-10-01, Volume 3, Pages S94-S94, Copyright © 2012

Purpose of the Study: Radiation therapy is a well-recognized modality of treatment for squamous and basal cell cancers of the skin. The purpose of this study was to evaluate the response rate, cosmesis, and safety of electron beam radiation therapy in geriatric patients with non-melanoma skin cancers.

Methods: One hundred and two patients with 332 separate epithelial skin cancers were treated definitively with superficial electron beam spray typically utilizing 6 MeV electrons to a depth dose of 90% utilizing topically applied bolus appropriate to the depth and size of the lesion. The ratio of squamous cell carcinomas to basal cell lesions was 1:3 with a small percentage of mixed basal and squamous cell components (~ 4%). The age range extended from ages 60–99 (average age 78, median age 75). Patients were treated with varying fractionation schedules depending on size and depth of invasion from 400 cGy in 12 fractions to 5000 cGy in 25 fractions. Tumor response was evaluated weekly during treatment, monthly after treatment for 2 visits, and every 4 months thereafter indeterminately. Cosmesis was graded on a 1–4 scale with 1 representing excellent cosmesis and 4 representing poor cosmesis. Patients were evaluated for complete or partial response at each visit. 331 of the lesions were stage T1–T3. One lesion was T4.

Results: One hundred and one patients and 331 separate cancers sustained a complete response. A total of 3 patients subsequently failed with recurrent cancer in the treatment site. One of those patients had deep bone invasion (T4) and 2 patients sustained a geographical marginal recurrence. Cosmesis was excellent in 85% depending on initial presentation with respect to size, previous treatment or local tissue damage. Fifteen percent of responses were considered good with no unacceptable cosmetic results. There were no RTOG long term Grade 2 or above complications from treatment. Acute side effects consisted of moist desquamation and/or scabbing which consistently healed within 4–6 weeks or sooner.



Journal of Geriatric Oncology

Volume 3

Conclusions : Electron beam spray radiation results in efficacy and safety comparable to any other form of treatment without the need for surgical intervention. There is no need for discontinuation of anticoagulants and minimal need for bandaging or other post treatment support. The treatment is generally painless, consumes less than 5 min for a treatment, and requires no significant skin or wound care. The only disadvantage is the number of visits required to complete treatment ranging from 10–25 depending on the size and depth of tumor involvement. This form of treatment for epithelial skin cancer represents an excellent noninvasive treatment for geriatric subjects. Surgery, postoperative wound care, suturing, cessation of anticoagulants and antibiotics are essentially unnecessary. X-ray irradiation is unnecessary, and electron beam treatment exposes only the treated area to irradiation.

Most Early-Stage CSCC May Be Curable with Complete Surgical Excision and/or Radiation[1-4]

Common Treatment Options for Early-Stage CSCC[1-3]

Surgery

- Surgical excision with clear margins
- Curettage and electrodessication
- Cryosurgery
- Mohs micrographic surgery
  (usually for more complicated cases, such as a difficult location)

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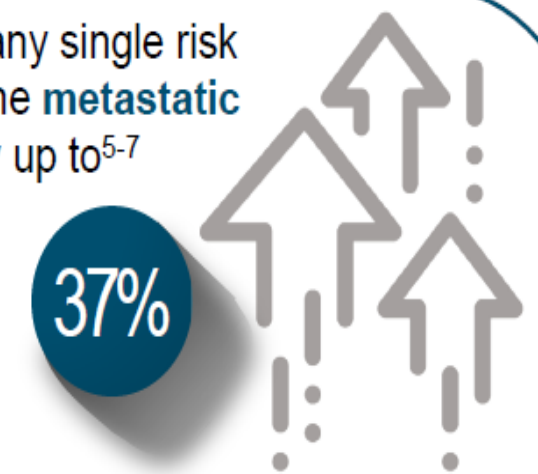

and increasing numbers of coincident risk factors correlate with **worse prognosis**[8]

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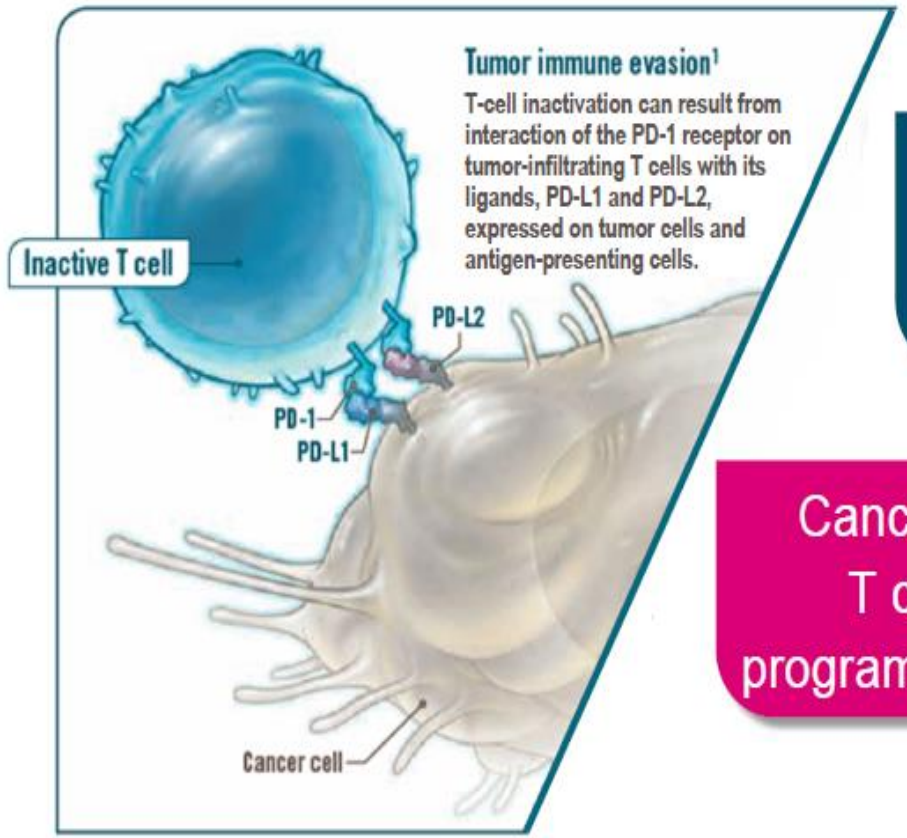
LIBTAYO Helps to Restore the Antitumor T-Cell Response



T cells normally target abnormal cells (including cancer cells) in order to attack and kill them

Cancer cells can avoid being attacked by T cells by using a defense called the programmed death receptor-1 (PD-1) pathway

PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2.

Please see additional Important Safety Information throughout and full Prescribing Information available at this presentation or on the right link for virtual attendees.

Reference: LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc and sanofi-aventis U.S. LLC.

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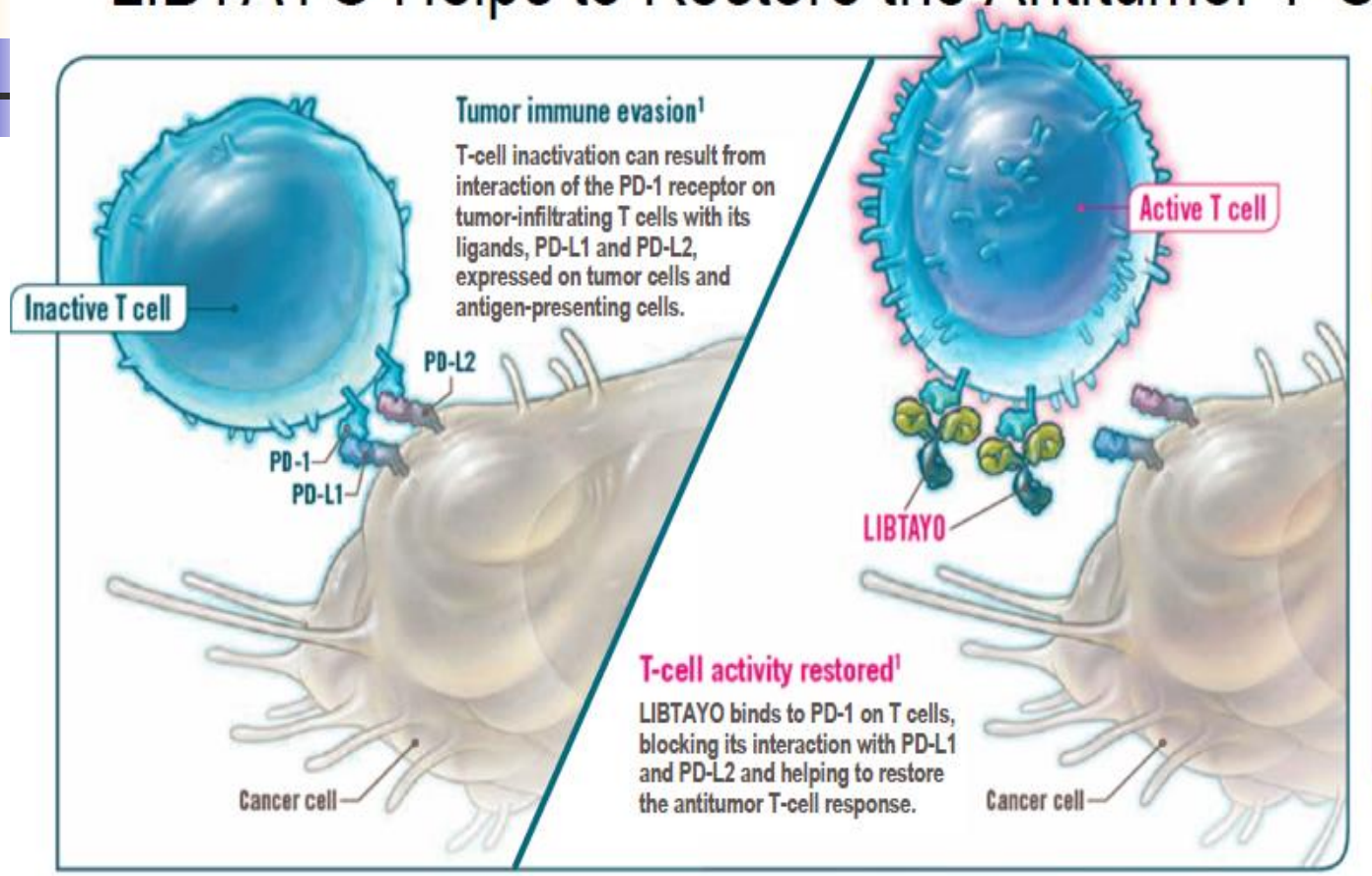
(cemiplimab-rwlc)
Injection 350 mg

LIBTAYO Helps to Restore the Antitumor T-Cell Response



LIBTAYO acts by blocking the PD-1 pathway

LIBTAYO binds to PD-1 on T cells, blocking its interaction with PD-L1 and PD-L2 expressed on tumor cells and helping to restore the antitumor T-cell response

Please see additional Important Safety Information throughout and full Prescribing Information available at this presentation or on the right link for virtual attendees.

LIBTAYO® (cemiplimab-rwlc) Injection 350 mg

Reference: LIBTAYO (cemiplimab-rwlc) injection full U.S. prescribing information. Regeneron Pharmaceuticals, Inc and sanofi-aventis U.S. LLC.

Radiation Drug Interactions

. 2020 Sep 1;108(1):6-16.
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The Promise of Combining Radiation Therapy With Immunotherapy

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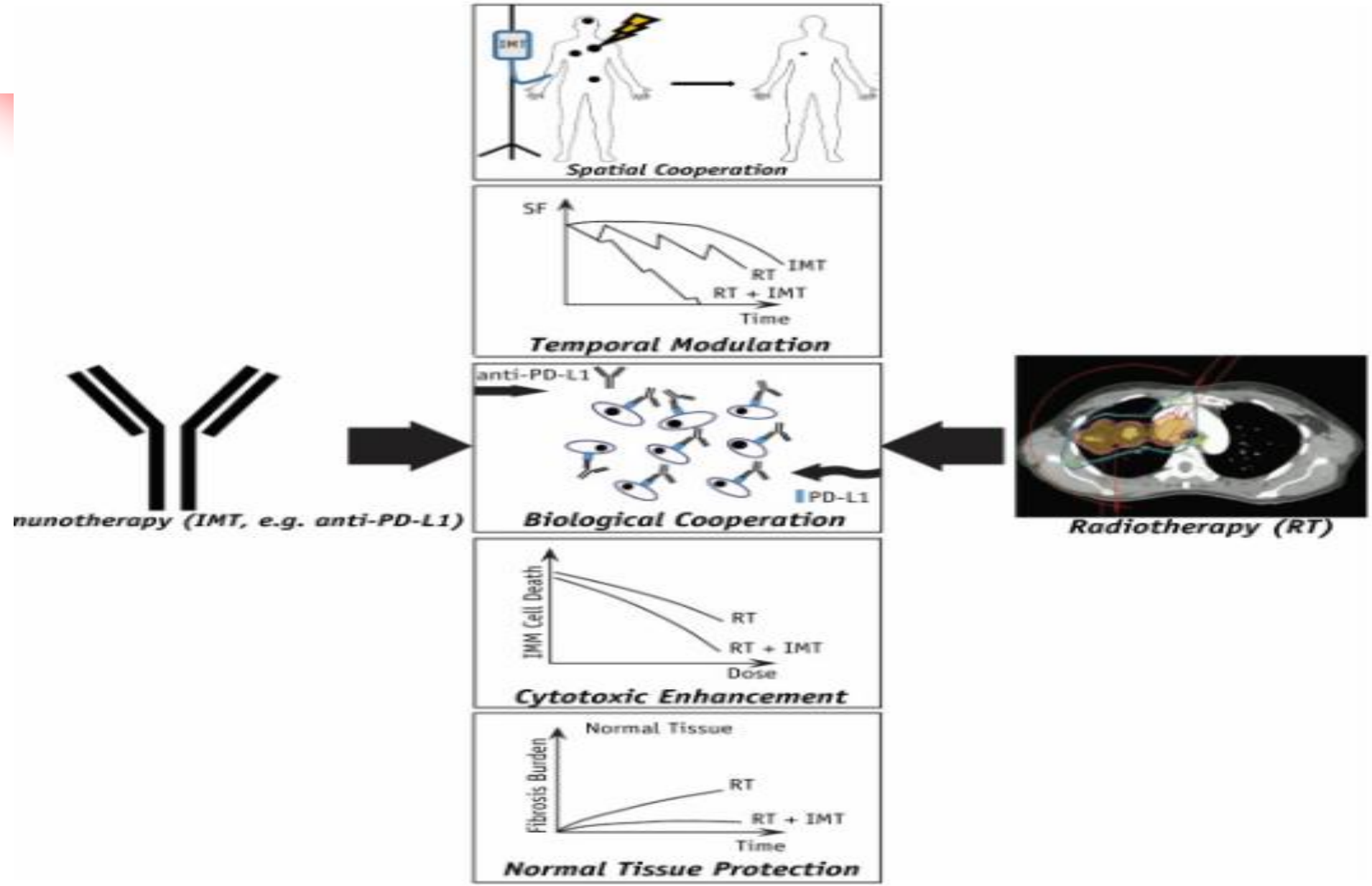
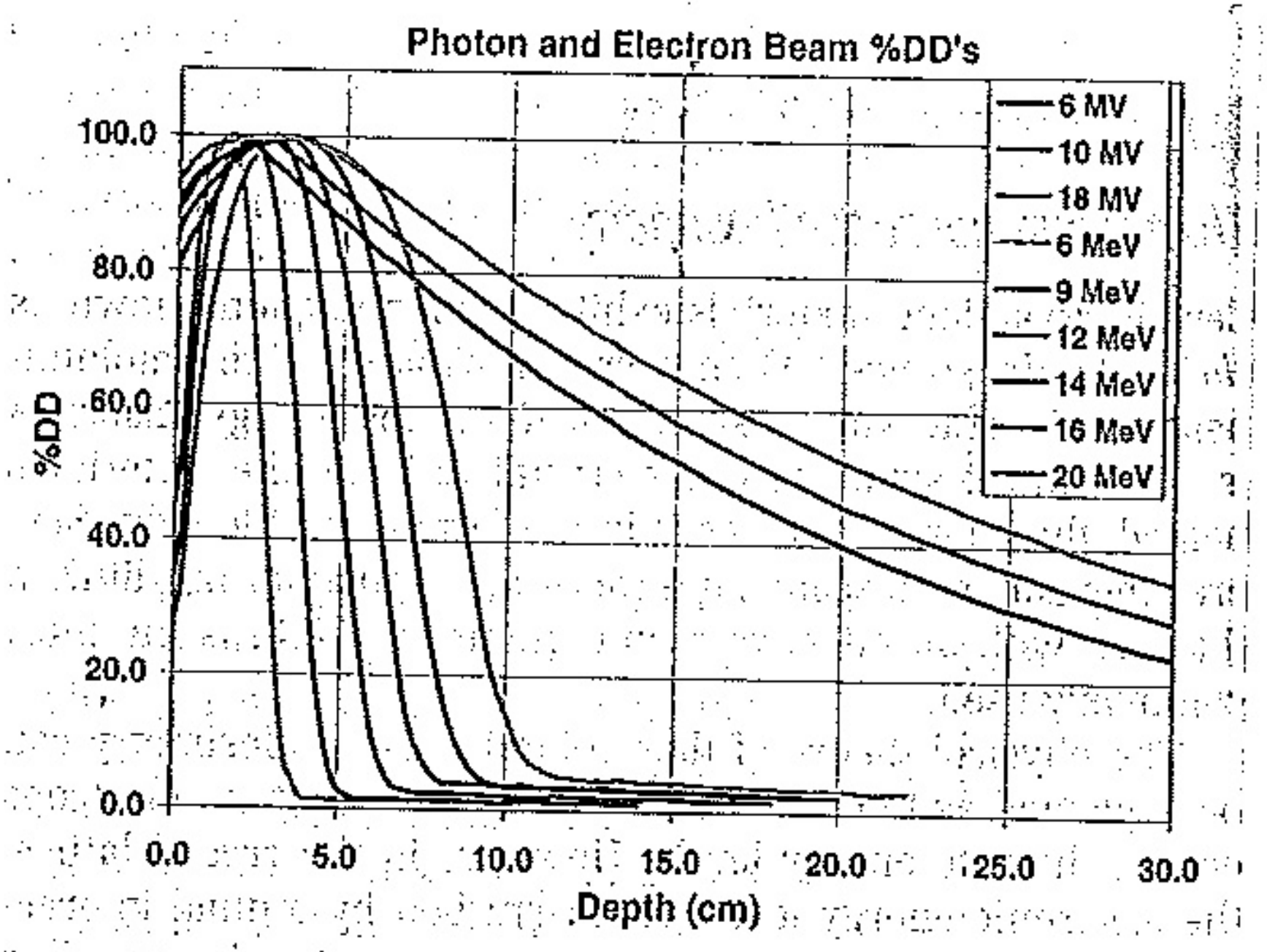
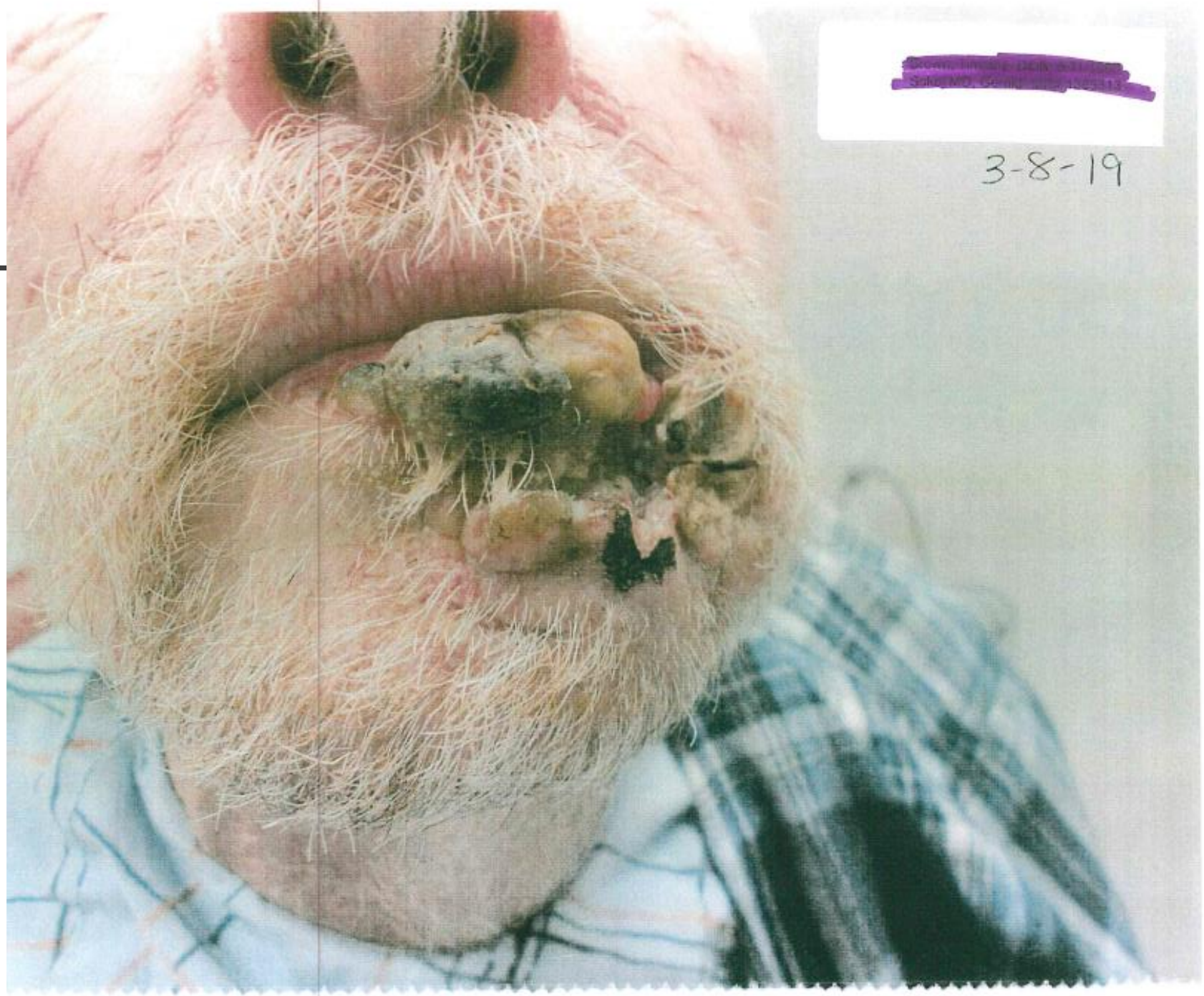
The development of immunotherapy in oncology builds upon many years of scientific investigation into the cellular mechanics underlying interactions between tumor cells and immune cell populations. The past decade has brought an accelerating pace to the clinical investigation of new immunotherapy agents, particularly in the setting of metastatic disease. The integration of immunotherapy into phase 3 clinical trial design has lagged in settings of advanced locoregional disease, where combination with radiation therapy may be critical. Yet, such may be the settings where immunotherapies have their greatest potential to affect patient survival and achieve curative outcomes. In this review, we discuss the interaction of radiation with the immune system and the potential to augment antitumor immunity through combined-modality approaches that integrate radiation and immunotherapies. The dynamics of cellular and tumor response to radiation offer unique opportunities for beneficial interplay with immunotherapy that may go unrecognized with conventional screening and monotherapy clinical testing of novel pharmaceutical agents. Using immune checkpoint blockade as a primary example, we discuss recent preclinical and clinical studies that illustrate the potential synergy of such therapies in combination with radiation, and we highlight the potential clinical value of such interactions. For various immunotherapy agents, their greatest clinical effect may rest in combination with radiation, and efforts to facilitate systematic investigation of this approach are highly warranted.


Spatial Cooperation
SF
IMT
RT
RT + IMT
Time
Temporal Modulation
anti-PD-L1
PD-L1
Biological Cooperation
nunotherapy (IMT, e.g. anti-PD-L1)
Radiotherapy (RT)
IMM Cell Death
RT
RT + IMT
Dose
Cytotoxic Enhancement
Normal Tissue
Fibrosis Burden
RT
RT + IMT
Time
Normal Tissue Protection


Photon and Electron Beam %DD's
100.0
80.0
60.0
40.0
20.0
0.0
%DD
0.0
5.0
10.0
15.0
20.0
25.0
30.0
Depth (cm)
6 MV
10 MV
18 MV
6 MeV
9 MeV
12 MeV
14 MeV
16 MeV
20 MeV



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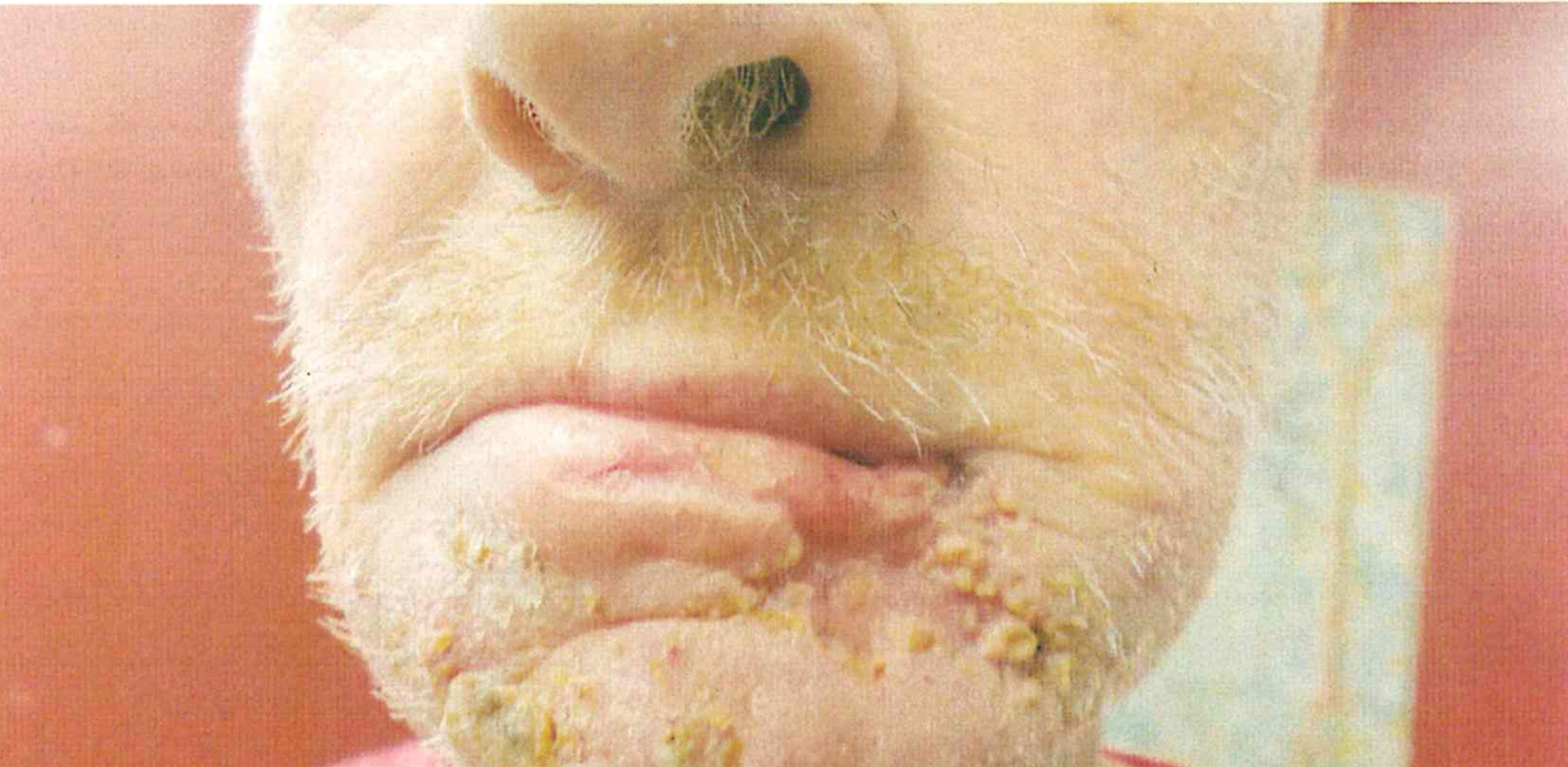

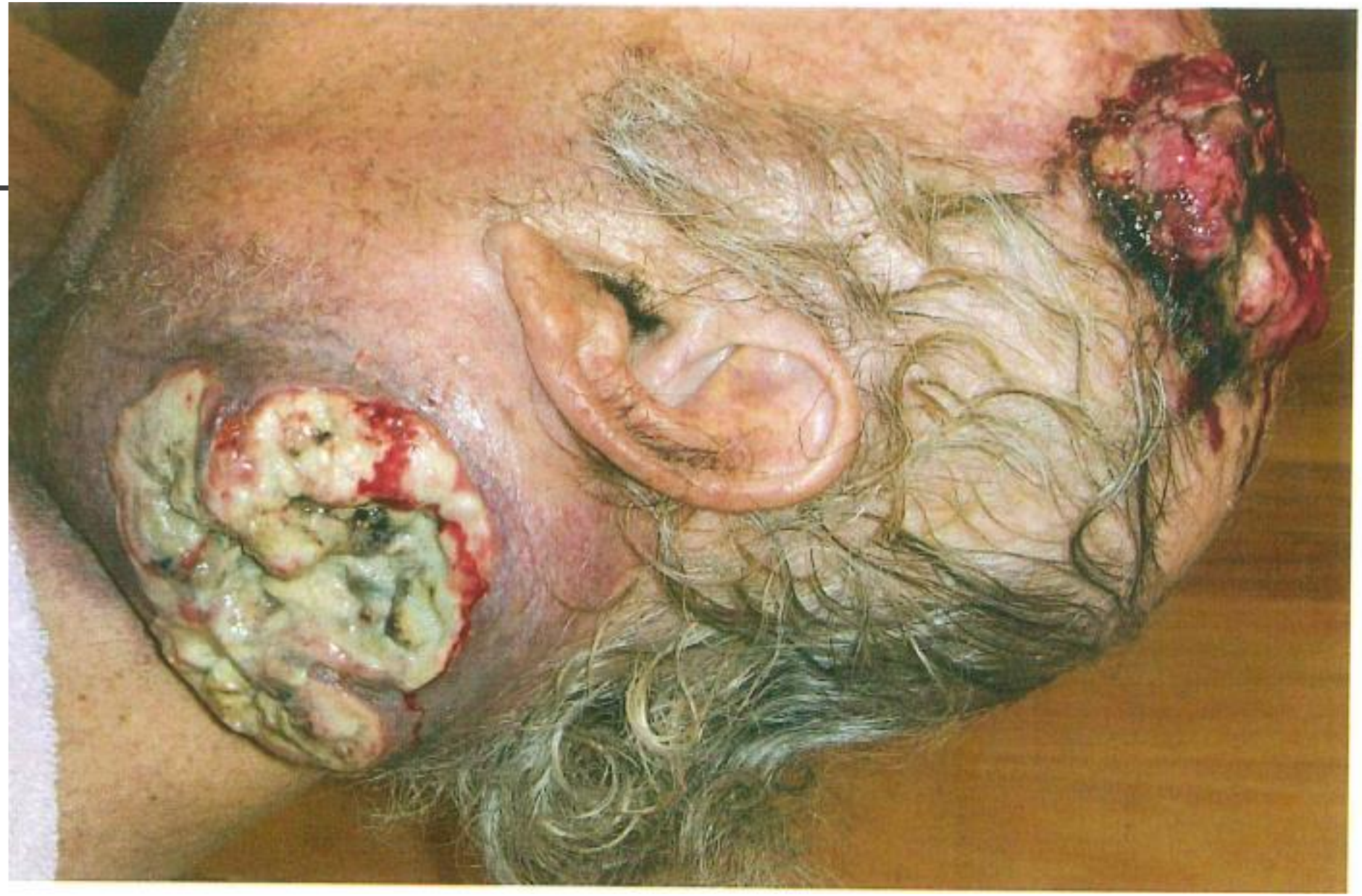

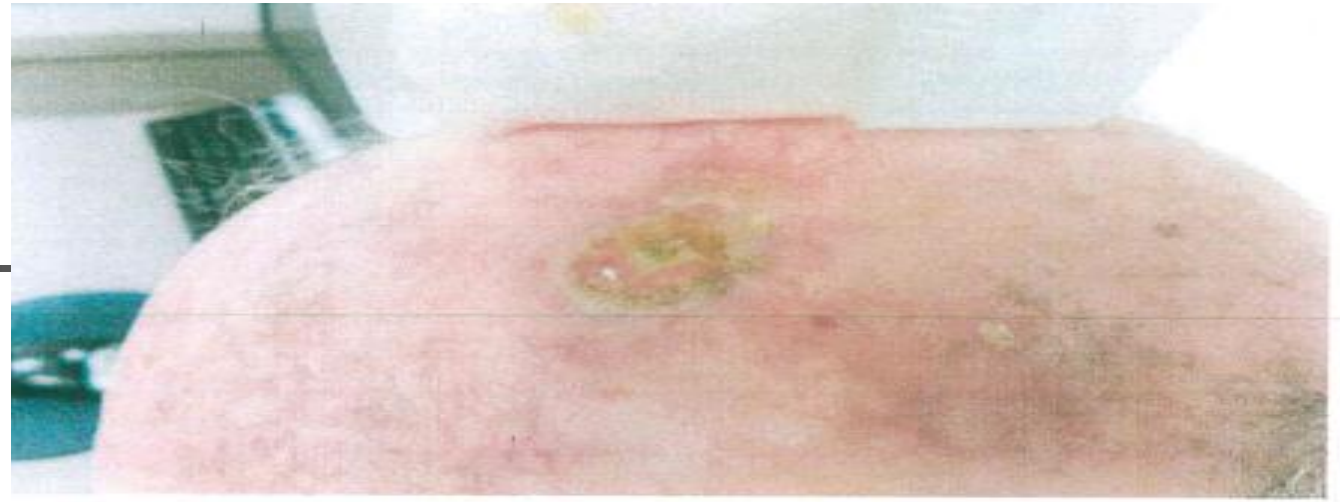

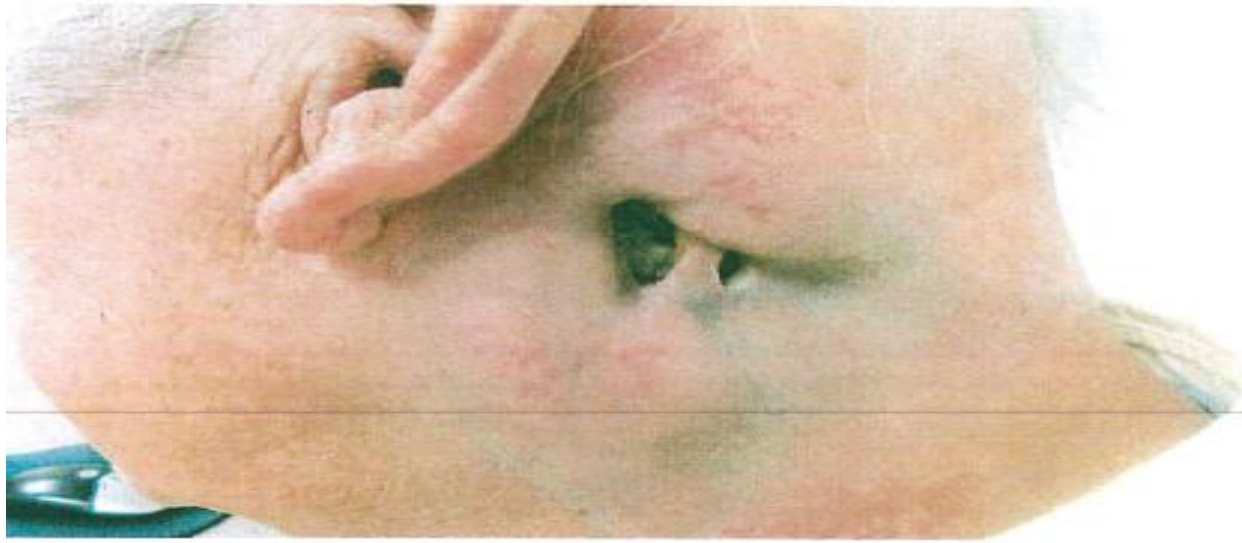

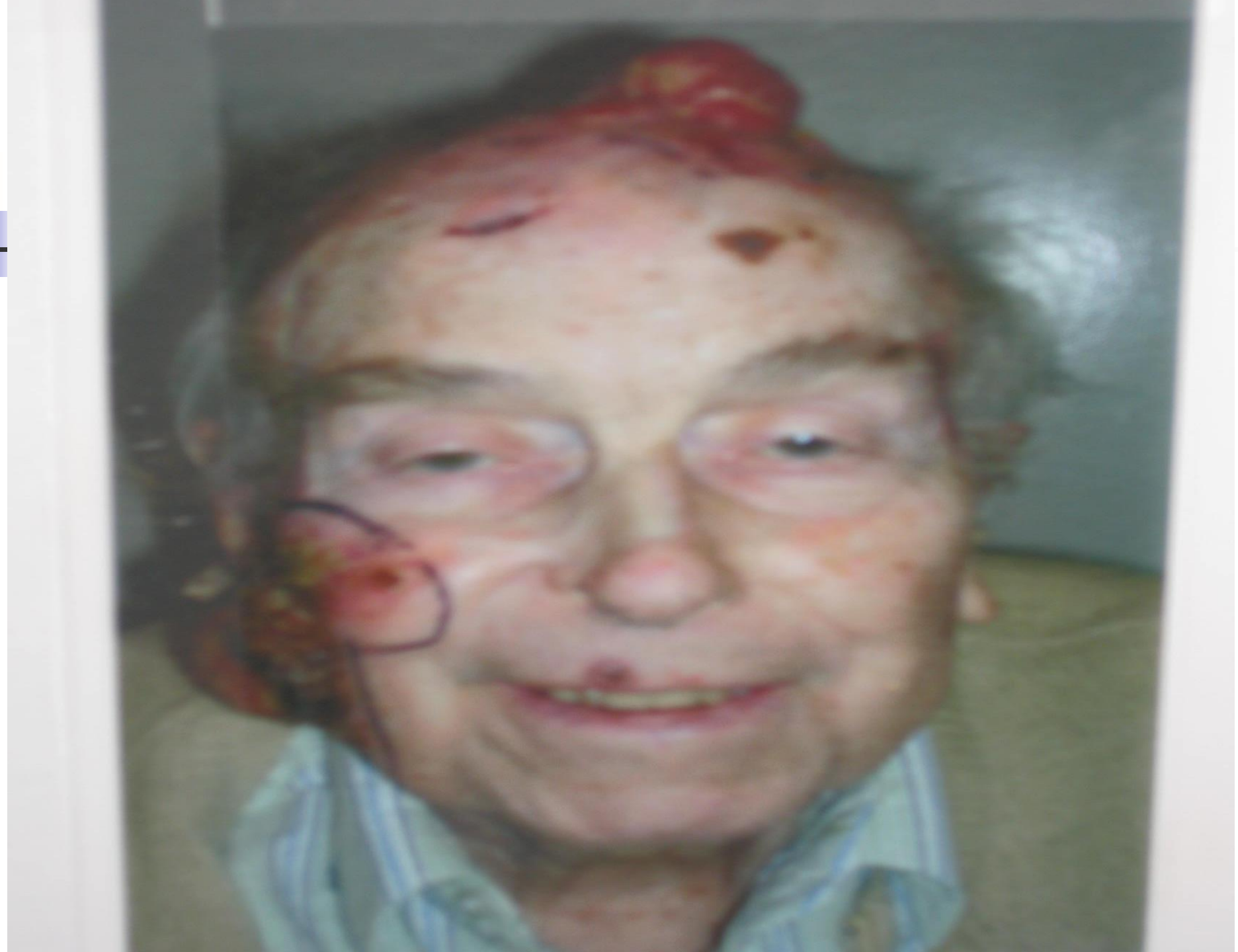

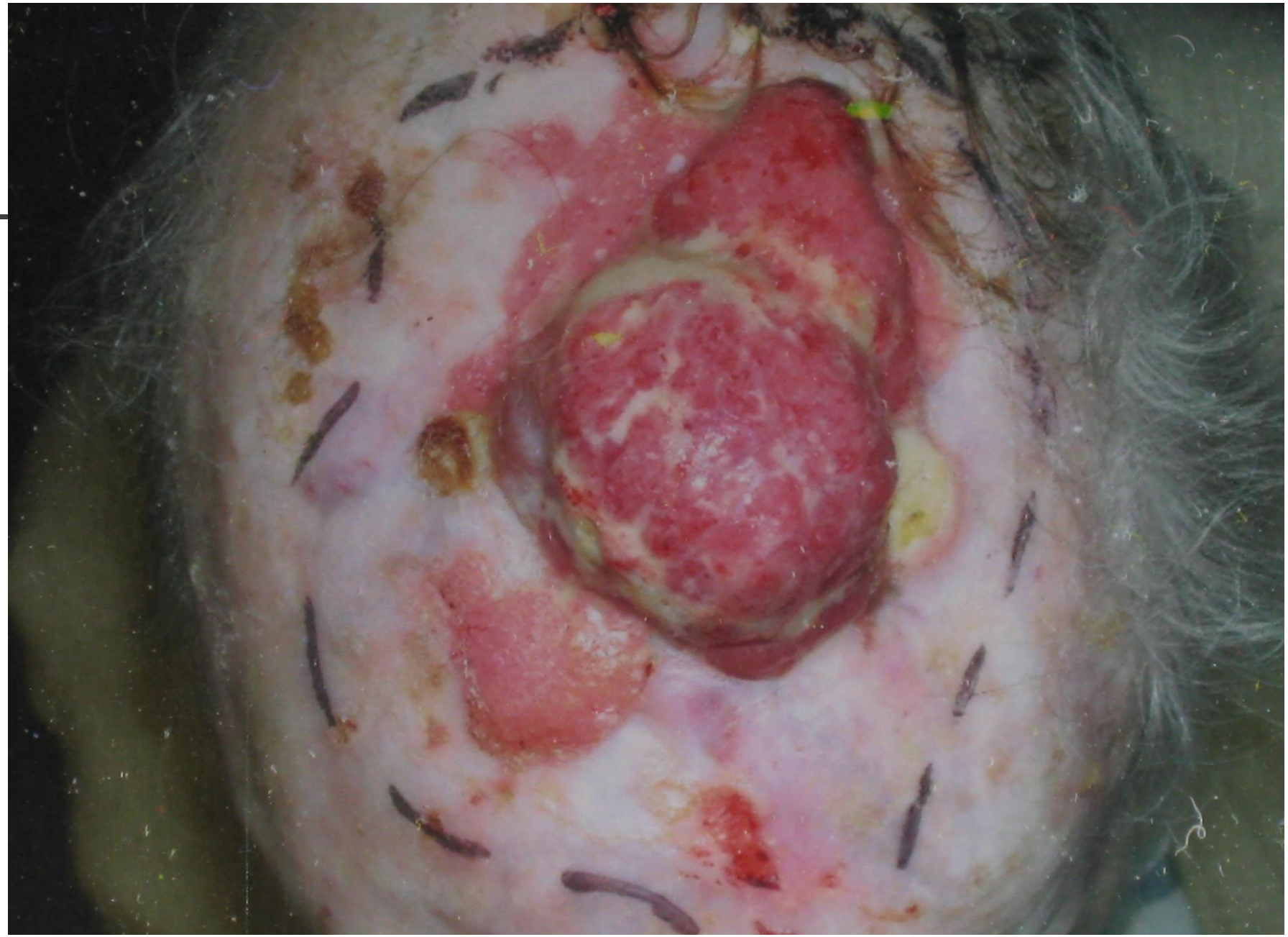

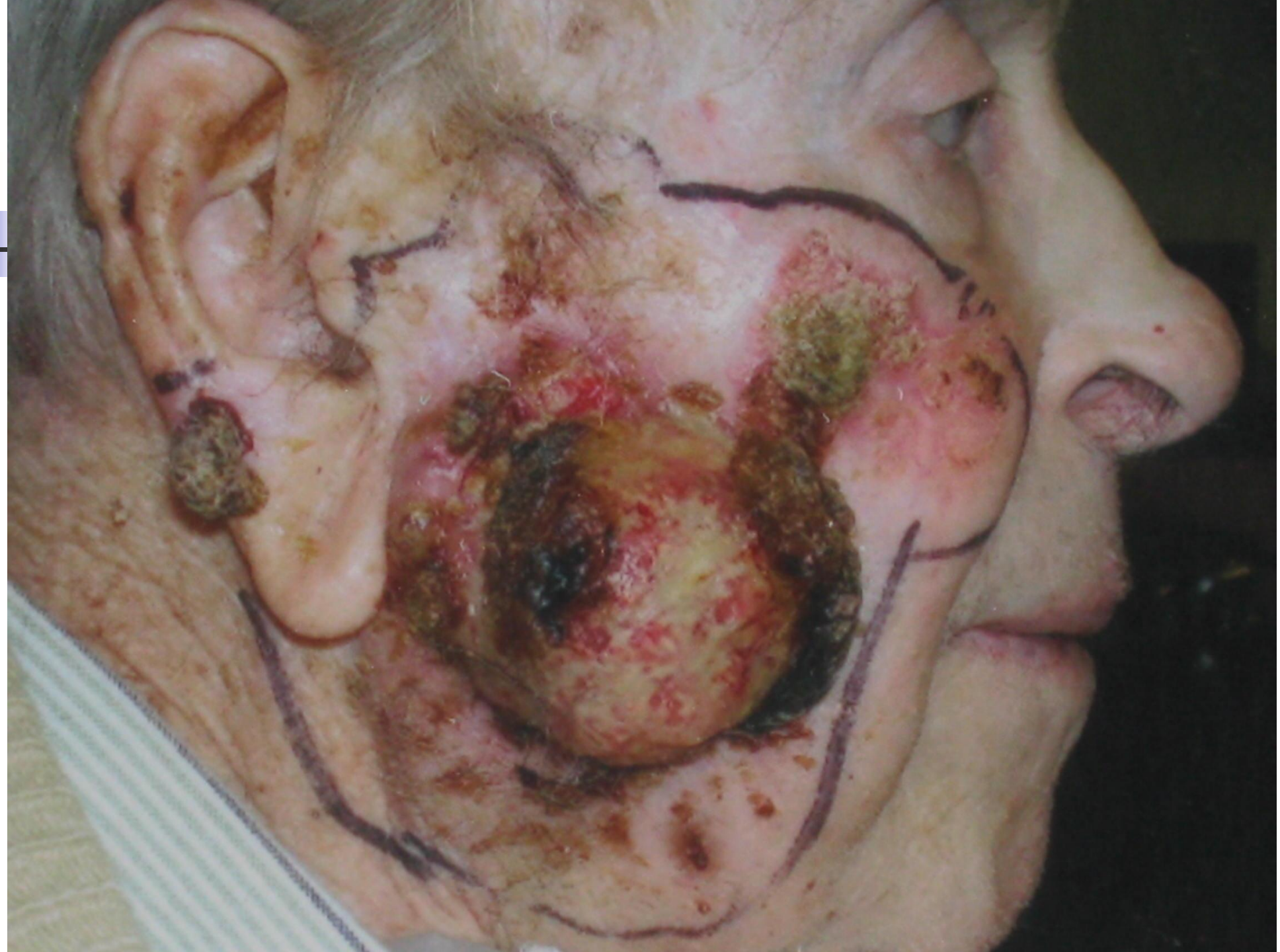

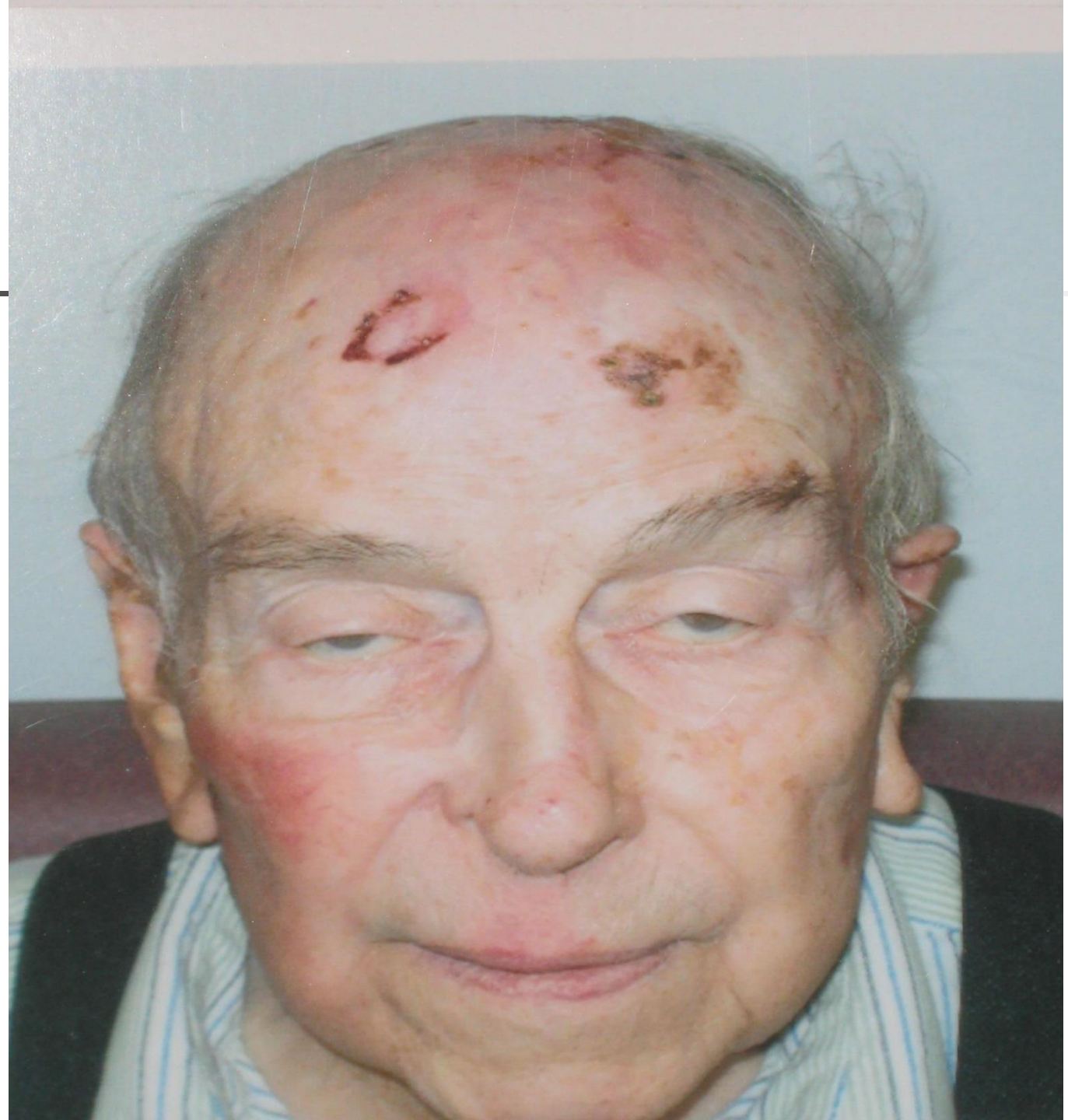

Conclusions:

1.UV is a dangerous cause of skin cancer worsened by photosensitizing drugs

2. The skin cancer team must work together

3. Immunotherapy is a potent new treatment for both Basal Cell and Squamous cell cancers

4. Radiotherapy has profound and equal curative potential for skin cancer without surgery, bleeding, significant infection, or prolonged healing times with excellent cosmesis

May the fleas of a thousand camels infest the crotch of the person who screws up your day and may their arms be too short to scratch...