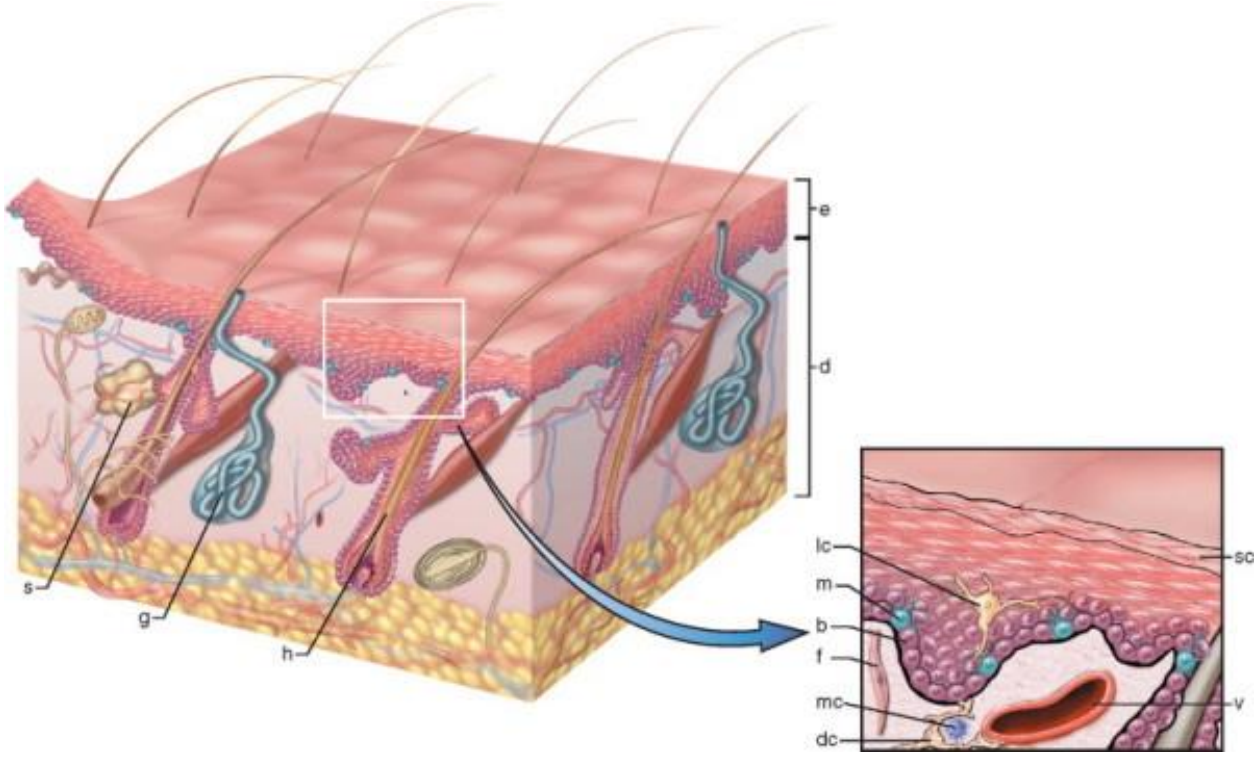
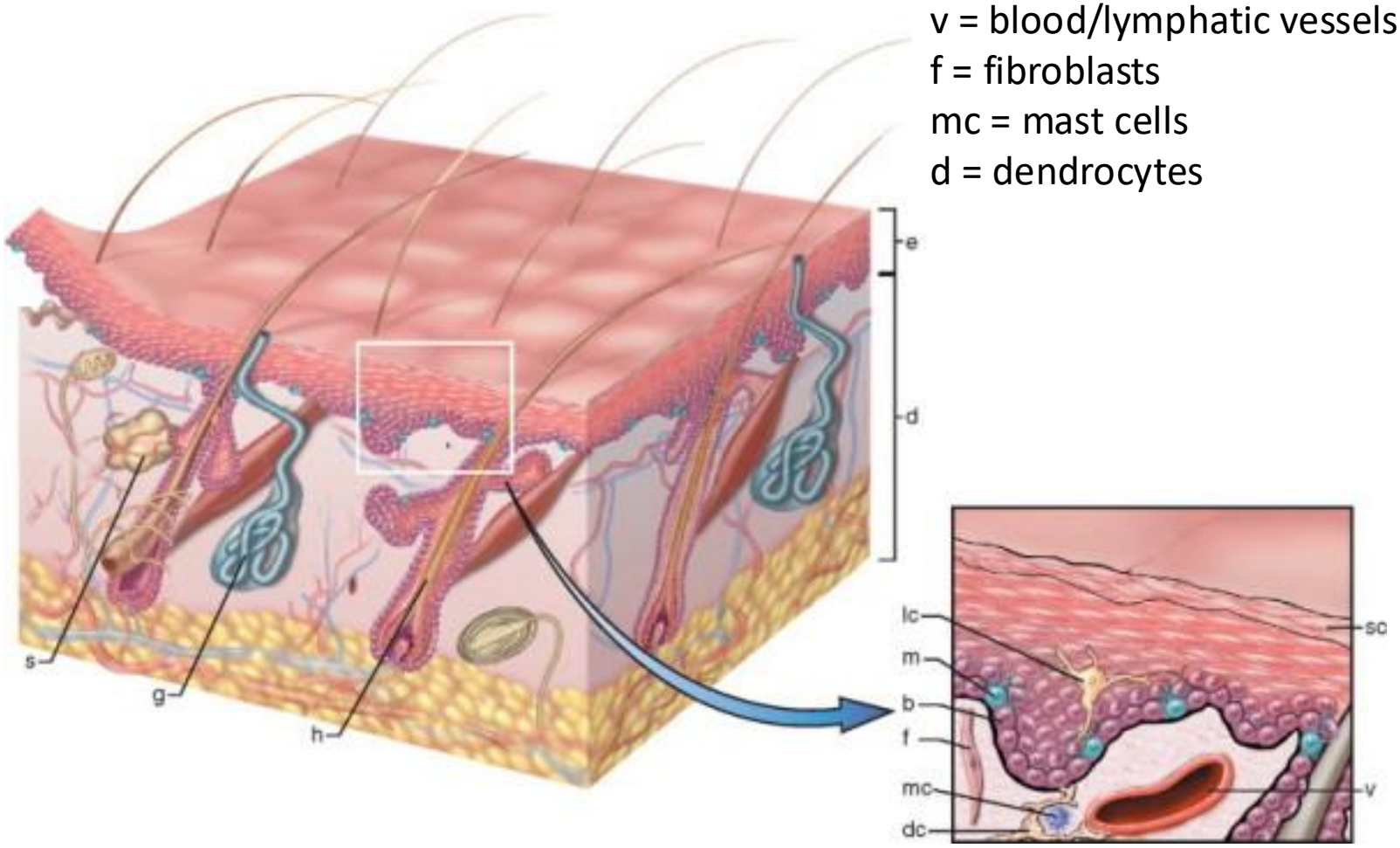
# Skin Cancer




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e = epidermal layer, 0.05-0.15 mm
includes:
b = basal cells
sc = stratum corneum
m = melanocytes or Merkel cells
lc = Langerhans cells

d = dermal layer, 1-2 mm
projecting from epidermis:
h = hair follicles
g = sweat glands
s = sebaceous glands
includes:
v = blood/lymphatic vessels
f = fibroblasts
mc = mast cells
d = dendrocytes



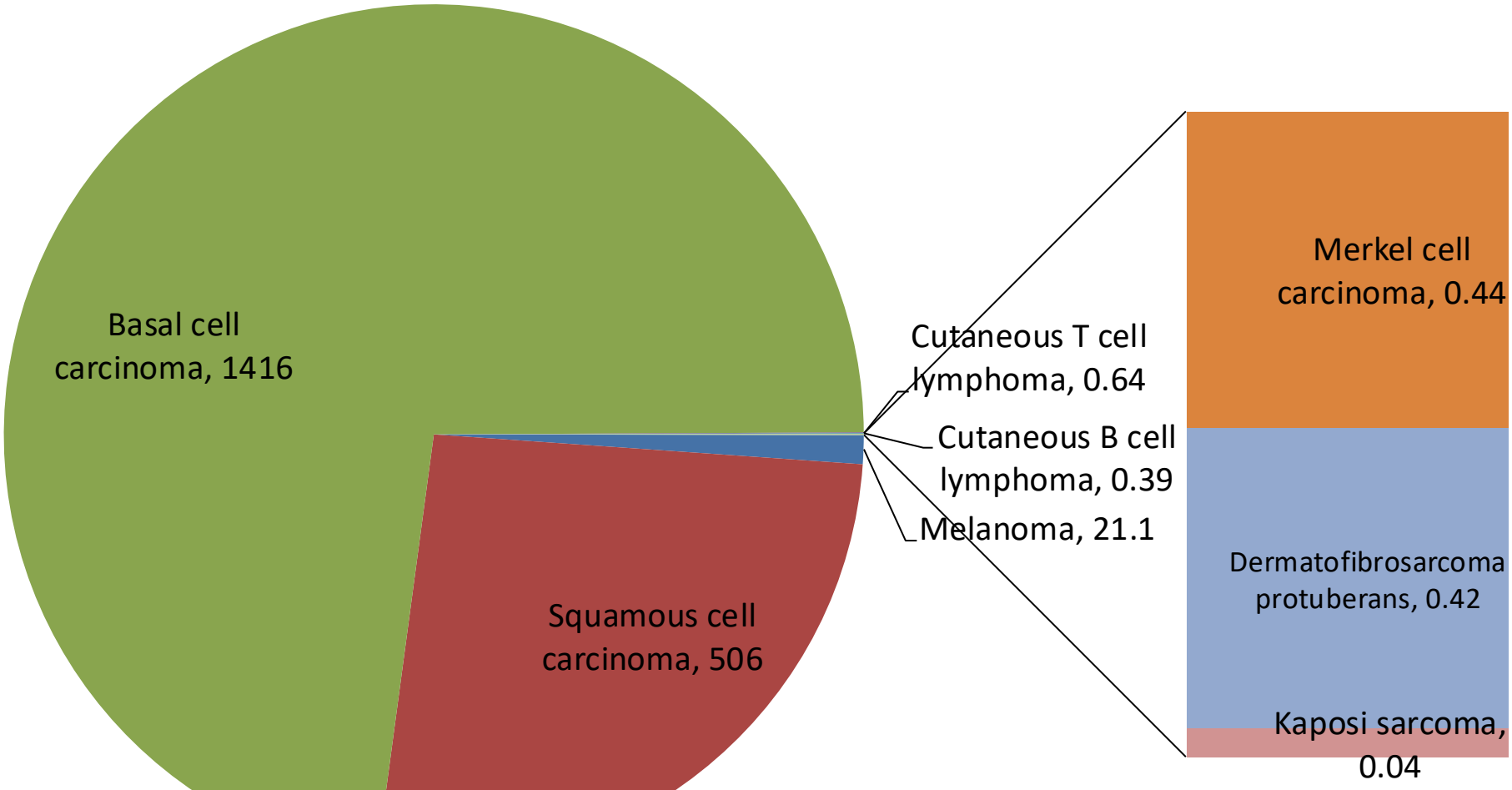

From Robbins and Cotran, Pathologic Basis of Disease, 8th edition

# “Skin Cancer”

- Cancer that forms in the tissues of the skin
- Types of skin cancer:
  - **Squamous cell carcinoma**: cancer that forms in squamous cells (flat cells that form the surface of the skin)
  - **Basal cell carcinoma**: cancer that forms in the lower part of the epidermis (the outer layer of the skin)
  - **Adnexal carcinoma**: cancer that forms from eccrine, apocrine or sebaceous glands (sweat glands)
  - **Melanoma**: cancer that forms in melanocytes (skin cells that make pigment)
  - **Merkel cell carcinoma** (neuroendocrine carcinoma of skin): cancer that forms in neuroendocrine cells (cells that release hormones in response to signals from the nervous system)
  - **Sarcoma**: cancer that forms in muscle, blood vessel or connective tissue cells (cells that support the skin)
  - **Lymphoma**: cancer that forms in lymphocytes (immune cells)

http://www.cancer.gov/cancertopics/types/skin

# Incidence of Skin Cancers (per 100k)




Eide MJ and Weinstock MA, "Epidemiology of Skin Cancer," in Cancer of the Skin, 2011

# Scope of the Problem

- >1 million cases of non-melanoma skin cancer/year in USA
  - More common than all other cancers combined
  - 1 in 5 Americans will develop skin cancer
  - <1000 deaths
- Rogers et al. recently estimated the total number of non-melanoma skin cancers in the US population at 3507693 in 2152500 people in 2006
  - A significant increase in procedures for skin cancer noted over the 15 year period (1992-2006)

http://www.cancer.gov/cancertopics/types/skin

# Number of Procedures and of Age-Adjusted Procedures for All Skin Cancers in the Medicare Fee-for-Service Population

**Table 1. Number of Procedures and of Age-Adjusted Procedures for All Skin Cancers in the Medicare Fee-for-Service Population**

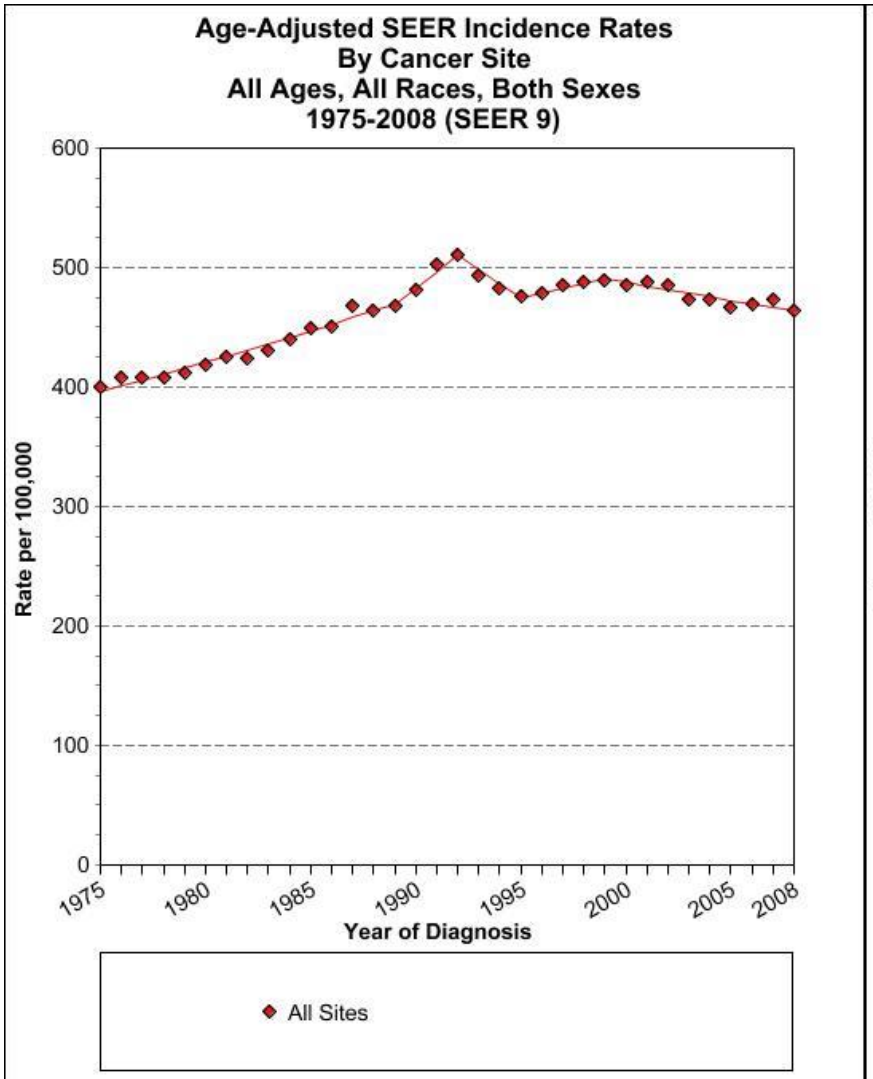
| Year | Total Skin Cancer Procedures | Age-Adjusted Procedure Rate per 100 000 Beneficiaries | Procedures to Treat NMSC, % |
|---|---|---|---|
| 1992 | 1 158 298 | 3514 | NA |
| 1996 | 1 377 741 | 4136 | NA |
| 1997 | 1 450 746 | 4400 | NA |
| 1998 | 1 473 728 | 4521 | NA |
| 1999 | 1 497 444 | 4647 | NA |
| 2000 | 1 577 165 | 4947 | NA |
| 2001 | 1 694 913 | 5173 | NA |
| 2002 | 1 785 136 | 5312 | 92.6 |
| 2003 | 1 834 443 | 5322 | 93.8 |
| 2004 | 1 905 121 | 5477 | 92.7 |
| 2005 | 2 007 826 | 5772 | 92.4 |
| 2006 | 2 048 517 | 6075 | 93.7 |

Abbreviations: NA, not available; NMSC, nonmelanoma skin cancer.

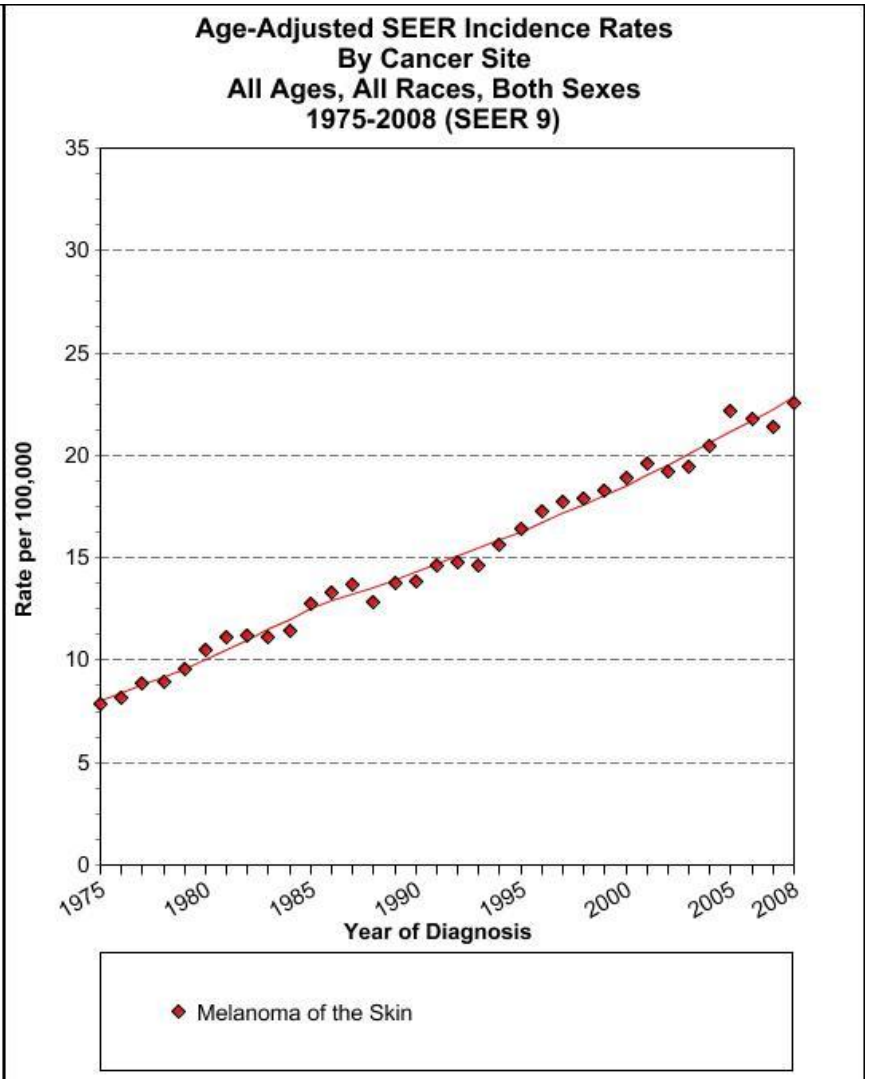
**Rogers, H. W. et al. Arch Dermatol 2010;146:283-287.**

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ARCHIVES OF DERMATOLOGY




Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute.




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http://seer.cancer.gov

# Risk Factors for Skin Cancer

| Risk Factor | Melanoma | Non-Melanoma Skin Cancer |
|---|---|---|
| Age | Older | Older |
| Family History | 1st/2nd degree relative<br>Familial atypical mole melanoma syndrome (FAMMS) | Family history linked to BCC, but not SCC |
| Gender | Male (slight) | Male (substantial) |
| Race | Whites | Whites |
| Skin type | Fair complexion, red hair, burn easily, tan poorly, freckled | Fair complexion |
| Nevi | Large # melanocytic nevi<br>Giant pigmented congenital nevi | Limited influence on risk |
| Smoking | | SCC (probably) |
| Occupation | Indoor workers of higher education and income | Outdoor workers |

Naldi L et al "Etiologic Factors in Skin Cancer," in Cancer of the Skin, 2011

# Risk Factors for Skin Cancer

| Risk Factor | Melanoma | Non-Melanoma Skin Cancer |
|---|---|---|
| Cumulative sun exposure | Head and neck primary | SCC (greatest risk factor)<br>BCC (head and neck primary) |
| Episodic sun exposure | Intense, intermittent exposure and blistering sunburns in youth | Intense, intermittent exposure and blistering sunburns in youth (for BCC, but not SCC) |
| Artificial UV | PUVA and tanning beds (probably) | PUVA, UVB, tanning beds |
| Ionizing radiation | Possibly | BCC (definite), SCC (probable) |

Naldi L et al "Etiologic Factors in Skin Cancer," in Cancer of the Skin, 2011
Solan M and Brady LW "Skin Cancer," in Clinical Radiation Oncology, 5th edition, 200

# Risk Factors for Skin Cancer

| Risk Factor | Melanoma | Non-Melanoma Skin Cancer |
|---|---|---|
| Gene mutations | *BRAF, NRAS, KIT, CDKN2A/p16, CDK4, MCR1, PTEN, BRCA2* | *PTCH* (BCC), *SHH* (BCC), *TP53* (BCC and SCC) |
| Genetic syndromes | | Syndromes: Gorlin's/basal cell nevus (BCC), Li-Fraumeni, xeroderma pigmentosum (SCC), Bazex (BCC), Muir-Torre, Rombo, oculocutaneous albinism, epidermodysplasia verruciformis, dystrophic epidermolysis bullosa, porokeratosis |
| Viruses | | HPV (possible), HHV8 (KS), polyomaviruses (MCC) |

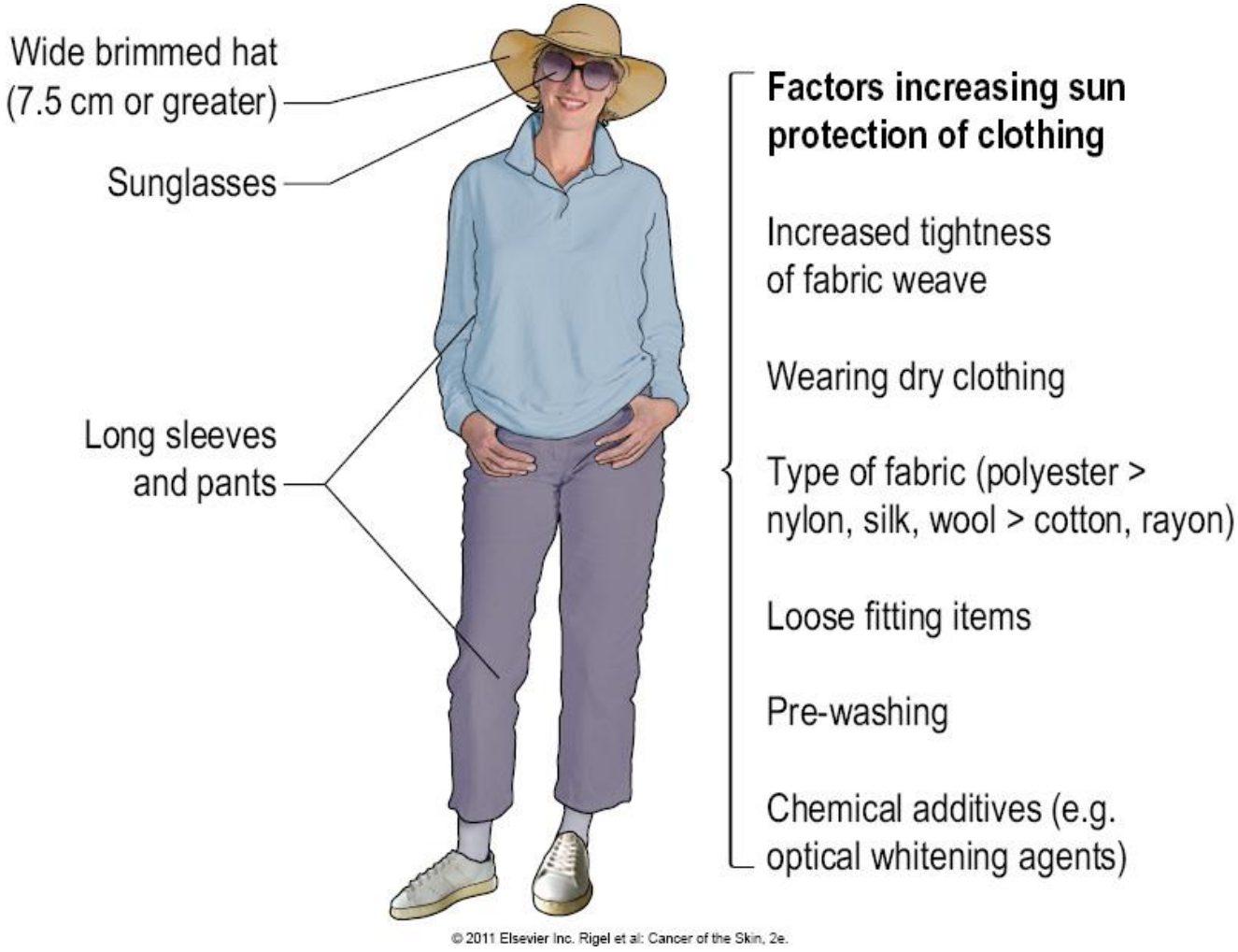
Naldi L et al "Etiologic Factors in Skin Cancer," in Cancer of the Skin, 2011
Solan M and Brady LW "Skin Cancer," in Clinical Radiation Oncology, 5th edition, 200

# Risk Factors for Skin Cancer

| Risk Factor | Melanoma | Non-Melanoma Skin Cancer |
|---|---|---|
| Immune suppression | Organ transplant recipient, chronic corticosteroid use | Organ transplant recipient (SCC>BCC, KS, MCC), HIV (KS, NMSC, MCC), pediatric cancer, CML, CLL, chemotherapy, SLE, RA, anti-TNF |
| Chemicals | Arsenic (possible) | Arsenic, polycyclic aromatic hydrocarbons, mineral oils, hexachlorobenzene, polychlorinated biphenyls |
| Chronic inflammation | | Lichen sclerosis, cutaneous tuberculosis |
| Prior skin cancer | NMSC, melanoma | NMSC |
| Diet | Higher BMI | Beta-carotene does not protect |

Naldi L et al "Etiologic Factors in Skin Cancer," in Cancer of the Skin, 2011

# Preventing Skin Cancer




© 2011 Elsevier Inc. Rigel et al: Cancer of the Skin, 2e.

Exposure to UVB (from sun) is most common, and preventable cause of skin cancer

# Clinical Presentation

- Symptom (that patient reports):
  - Rash, bump, lump, or lesion
  - Enlarged lymph nodes
  - Anesthesia, paresthesia (formication, burning, stinging, shooting pain), facial muscle weakness, ptosis, diplopia, blindness, stroke
- Sign (on physical exam):
  - Rash, bump, lump, or lesion
  - Lymphadenopathy
  - Neurologic deficits

# Detection and Diagnosis

- Physical exam:
  - Describe the rash/bump/lump/lesion
  - Total skin examination
  - Assess for local-regional spread:
    - Examine regional lymph nodes
    - Neurologic examination for perineural invasion
- Imaging:  As clinically warranted (CT, MRI, PET)
- Laboratory studies:  As clinically warranted
- Biopsy:  Necessary and dictates treatment!

# Premalignant Lesions
# Risk of Progression and Treatment

- Actinic (solar) keratosis
  - On sun exposed areas, in multiple locations
  - Progress to SCC in 1% (lifetime risk of 6-10%)
  - Treatment: excision, cryotherapy, EDC, dermabrasion, laser, topical chemotherapy
- Bowen's disease (squamous cell carcinoma in situ)
  - On sun exposed areas, single or multiple, sharp demarcation
  - Progress to SCC in 5-20%
  - Treatment: surgery (preferred), **RT** (45-56 Gy/13-28 fractions)
- Keratoacanthoma
  - Can coexist with SCC, grow rapidly and destroy large volumes of tissue
  - Treatment: consider **RT** 35-60 Gy/12-24 fractions
- Lentigo maligna (melanoma in situ)
  - On sun exposed areas, in elderly, may progress to melanoma
  - Treatment: surgery, cryotherapy, **RT** (45-50 Gy/15-20 fractions)
- Nevi (dysplastic and congenital)
  - Associated with risk of melanoma; if >2 cm, risk of progression to melanoma is 20%
  - Treatment: surgery

# 2010 AJCC Staging Systems for "Skin Cancer"

- Cutaneous Squamous Cell and other Carcinomas
- Melanoma of the Skin
- Soft tissue sarcoma (excluding Kaposi sarcoma and desmoid tumor) *including dermatofibrosarcoma protuberans and angiosarcoma*
- Merkel Cell Carcinoma
- Carcinoma of the Eyelid
- Primary Cutaneous Lymphoma

# Basal Cell Carcinoma

- Also called “rodent ulcer” because ability to burrow deeply, infiltrating vital structures
  - Smooth raised pearly nodule with central depression from necrosis
  - Bleed with minor trauma
- Usually on hair-bearing skin of head and neck (may infiltrate deeply in “H-zone” of face)
- Rarely metastasize (to lymph nodes or distant)
- Subtypes: Nodular, Superficial, Pigmented, Microndular, *Morpheaform infiltrating, *Morpheaform desmoplastic, *Morpheaform sclerosing (deep, diffuse dermal infiltration, sparing skin surface)
- Risk factors for recurrence (usually within 3 years): Larger size, Location, Poorly defined borders, Recurrent, Immunosuppressed, Site of prior RT, *Aggressive histology (morpheaform types), Multifocal, Perinerual invasion

# Squamous Cell Carcinoma

- Round-to-irregular, plaquelike or nodular, overlaid with warty keratotic scale or conical keratinized cutaneous horn
- Invasion of subcutis into muscle, bone, along periosteum, perineural and lymphovascular spaces
- Nodal and distant metastasis occurs in 10%
- 70% 3-year disease specific survival with: ≥4 cm tumor, perineural invasion, invasion beyond subcutis (100% DSS without these)
- Clinical risk factors for recurrence: tumors size, location, poorly defined border, recurrent tumor, immunosuppression, site of prior RT, site of chronic inflammatory process, rapid tumor growth, neurologic symptoms
- Histologic factors for recurrence: moderate-to-poorly differentiated (acantholytic), adenosquamous or desmoplastic histology, deep invasion (Clark IV-V, ≥4 mm), perineural or lymphovascular invasion

# 2010 AJCC Staging System, 7th Edition cSCC/Other Cutaneous Carcinoma

| CLINICAL *Extent of disease before any treatment* | STAGE CATEGORY DEFINITIONS | PATHOLOGIC *Extent of disease through completion of definitive surgery* |
|---|---|---|
| ❑ y clinical–staging completed after neoadjuvant therapy but before subsequent surgery | TUMOR SIZE: _____ LATERALITY: ☐ midline ☐ left ☐ right ☐ bilateral | ❑ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery |
| | **PRIMARY TUMOR (T)** | |
| ❑ TX | Primary tumor cannot be assessed | ❑ TX |
| ❑ T0 | No evidence of primary tumor | ❑ T0 |
| ❑ Tis | Tis Carcinoma *in situ* | ❑ Tis |
| ❑ T1 | Tumor 2 cm or less in greatest dimension with less than two high risk features** | ❑ T1 |
| ❑ T2 | Tumor greater than 2 cm in greatest dimension *or* Tumor any size with two or more high risk features* | ❑ T2 |
| ❑ T3 | Tumor with invasion of maxilla, orbit, or temporal bone | ❑ T3 |
| ❑ T4 | Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base | ❑ T4 |
| | * Excludes cSCC of the eyelid – See Chapter 48. | |
| | **High Risk Features for the Primary Tumor (T) Staging: Depth/Invasion: >2 mm thickness, Clark level ≥ IV, Perineural invasion Anatomic Location: Primary site ear, Primary site hair-bearing lip Differentiation: Poorly differentiated or undifferentiated | |
| | **REGIONAL LYMPH NODES (N)** | |
| ❑ NX | Regional lymph nodes cannot be assessed | ❑ NX |
| ❑ N0 | No regional lymph node metastasis | ❑ N0 |
| ❑ N1 | Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension | ❑ N1 |
| ❑ N2 | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension | ❑ N2 |
| ❑ N2a | Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension | ❑ N2a |
| ❑ N2b | Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension | ❑ N2b |
| ❑ N2c | Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension | ❑ N2c |
| ❑ N3 | Metastasis in a lymph node, more than 6 cm in greatest dimension | ❑ N3 |
| | **DISTANT METASTASIS (M)** | |
| ❑ M0 | No distant metastasis (no pathologic M0; use clinical M to complete stage group) | |
| ❑ M1 | Distant metastasis | ❑ M1 |

**ANATOMIC STAGE • PROGNOSTIC GROUPS**

| CLINICAL | | | | PATHOLOGIC | | | |
|---|---|---|---|---|---|---|---|
| GROUP | T | N | M | GROUP | T | N | M |
| ❑ 0 | Tis | N0 | M0 | ❑ 0 | Tis | N0 | M0 |
| ❑ I | T1 | N0 | M0 | ❑ I | T1 | N0 | M0 |
| ❑ II | T2 | N0 | M0 | ❑ II | T2 | N0 | M0 |
| ❑ III | T3 | N0 | M0 | ❑ III | T3 | N0 | M0 |
| | T1 | N1 | M0 | | T1 | N1 | M0 |
| | T2 | N1 | M0 | | T2 | N1 | M0 |
| | T3 | N1 | M0 | | T3 | N1 | M0 |
| ❑ IV | T1 | N2 | M0 | ❑ IV | T1 | N2 | M0 |
| | T2 | N2 | M0 | | T2 | N2 | M0 |
| | T3 | N2 | M0 | | T3 | N2 | M0 |
| | T Any | N3 | M0 | | T Any | N3 | M0 |
| | T4 | N Any | M0 | | T4 | N Any | M0 |
| | T Any | N Any | M1 | | T Any | N Any | M1 |
| ❑ Stage unknown | | | | ❑ Stage unknown | | | |

**PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)**

**REQUIRED FOR STAGING:**
Tumor thickness (in mm) _____
Clark's Level _____
Presence / absence of perineural invasion _____
Primary site location on ear or hair-bearing lip _____
Histologic grade _____
Size of largest lymph node metastasis _____

**CLINICALLY SIGNIFICANT:** No additional factors

*Histologic Grade (G) (also known as overall grade)*

| *Grading system* | *Grade* |
|---|---|
| ❑ 2 grade system | ❑ Grade I or 1 |
| ❑ 3 grade system | ❑ Grade II or 2 |
| ❑ 4 grade system | ❑ Grade III or 3 |
| ❑ No 2, 3, or 4 grade system is available | ❑ Grade IV or 4 |

**ADDITIONAL DESCRIPTORS**

***Lymphatic Vessel Invasion (L) and Venous Invasion (V)*** have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

❑ Lymph-Vascular Invasion Not Present (absent)/Not Identified
❑ Lymph-Vascular Invasion Present/Identified
❑ Not Applicable
❑ Unknown/Indeterminate

**General Notes:**
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

**m suffix** indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

**y prefix** indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

**r prefix** indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

**a prefix** designates the stage determined at autopsy: aTNM.

*Residual Tumor (R)*
The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

❑ RX Presence of residual tumor cannot be assessed
❑ R0 No residual tumor
❑ R1 Microscopic residual tumor
❑ R2 Macroscopic residual tumor

**General Notes (continued):**

**surgical margins** is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

**neoadjuvant treatment** is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

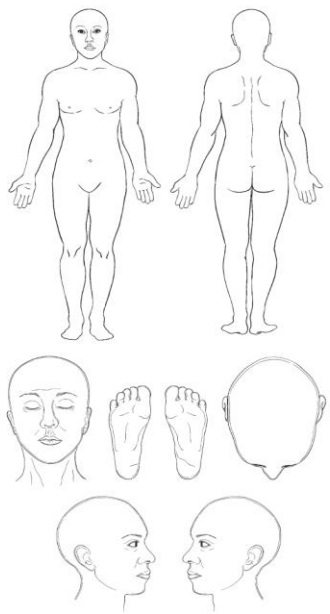
❑ Clinical stage was used in treatment planning (describe): _____

❑ National guidelines were used in treatment planning ❑ NCCN ❑ Other (describe): _____

_____

Physician signature Date/Time

**Illustration**
Indicate on diagram primary tumor and regional nodes involved.



# Treatment

- Cure rates with surgery or RT is 90-95%
- Treatment approach based on risk factors and patient characteristics

# Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study

M-F Avril[1], A Auperin[2], A Margulis[3], A Gerbaulet[4], P Duvillard[5], E Benhamou[2], J-C Guillaume[6], R Chalon[1], J-Y Petit[7], H Sancho-Garnier[8], M Prade[5], J Bouzy[2] and D Chassagne[4]

- Prospective randomized controlled trial of 347 patients with BCC of the face treated between 1982 – 1988 at a single center in France (Gustave Roussy Institute)
- Main end point: cure rate after 4 years of follow-up
- Secondary end point: cosmetic results

*British Journal of Cancer* (1997) **76**(1), 100–106
© 1997 Cancer Research Campaign

# Patients and Methods

- Previously untreated, biopsy-confirmed BCC of the face <4 cm in size
- Excluded: patients with contraindications to surgery and radiotherapy, inability to consent, BCC on scalp or neck, BCC completely removed with biopsy, ≥5 BCCs, life expectancy <3 years
- Follow-up:  3, 6, 12 months after treatment, then yearly by physical exam by dermatologist and photographs

# Treatment

- Largest BCC (if multiple) randomized to:
  - Surgery:  resection of whole tumor with 2 mm margin from visible borders +/- frozen sections, until negative margins, closure at surgeons discretion under local or general anesthesia
  - RT:  1 of 3 options at radiation oncologist discretion
    - Interstitial brachytherapy – Ir192 afterloaded wires to 65-70 Gy over 5-7 days under local or general anesthesia
    - Superficial contact therapy – 50 kV with 1.5-2 cm localizers to 36-40 Gy / 2 fractions / 2 weeks (for tumors < 2 cm in diameter)
    - Conventional RT – 85-250 kV with custom field size 60 Gy / 15-30 fractions / 4-10 weeks

# Outcomes Assessed

- Main: histologically confirmed persistent tumor or recurrence after 4 years of follow-up
- Secondary: cosmetic result
  - Patient reported satisfaction on VAS
  - Patient reported to dermatologist: good/fair/bad
  - Dermatologist reported on scar: slightly visible/clearly marked/bad
  - Photographs blindly assessed by photographer, data manager, medical secretary: good/fair/bad

# Results – Patients and BCCs

- 360 patients recruited, 347 analyzed
- 50% men
- Mean age 66 years
- 5% <45 years old

**Table 1** Characteristics of initial BCC

| Characteristics | Surgery ($n$ = 174) | Radiotherapy ($n$ = 173) |
|---|---|---|
| | Number of patients (%) | |
| BCC clinical type | | |
| Nodular | 79 (45) | 74 (43) |
| Ulcerated | 52 (30) | 50 (29) |
| Superficial and pagetoid | 36 (21) | 41 (23) |
| Sclerosing | 7 (4) | 8 (5) |
| Other clinical characteristics | | |
| Infiltration determined clinically[a] | 45 (26) | 60 (35) |
| Well-defined limits | 86 (49) | 95 (55) |
| Largest diameter (mm) | | |
| 3–5 | 19 (11) | 17 (10) |
| 6–10 | 87 (50) | 75 (43) |
| 11–20 | 58 (33) | 68 (39) |
| 21–30 | 8 (5) | 12 (7) |
| 31–40 | 2 (1) | 1 (1) |
| Site | | |
| Nose | 53 (30) | 49 (28) |
| Cheek, pre- and retroauricular areas | 36 (21) | 42 (24) |
| Eyelids, internal and external eye angles | 34 (19) | 35 (20) |
| Forehead, temple, between eyebrows | 36 (21) | 29 (17) |
| Chin, cutaneous superior lip | 10 (6) | 12 (7) |
| Ear | 5 (3) | 6 (3) |

[a] $P = 0.07$

# Results - Treatments

- Surgery
  - 91% had frozen sections; 39% required additional resection
  - 44% hospitalized for mean stay of 2.8 days
- RT
  - 55% had interstitial brachytherapy (average tumor 1.29 cm) with mean stay of 6.9 days
  - 33% had contact therapy (average tumor 0.84 cm)
  - 12% had conventional RT (average tumor 1.55 cm)

# Results – Tumor recurrence

- Failure rates significantly higher with RT
  - Brachytherapy 8.8%
  - Contact therapy 6.6%
  - Conventional RT 5%

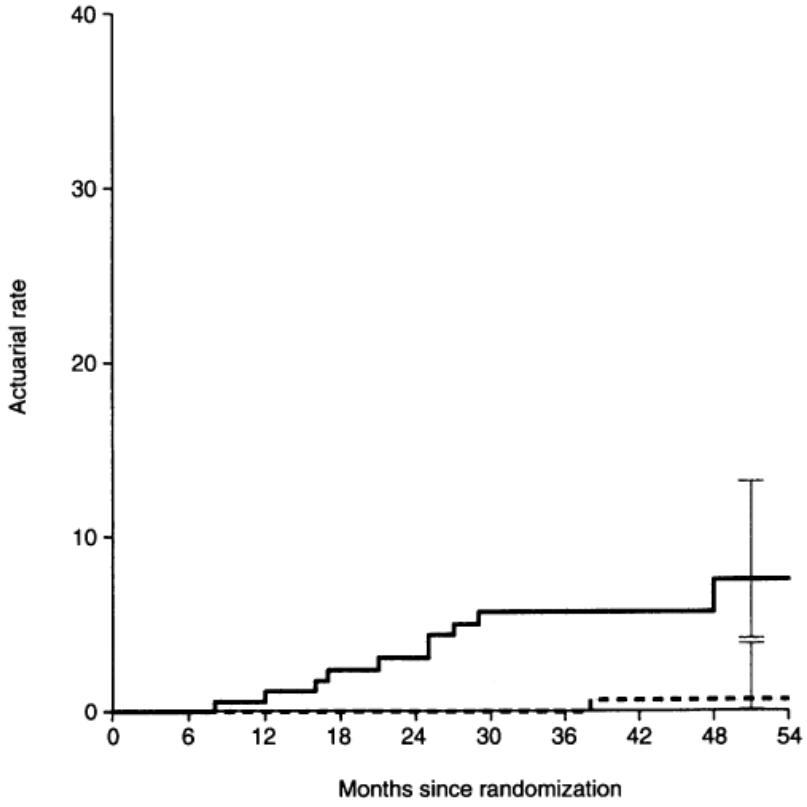



**Figure 1** Kaplan–Meier plot of recurrent or persistent BCC in patients treated with surgery or radiotherapy. Bars indicate 95% confidence intervals. - - -, Surgery ($n$ = 174, one event); ——, radiotherapy ($n$ = 173, 11 events)

# Results – Cosmetic

**Table 2** Cosmetic results

| | 3 months | | 6 months | | 12 months | | 24 months | | 36 months | | 48 months | | $P^a$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sg | Rt | Sg | Rt | Sg | Rt | Sg | Rt | Sg | Rt | Sg | Rt | |
| Patient scale | | | | | | | | b | | c | | d | 0.004 |
| Mean | 8.8 | 8.8 | 8.9 | 8.6 | 9.1 | 8.8 | 9.1 | 8.6 | 9.0 | 8.3 | 9.1 | 8.1 | |
| (s.d.) | (1.9) | (1.8) | (1.6) | (1.8) | (1.3) | (1.5) | (1.5) | (2.1) | (1.6) | (2.0) | (1.6) | (2.0) | |
| Patient | | | | | | | | | | | | | |
| Cosmetic result | | | | | | | | b | | b | | c | 0.05 |
| Good (%) | 75 | 74 | 79 | 73 | 83 | 76 | 84 | 74 | 82 | 69 | 87 | 69 | |
| Fair (%) | 24 | 24 | 18 | 24 | 16 | 20 | 15 | 22 | 15 | 26 | 11 | 22 | |
| Bad (%) | 1 | 2 | 3 | 3 | 1 | 3 | 1 | 4 | 3 | 5 | 2 | 8 | |
| Dermatologist | | | | | | | | | | | | | |
| Scar | | | | | | | | c | | d | | d | 0.0001 |
| Slightly visible (%) | 56 | 55 | 66 | 64 | 74 | 65 | 77 | 60 | 77 | 50 | 79 | 40 | |
| Clearly marked (%) | 42 | 43 | 31 | 34 | 26 | 32 | 21 | 35 | 22 | 46 | 19 | 47 | |
| Bad (%) | 2 | 2 | 3 | 2 | 0 | 3 | 1 | 5 | 1 | 4 | 2 | 13 | |
| Photographer | | | | | | | | | | | | | |
| Cosmetic result | | | | | | | | b | | d | | d | 0.0001 |
| Good (%) | 30 | 25 | 38 | 40 | 50 | 41 | 53 | 35 | 65 | 38 | 62 | 29 | |
| Fair (%) | 36 | 42 | 38 | 36 | 35 | 36 | 34 | 45 | 19 | 41 | 27 | 39 | |
| Bad (%) | 34 | 33 | 24 | 24 | 15 | 23 | 13 | 20 | 16 | 21 | 11 | 32 | |
| Data manager | | | | | | | | | | | | | |
| Cosmetic result | | | | | | | | d | | c | | d | 0.03 |
| Good (%) | 27 | 30 | 43 | 39 | 51 | 43 | 54 | 28 | 50 | 28 | 50 | 24 | |
| Fair (%) | 42 | 43 | 37 | 46 | 32 | 42 | 33 | 55 | 37 | 55 | 37 | 48 | |
| Bad (%) | 30 | 27 | 20 | 15 | 17 | 14 | 13 | 17 | 13 | 17 | 13 | 28 | |
| Secretary | | | | | | | | | | | | | |
| Cosmetic result | | | | | | | | | | | | | 0.14 |
| Good (%) | 33 | 45 | 52 | 51 | 52 | 49 | 54 | 41 | 50 | 43 | 54 | 35 | |
| Fair (%) | 48 | 39 | 37 | 39 | 39 | 37 | 36 | 46 | 40 | 42 | 39 | 44 | |
| Bad (%) | 19 | 16 | 11 | 10 | 9 | 14 | 10 | 13 | 10 | 15 | 7 | 21 | |

Sg, surgery; Rt, radiotherapy; [a]Global comparison of surgery and radiotherapy for the 4 years of follow-up; if the global test was significant, comparisons of surgery and radiotherapy were performed at each time; [b]$0.01 < P < 0.05$; [c]$0.001 < P < 0.01$; [d]$P < 0.001$.

# Results - Cosmetic

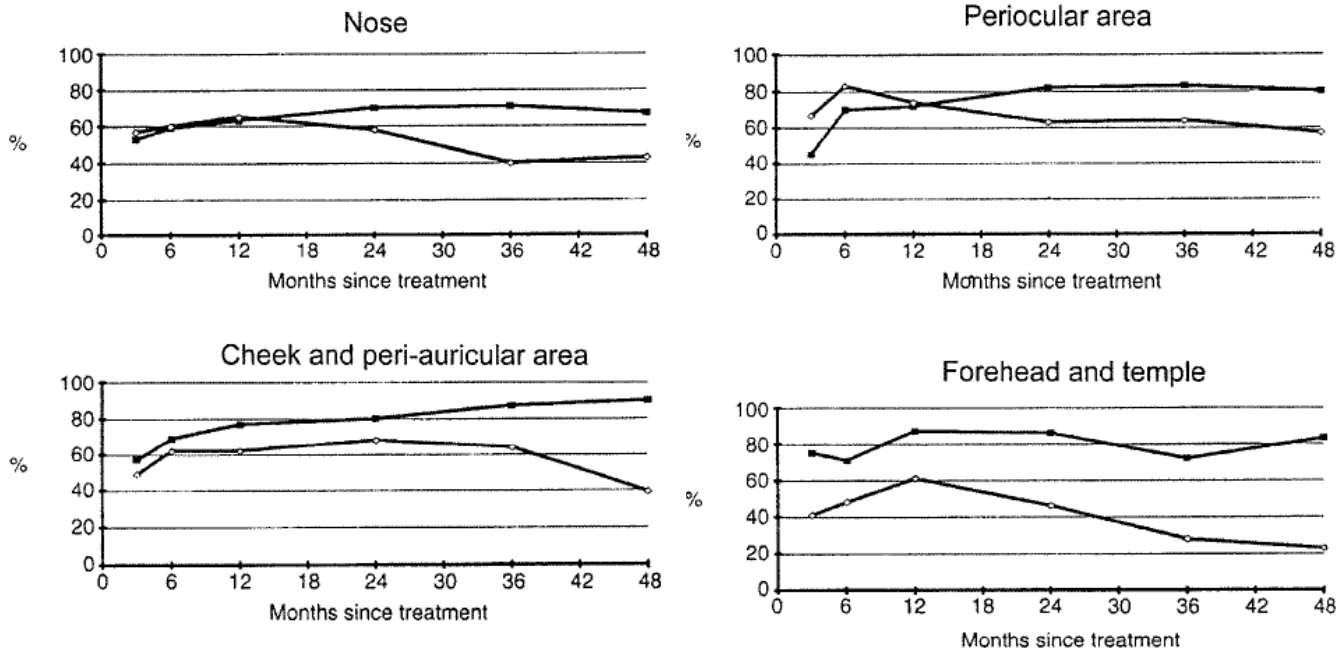



FIG. 3. Percentage of slightly visible scar assessed by the dermatologist, from treatment until 4 years, according to location. ■, surgery; ◇, radiotherapy.

- Significantly greater “good” cosmetic results for all locations, except the nose

# Criticisms

- Surgery often required re-operation for positive margins (~40% of the time)
- “RT” results represent a variety of therapeutic techniques, some known to be associated with poor outcome
  - Interstitial brachytherapy known to be associated with high dose inhomogeneity
  - Large dose/fraction known to be associated with inferior cosmetic outcomes
  - Conventional RT over 10 weeks likely to be associated with tumor repopulation
  - Conventional RT (most similar to contemporary practice) used in only 12% of patients
- “Face” is a anatomic site with significantly different areas; no subset analysis of patterns of failure by site
- Absolute difference in cosmetic outcome after 3 years was relatively minor
  - According to patients, 9/10 for surgery vs 8/10 for RT
- RT and surgery may yield equivalent cosmetic results for nose; efficacy at this subsite unclear

# NCCN guidelines for Radiation Therapy

- “RT can result in very good cure rates and cosmesis
- In order to achieve those cure rates and cosmesis, RT must be properly applied
- The details of RT are important and need to be included in the algorithms”

# Radiation Therapy Technique

- External Beam Radiation Therapy
  - Focal therapy / Involved field
    - High energy photons (MV)
    - Low energy photons (superficial or orthovoltage, kV)
    - High energy electrons (MeV)
  - Total Skin Electron Beam (TSEB)
- Brachytherapy
  - Skin surface brachytherapy
  - Interstitial brachytherapy

# NCCN guidelines for RT (BCC)

**PRINCIPLES OF RADIATION THERAPY FOR BASAL CELL SKIN CANCER**

**Dose and Field Size**

| Tumor Diameter | Margins | Examples of Electron Beam Dose and Fractionation |
|---|---|---|
| < 2 cm | 1 - 1.5 cm[1] | 64 Gy in 32 fractions over 6 - 6.4 weeks[2]<br>55 Gy in 20 fractions over 4 weeks<br>50 Gy in 15 fractions over 3 weeks<br>35 Gy in 5 fractions over 5 days |
| ≥ 2 cm | 1.5 - 2 cm[1] | 66 Gy in 33 fractions over 6 - 6.6 weeks<br>55 Gy in 20 fractions over 4 weeks |
| Postoperative adjuvant | | 50 Gy in 20 fractions over 4 weeks<br>60 Gy in 30 fractions over 6 weeks |

- Protracted fractionation is associated with improved cosmetic results.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, scleroderma)

# NCCN guidelines for RT (SCC)

**PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER**

| Primary Tumor[1] | Dose Time Fractionation Schedule |
|---|---|
| Tumor Diameter | Dose Fractionation and Treatment Duration |
| < 2 cm | 64 Gy in 32 fractions over 6-6.4 weeks<br>55 Gy in 20 fractions over 4 weeks<br>50 Gy in 15 fractions over 3 weeks<br>35 Gy in 5 fractions over 5 days |
| ≥ 2 cm | 66 Gy in 33 fractions over 6 - 6.6 weeks<br>55 Gy in 20 fractions over 4 weeks |
| Postoperative adjuvant | 50 Gy in 20 fractions over 4 weeks<br>60 Gy in 30 fractions over 6 weeks |
| Regional Disease–all doses at 2 Gy per fraction using shrinking field technique | |
| • After Lymph node dissection | |
| ▸ Head and neck; with ECE: | 60-66 Gy over 6 - 6.6 weeks |
| ▸ Head and neck; without ECE: | 56 Gy over 5.6 weeks |
| ▸ Axilla, groin; with ECE: | 60 Gy over 6 weeks |
| ▸ Axilla, groin; without ECE: | 54 Gy over 5.4 weeks |
| • No lymph node dissection | |
| ▸ Clinically (-) but at risk for subclinical disease: | 50 Gy over 5 weeks |
| ▸ Clinically evident adenopathy: head and neck: | 66-70 Gy over 6.6 - 7 weeks |
| ▸ Clinically evident adenopathy: axilla, groin: | 66 Gy over 6.6 weeks |

ECE= Extracapsular extension

- **Protracted fractionation is associated with improved cosmetic results.**
- **Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, scleroderma).**

[1]Field margins for < 2 cm primary tumors should be 1-1.5 cm; for tumors >2 cm, field margins should be 1.5-2 cm. Tighter field margins can be used with electron beam adjacent to critical structures (eg, the orbit) if lead skin collimation is used. Bolus is necessary when using electron beam to achieve adequate surface dose. An electron beam energy should be chosen which achieves adequate surface dose and encompasses the deep margin of the tumor by at least the distal 90% line. Electron beam doses are specified at 90% of the maximal depth dose (Dmax). Orthovoltage x-ray doses are specified at Dmax (skin surface) to account for the relative biologic difference between the two modalities of radiation. If intensity modulated radiation therapy is used to treat primary tumors, appropriate focus must be directed at assuring that there is adequate surface dose. Appropriate medical physics support is essential.

# External Beam Radiation Therapy – Focal field Dose and Fractionation Schedules for BCC/SCC

**UCSF**

*Superficial or Orthovoltage X-rays*

| Size of skin cancer | Energy | Filtration (HVL) | Dose/fraction* | # of fractions | Total dose |
|---|---|---|---|---|---|
| 0.5-2.0 cm | 50-150 kV | 0.7 mm Al - 0.52 mm Cu | 3 Gy | 15-17 | 45-51 Gy |
| >2.0 cm without bone involvement | 180-300 kV | 0.87 - 3.7 mm Cu | 2.5 Gy | 20-22 | 50-55 Gy |

*Megavoltage Electrons or Photons (or Both), with 0.5-1.5 cm bolus*

| Size of skin cancer | Energy | Dose/fraction* | # of fractions | Total dose |
|---|---|---|---|---|
| 0.5-2.0 cm | 6-9 MeV electrons | 3.3 Gy | 15-17 | 49.5-56 Gy |
| >2.0 cm without bone involvement | 9-16 MeV electrons | 2.75 Gy | 20-22 | 55-60.5 Gy |
| >2.0 cm with bone involvement | 4-6 MV photons or 9-20 MeV electrons (or both) | 2 Gy | 34-36 | 68-72 Gy |

*Prescribed to the 100% isodose line, including buildup bolus, giving 5 fractions/week.

**Table 30.3 COMPARISON OF DIFFERENT TIME-DOSE-FRACTIONATION (TDF) SCHEDULES FOR MANAGEMENT OF NONMELANOMA SKIN CANCER**

| Tumor Characteristics | Dose Fractionation | TDF |
|---|---|---|
| **MGH (75)**[a] | | |
| <1 cm tumor; debilitated patient | 20–24 Gy in 1 fraction | — |
| <2 cm tumor | 45 Gy in 5–9 fractions | 122—131 |
| 2–4 cm or cosmetic concerns | 52 Gy in 13 fractions | 125 |
| >4 cm tumor | 60 Gy in 20 fractions | 123 |
| | 64 Gy in 25 fractions | 116 |
| **MDACC (51)**[b] | | |
| ≤1 cm; elderly patient | 40 Gy in 8 fractions | 125 |
| >1–2 cm in elderly or ≤2 cm in young patient | 50 Gy in 15–20 fractions | 108–127 |
| Large fields needing good cosmesis | 60 Gy in 30 fractions | 115 |
| Large, infiltrating tumors | 64 to 66 Gy in 32–33 fractions | 122–126 |
| **University of Florida (49)**[b] | | |
| Large, untreated + bone/cartilage invasion or large, recurrent | 65 Gy in 35 fractions | 115 |
| Large, untreated + minimal or suspected bone/cartilage invasion | 60 Gy in 34 fractions | 112 |
| Moderate-to-large inner canthus, eyelid, nasal, pinna (20–30 $cm^2$) | 55 Gy in 30 fractions | 99 |
| Small, thin (<1.5 cm) eye, nose, ear (10 $cm^2$) | 50 Gy in 20 fractions | 108 |
| Moderate or postoperative cut-through on free skin | 45 Gy in 15 fractions | 107 |
| Small (1 cm) on free skin | 40 Gy in 10 fractions | 111 |
| | 30 Gy in 5 fractions | 103 |
| Cosmesis not important | 40 Gy in 10 fractions | 111 |
| | 30 Gy in 5 fractions | 89 |
| | 20 Gy in 1 fractions | |

MGH, Massachusetts General Hospital; MDACC, M.D. Anderson Cancer Center.
[a]Megavoltage.
[b]Orthovoltage doses. For megavoltage, prescribe dose to D90% or add 10% to total dose and prescribe to $D_{max}$.

Chen A et al "Skin Cancer," in Textbook of Radiation Oncology, 3rd edition, 2010

Solan M and Brady LW "Skin Cancer," in Clinical Radiation Oncology, 5th edition, 2004

# Radiation Qualities for Skin RT

| Type | kV | FSD (cm) | HVL (mm) | $D_{1/2}$ (mm) |
|---|---|---|---|---|
| Grenz rays (ultrasoft, supersoft, Bucky therapy) | 10–20 | 10–30 | 0.03 Al | 0.2–1.0 |
| Soft x-ray | 20–100 | 10–30 | 0.1–2.0 Al | 1–20 |
| Contact therapy (Chaoul therapy) | 50–60 | 1.5–3.0 | 2.0–4.0 Al | 4–30 |
| Superficial x-ray (low voltage) | 60–150 | 15–30 | 0.7–2.0 Al | 7–10 |
| Orthovoltage therapy (deep x-ray therapy, conventional x-ray therapy) | 150–400 | 50–80 | 2–4 Cu | 50–80 |
| Supervoltage therapy | 400–800 | 50–80 | 5–10 Pb | 80–110 |
| Megavoltage therapy (betatron, particle accelerators) | > 1000 | 80 | > 10 Pb | 10–200 |

FSD = focus-skin distance; HVL = half-value layer; $D_{1/2}$ = half-value depth.

# Target Delineation

- Gross tumor volume determined by physical examination and imaging
- Clinical target volume includes
  - GTV + 0.5-1 cm laterally for tumors ≤2 cm*
  - GTV + 1.5-2 cm laterally for tumors >2 cm*

    *for morphea histology, add 0.5 cm

    *for SCC histology, minimum 2 cm expansion on GTV

    *if using electrons, add 0.5 cm
  - GTV + 0.5-1 cm deep to suspected invasion for tumors ≤4 cm **

    **for clinical or radiographic perineural invasion, included nerve to bony outlet

    **for larger, recurrent, high-grade, or tumors on embryologic fusion lines, add 1-1.5 cm
- Planning target volume depends on treatment setup and immobilization

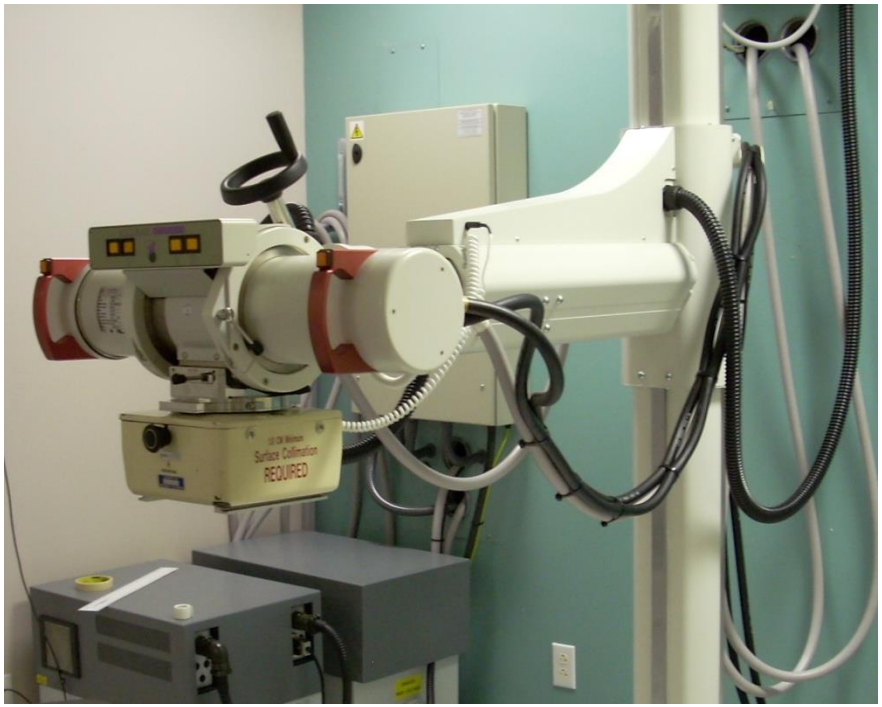
# Local control after external beam RT for BCC and SCC of skin

| AUTHOR | TUMOR LOCALISATION | n | TREATMENT | FUP | LOCAL CONTROL |
|---|---|---|---|---|---|
| Locke (2001) (13) | all skin | 531 | external RT | meadian 6y | 93 % if primary treatment<br>80 % if recurrence |
| Abatucci (1989) (1) | Face excl. Lip/ear/eyelid | 675 | contact RT | min 2y | 96 % |
| Childers (1994) (5) | Nose | 26 | contact RT | 9y | 96 % |
| Fitzpatrick (1984) (10) | Eyelid | 1166 | external RT | 5y | 95 % if BSC<br>93 % if SCC |
| Schlienger (1996) (20) | Eyelid | 850 | external RT | 5y | 97.5 % |
| Buatois (1996) (4) | Eyelid | 52 | contact RT | median 4y | 94 % |

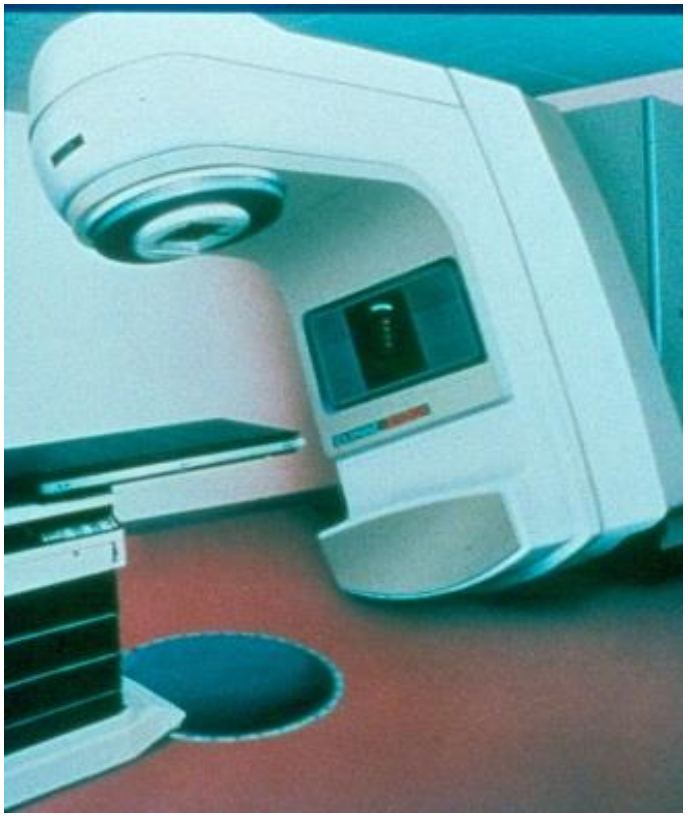
Chapter 28, “Skin Cancer,” GEC ESTRO Handbook of Brachytherapy, 2002

# Controversy in external beam RT for skin cancer

**Orthovoltage Photons (low energy)**



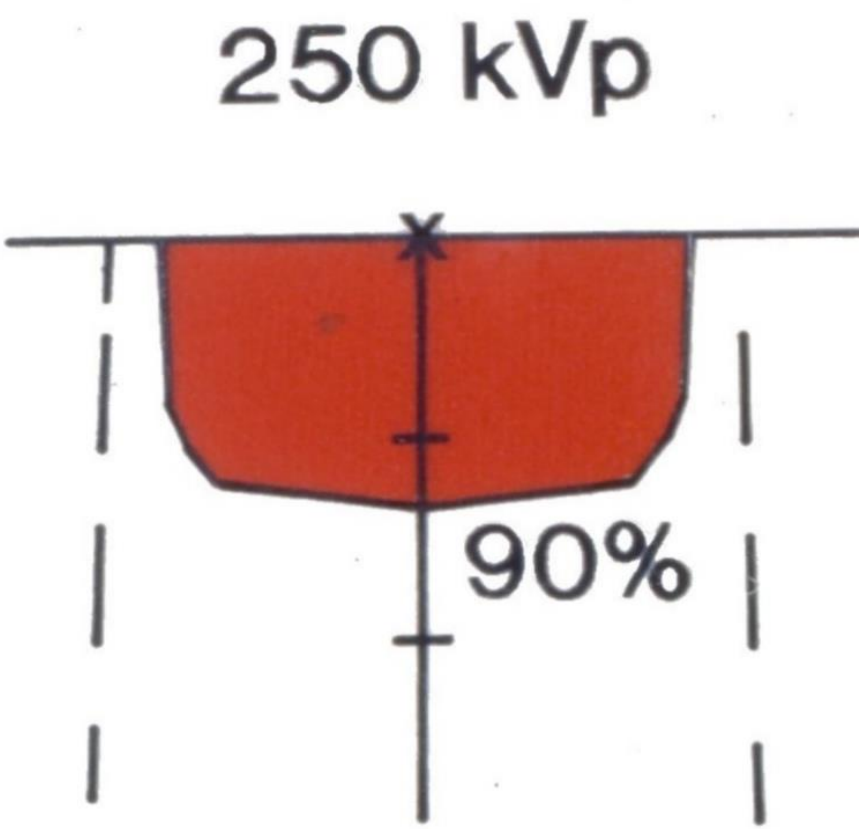

**Megavoltage Electrons (high energy)**



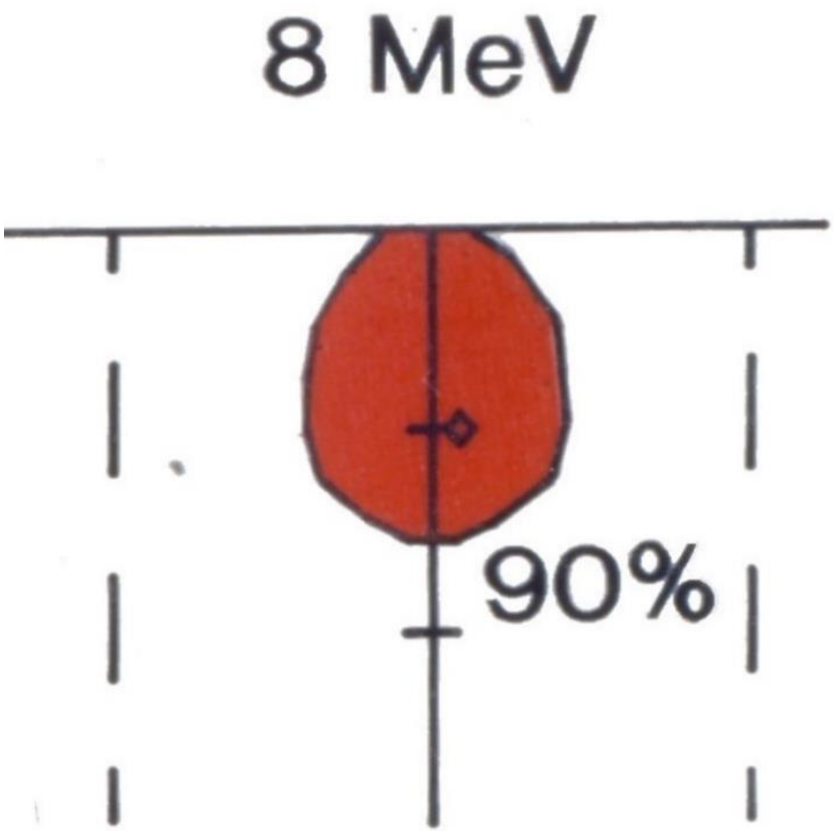
Courtesy, R. Amdur

# Controversy in external beam RT for skin cancer

**Orthovoltage Photons (low energy)**




**Megavoltage Electrons (high energy)**

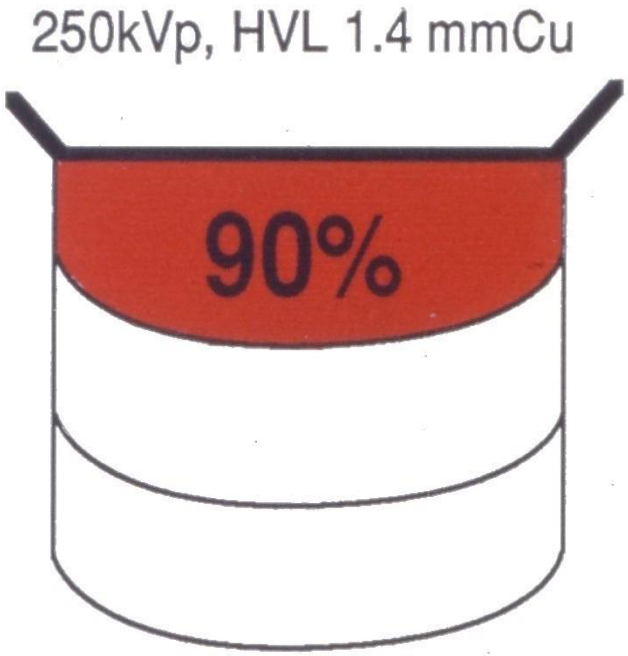



Dose distribution for 3x3 cm field *with no surface collimation*

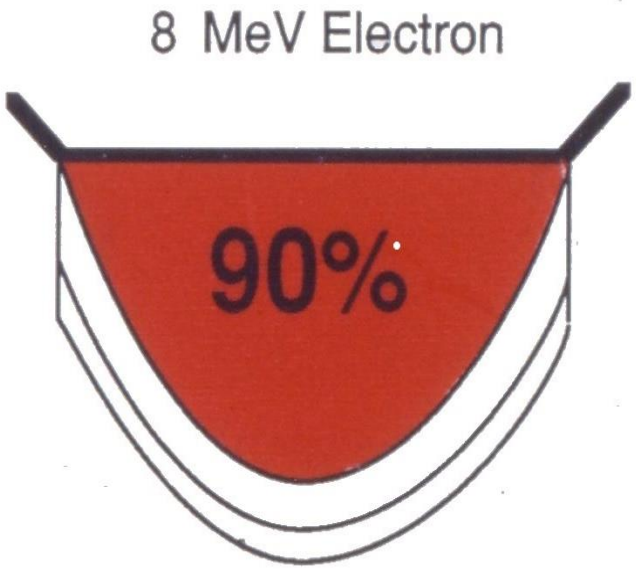
Courtesy, R. Amdur

# Controversy in external beam RT for skin cancer

**Orthovoltage Photons (low energy)**




**Megavoltage Electrons (high energy)**




Dose distribution for 2.5x2.5 cm field *with surface collimation and bolus*

Courtesy, R. Amdur

# Shielding Considerations

- Eye (lens)
- Buccal mucosa / gingivae
- Hair-bearing scalp
- Middle ear
- Nasal mucosa

- Remember – thickness of shielding depends on HVL (quality of the beam)

# What about brachytherapy?

- Brachytherapy (*brachy* (Gr.) = short-distance) is a RT modality used for the treatment of BCCs and SCCs for many years
  - *Interstitial* brachytherapy requires implant of radioactive source or device inside tissues (needles, catheters)
  - *Surface* brachytherapy requires contact of radioactive source or device with tumor (applicator-based)
  - High dose rate (HDR) or low dose rate (LDR)
- General advantage over external beam RT is that less normal, healthy tissue is irradiated
- Requires specialized facilities, physicists, training, etc

# Local control after brachytherapy for BCC and SCC of skin

| AUTHOR | TUMOR LOCALISATION | n | TREATMENT | FUP | LOCAL CONTROL |
|---|---|---|---|---|---|
| Guix (2000) (12) | Face | 136 | HDR brachy | 5y | 99 % if primary treatment<br>87 % if recurrence |
| Maes (2001) (15) | Face | 173 | Iridium 192 | 45 months | 95 % |
| Debois (1994) (8) | Nose | 370 | Cesium 137 | 2y | 97 % if primary treatment<br>94 % if recurrence |
| Crook (1990) (6) | Nose | 468 | Iridium 192 | 5y | 97.5 % |
| GEC (1989) | Nose | 1676 | RT | min 2y | 95 % if primary treatment<br>88% if recurrence |
| Daly (1984) (7) | Eyelid | 165 | Iridium 192 | 5y | 97 % if primary treatment<br>94 % if recurrence |
| Gambaro (2001) (11) | Eyelid | 50 | Iridium 192 | median 82 months | 96 % |
| Mazeron (1986) (16) | Ear | 70 | Iridium 192 | mean 5y | 99 % |
| Baris (1985) (3) | nasal vestibule | 22 | Iridium | 2y | 96.4 % |

(all HDR, mostly interstitial/invasive)

Chapter 28, “Skin Cancer,” GEC ESTRO Handbook of Brachytherapy, 2002

# Surface HDR brachytherapy

- Suitable for superficial lesions
- Non-invasive (no needles or anesthesia)
- “Leipzig” technique using $^{192}$Iridium
- Disadvantages:
  - Requires experienced personnel
  - Shielded radiation treatment room
  - Special handling of the isotopes

# An alternative to $^{192}$Iridium: Electronic Brachytherapy

- Uses low energy x-ray source (50 kVp)
- Developed by Xoft, Inc (now iCAD) as Axxent® system
- First used clinically in July 2009 (WI, AZ)
- Advantages:
  - Less shielding requirements (scheduling and delivering treatment in shielded room not required)
  - Lower exposure rate (allows personnel to remain in the treatment room with close proximity to the patient)

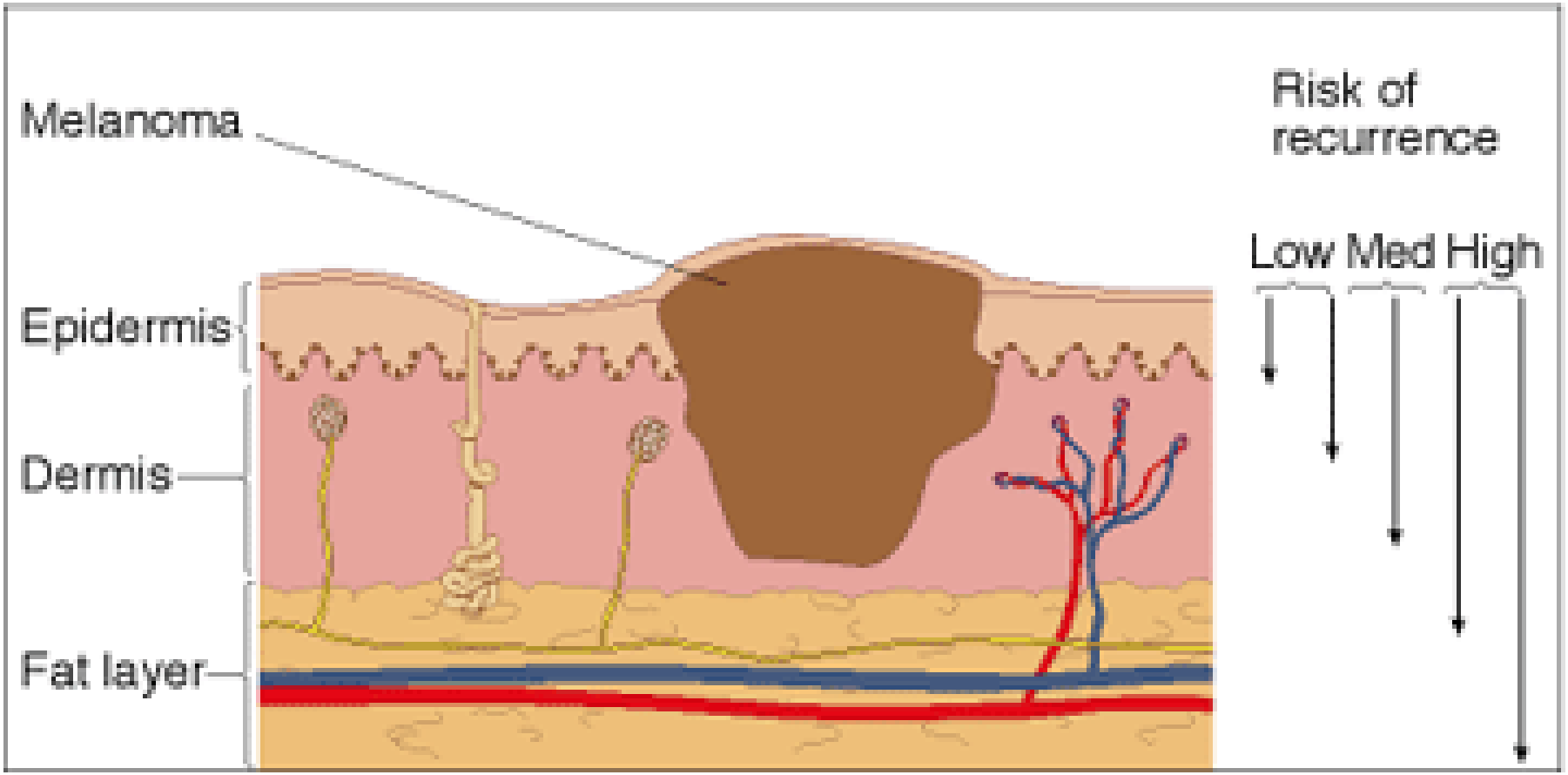
# RT for BCCs and SCCs

- Surgery and RT are the most common treatments for early BCCs and SCCs
  - Control rate >90%
- RT considered a standard therapeutic option by NCCN
  - For patients >60 years old
  - For non-surgical candidates
- RT should also be considered in other situations
  - Functional outcome
  - Cosmetic outcome
  - Patient preference
- Major concern about RT is toxicity
  - Patient and technique dependent

# RT for Cutaneous Melanoma

- Clear role for palliation (brain and bone metastases)
  - Considered “resistant,” but response rate of 50%
- Possible role in adjuvant therapy (after resection of pN+ disease)
- Possible role for unresectable primary (lentigo maligna melanoma)
- Hypofractionated RT frequently used, but no clear evidence of superiority to conventional RT
  - 30 Gy / 5 fractions

# Breslow Scale




Low risk - the melanoma is less than 0.76 mm thick
Medium risk - the melanoma is 0.76 mm to 1.5 mm thick
High risk - the melanoma is more than 1.5 mm thick

# Clark Staging System

- level I melanoma *in situ*
- level II invasion of papillary dermis
- level III invasion to junction between papillary and reticular dermis
- level IV invasion of reticular dermis
- level V invasion of subcutis
- *Breslow→measured depth; Clark→histologic depth*
- TNM staging also based on measured depth

# RT for Kaposi Sarcoma

- 4 variants
  - Classic (in people of Mediterranean origin)
  - Endemic (in Africa)
  - Epidemic (associated with HIV/AIDS)
  - Iatrogenic (associated with immunosuppression/transplant)
- Very responsive to moderate dose RT
  - 90% response; 50% are complete and durable
  - Improved response at doses of ≥30 Gy / 10 fractions

# A RANDOMIZED PROSPECTIVE TRIAL OF RADIATION THERAPY FOR AIDS-ASSOCIATED KAPOSI'S SARCOMA

KEITH J. STELZER, M.D., PH.D. AND THOMAS W. GRIFFIN, M.D.

Department of Radiation Oncology, University of Washington Medical Center, Seattle, WA 98195

- First prospective randomized controlled trial of 71 cutaneous AIDS-associated KS lesions from 1991-1992 in 14 patients at University of Washington

# Patients and Methods

- 14 patients with AIDS-associated KS
- 71 KS lesions treated
- Excluded: KPS <60, prior diagnosis of primary CNS lymphoma, concurrent chemotherapy or interferon, lesions regressing after any other form of treatment, prior RT in the planned field

# Treatment Randomization

- All received 6 MeV electrons with 0.5 cm bolus, 5 fractions/week
- Field included palpable tumor + 2 cm margin
- Randomized to:
  - 8 Gy / 1 fraction
  - 20 Gy / 10 fractions
  - 40 Gy / 20 fractions

# Outcomes Assessed

- Toxicity according to RTOG system
- Response
  - CR = all palpable tumor within RT field resolved, regardless of residual pigmentation
  - OR = >50% decrease in palpable tumor area
  - NR = <50% decrease in palpable tumor area
  - Failure = time of growth of palpable tumor

# Results - Patients

Table 1. Patient characteristics

| | |
|---|---|
| Number | 14 |
| Age | |
| Median | 34 |
| Range | 26–54 |
| Months since diagnosis as HIV positive | |
| Median | 11 |
| Range | 6–120 |
| Number of lesions treated | |
| Median | 4 |
| Range | 2–11 |
| KS as first manifestation of AIDS | 11 (71%) |
| Previous opportunistic infection | 12 (86%) |
| Chemotherapy prior to radiation | 2 (14%) |
| Chemotherapy after radiation | 6 (43%) |
| Interferon prior to radiation | 4 (29%) |
| AZT during radiation | 7 (50%) |
| Karnofsky performance status | |
| Median | 80 |
| Range | 60–90 |
| CD4+ T cell count (cells/$\mu$l) | |
| Median | 62 |
| Range | 10–650 |
| Surviving patients | 12 (86%) |

# Results – Lesion Characteristics and Response Rates

Table 2. Lesion characteristics

| | Dose (Gy) | | | |
|---|---|---|---|---|
| | 8 | 20 | 40 | *p* value |
| Number | 24 | 24 | 23 | |
| Size ($mm^2$) | | | | |
| Mean ± s.d. | 1155 ± 1582 | 936 ± 1454 | 1319 ± 1890 | .56 |
| < 400 | 10 | 9 | 11 | |
| 400–1000 | 7 | 8 | 5 | .92 |
| > 1000 | 7 | 7 | 7 | |
| Location | | | | |
| Face | 2 | 5 | 4 | |
| Trunk | 8 | 5 | 8 | .63 |
| Extremity | 14 | 14 | 11 | |
| Treatment intent | | | | |
| Cosmetic | 10 | 8 | 8 | |
| Pain | 13 | 16 | 14 | .84 |
| Edema | 1 | 0 | 1 | |

| | Dose (Gy) | | | |
|---|---|---|---|---|
| | 8 | 20 | 40 | *p* value |
| Number | 24 | 24 | 23 | |
| Follow-up (weeks) | | | | |
| Mean ± s.d. | 35 ± 14 | 38 ± 13 | 37 ± 14 | .76 |
| Median | 37 | 40 | 40 | |
| Range | 8–54 | 4–54 | 4–56 | |
| Response | | | | |
| Outcome | 12 | 19 | 19 | .04 |
| Objective | 21 | 21 | 23 | .23 |
| RPP absent | 2 | 2 | 10 | .005 |
| CR without RPP | 2/12 (17%) | 2/19 (11%) | 10/19 (53%) | .01 |
| Failure | | | | |
| Crude | 21 | 16 | 12 | .03 |
| At week 40 | 84% | 62% | 48% | .003 |
| Median time to failure (weeks) | 13 | 26 | 43 | .003 |

# Results – Tumor Control

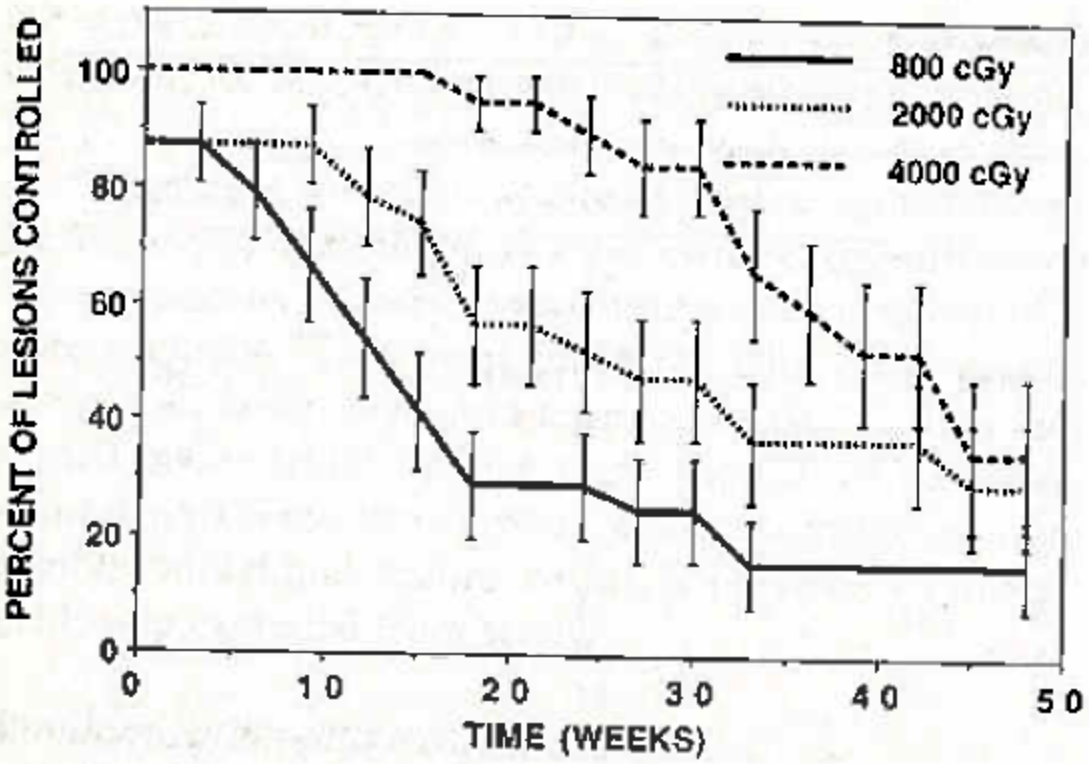



Fig. 1. Kaplan-Meier analysis of lesion control as a function of time from start of radiation for 8 Gy in one dose, 20 Gy in 10 fractions, and 40 Gy in 20 fractions. The difference in lesion control between the three regimens is significant by log rank analysis ($p = .003$).

# Results - Toxicity

Table 4. Treatment complications

| | Dose (Gy) | | | |
|---|---|---|---|---|
| | 8 | 20 | 40 | *p* value |
| Number | 24 | 24 | 23 | |
| Acute toxicity* | 3 | 11 | 22 | $10^{-8}$ |
| Late toxicity† | 0 | 0 | 6 | .0007 |

* Acute toxicity did not exceed grade 1 (skin erythema, dry desquamation, or alopecia).

† Late toxicity did not exceed grade 1 (slight hyperpigmentation or alopecia).

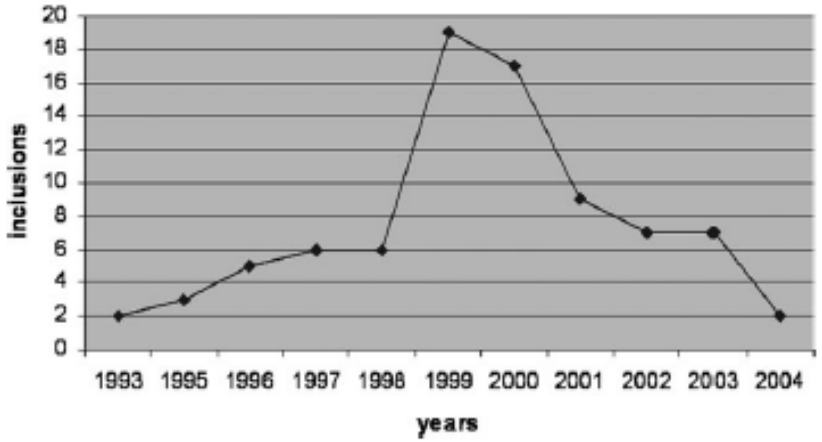
# RT for Merkel Cell Carcinoma

- Rare neuroendocrine cancer of the skin that frequently metastasizes to lymph nodes and distant sites
- Standard therapy includes wide local excision of primary tumor and sentinel lymph node biopsy
- Role of RT to primary tumor bed and regional lymphatics is controversial

**Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study**

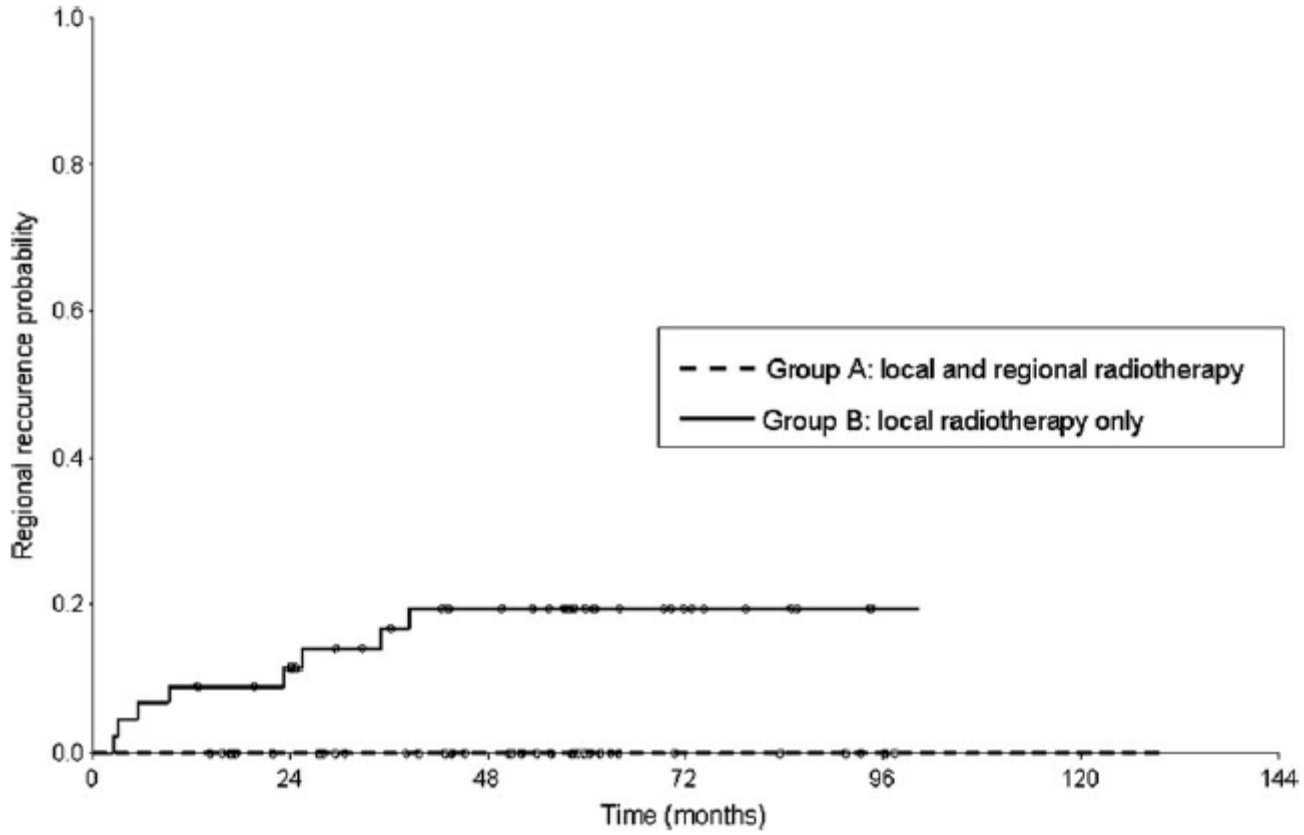
T. Jouary[1*], C. Leyral[1], B. Dreno[2], A. Doussau[3], B. Sassolas[4], M. Beylot-Barry[5], C. Renaud-Vilmer[6], B. Guillot[7], P. Bernard[8], C. Lok[9], C. Bedane[10], F. Cambazard[11], L. Misery[12], E. Estève[13], S. Dalac[14], L. Machet[15], F. Grange[16], P. Young[17], F. Granel-Brocard[18], F. Truchetet[19], B. Vergier[20], M. M. Delaunay[1] & J. J. Grob[21] for the Groupe de Cancérologie Cutanée of the Société Française de Dermatologie

- First prospective, randomized controlled trial in MCC
- 83 patients with "Stage I" MCC randomized to regional (lymph node basin) RT or observation after WLE and tumor bed RT at 20 French centers 1993-2005
- Stopped in 2005 because of poor accrual




Annals of Oncology Advance Access published July 12, 2011

# Results – Regional Recurrence



# Total Skin Electron Beam (TSEB) Radiotherapy

- Developed in the late 1950s to administer therapeutic ionizing radiation to the entire skin surface
- Typically uses low energy (6-9 MeV) electrons
- Requires specialized facilities for setup, and accurate dose delivery
- Used in the management of disseminated cutaneous diseases

# Mycosis fungoides (MF)

- Most common cutaneous T-cell lymphoma
- Estimated incidence of 4 in 1 million
- Neoplastic process of mature clonal CD4+ CD45RO+ T-cells with homing capacity for the dermis and epidermis
- Patients may present with pruritic cutaneous lesions
- Diagnosis depends on clinical and histopathologic criteria, but is often difficult and delayed for months to years

# International Society for Cutaneous Lymphoma (ISCL) Staging System

TNMB stages

| | T | N | M | B |
|---|---|---|---|---|
| IA | 1 | 0 | 0 | 0,1 |
| IB | 2 | 0 | 0 | 0,1 |
| II | 1,2 | 1,2 | 0 | 0,1 |
| IIB | 3 | 0-2 | 0 | 0,1 |
| III | 4 | 0-2 | 0 | 0,1 |
| IIIA | 4 | 0-2 | 0 | 0 |
| IIIB | 4 | 0-2 | 0 | 1 |
| $IVA_1$ | 1-4 | 0-2 | 0 | 2 |
| $IVA_2$ | 1-4 | 3 | 0 | 0-2 |
| IVB | 1-4 | 0-3 | 1 | 0-2 |

Blood 110: 1713-1722; 2007

# TSEB in MF: 2002 EORTC Consensus Recommendations

| | |
|---|---|
| 1. Patients with a new diagnosis of mycosis fungoides | |
| "Minimal" stage IA | Not recommended (consider local radiation only) |
| Stage IA & T1N1 | A brief therapy with potential for long-term progression-free survival |
| Stage IB & T2N1 | As in stage IA, consider combination therapy (eg, with psoralen plus UV light) |
| Stage IIB | Effective palliation, consider combination therapy |
| Stage III | Potential for long-term progression-free survival from erythroderma |
| Stage IVA | Consider the combination with involved-node photon-radiation |
| Stage IVB | Effective palliation, consider combination therapy |
| Sézary syndrome | Consider the combination with extracorporeal photochemotherapy |
| 2. Patients for whom prior therapies failed | |
| IA - IIA | A brief therapy with potential for long-term progression-free survival |
| All others | Consider combination therapies |
| 3. Patients considering repetition of total skin electron radiation | |
| Stable disease | Consider minicourse or complete course of total skin electron radiation |
| Progressive | Consider combination therapies |

J Am Acad Dermatol 47: 364-370; 2002

# Dose?

| Institution | Response @ <25 Gy | Response @ 25-34 Gy | Response @ 35-36 Gy |
|---|---|---|---|
| Stanford | 29% | 50% | 70% |
| Hamilton | 43% | 63% | 80% |
| "all others" | 65% | 65% | 73% |

*Full dose for second course of TSEB has been reported, but often use a reduced dose is recommended (minimum of 4-8 Gy)

Stanford

| T (any N, M) | Energy (MeV) | No. Remissions/No. Patients Treated: 25 Gy | 25 to 35 Gy | 35 Gy | Totals |
|---|---|---|---|---|---|
| T1 | 2.5–9 | 5/5 | 4/4 | 26/27 | *35/36* |
| T2 | 2.5–9 | 18/49 | 9/15 | 33/44 | *60/108* |
| T3 | 2.5–9 | 5/27 | 0/4 | 6/17 | *11/48* |
| T4 | 2.5–9 | 6/35 | 0/3 | 5/11 | *11/49* |
| *Totals* | | *34/116* | *13/26* | *70/99* | *117/241* |

Hamilton

| T (any N, M) | Energy (MeV) | No. Remissions/No. Patients Treated: 25 Gy | 25 to 35 Gy | 35 Gy | Totals |
|---|---|---|---|---|---|
| T1 | 4 | 0/1 | 1/1 | 75/88 | *76/90* |
| | 3 | 2/4 | 18/21 | — | *20/25* |
| T2 | 4 | 1/3 | 1/1 | 70/86 | *72/90* |
| | 3 | 6/13 | 20/29 | — | *26/42* |
| T3 | 4 | 1/1 | — | 13/24 | *14/25* |
| | 3 | 3/5 | 9/18 | — | *12/23* |
| T4 | 4 | 1/2 | 0/2 | 7/10 | *8/14* |
| | 3 | 1/6 | 1/5 | — | *2/11* |
| *Totals* | | *15/35* | *50/77* | *165/208* | *230/320* |

"all others"

| Tumor Stage (Any N, M) | Energy (MeV) | No. Remissions/No. Patients Treated: 25 Gy | 25 to 35 Gy | 35–36 Gy | Totals |
|---|---|---|---|---|---|
| T1 | ≥3.5 | — | 8/8 | 41/42 | *49/50* |
| | <3.5 | 4/4 | 9/9 | — | *13/13* |
| T2 | ≥3.5 | — | 12/15 | 78/88 | *90/103* |
| | <3.5 | 6/9 | 10/29 | — | *16/38* |
| T3 | ≥3.5 | — | 1/1 | 47/62 | *48/63* |
| | <3.5 | 0/5 | 6/14 | — | *6/19* |
| T4 | ≥3.5 | — | 8/8 | 20/33 | *28/41* |
| | <3.5 | 1/3 | 0/3 | — | *1/6* |
| *Totals* | | *11/21* | *54/87* | *186/225* | *251/333* |
| Other reports (any *) | ≥3.5 | 23/34 | 32/45 | 43/64 | 98/143 |
| | <3.5 | 40/58 | — | 34/70 | 74/128 |
| *Grand Totals* | | *74/113* | *86/132* | *263/359* | *423/604* |

Hem/Onc Clin North America 9: 1057-1076; 1995

# Toxicity of TSEB

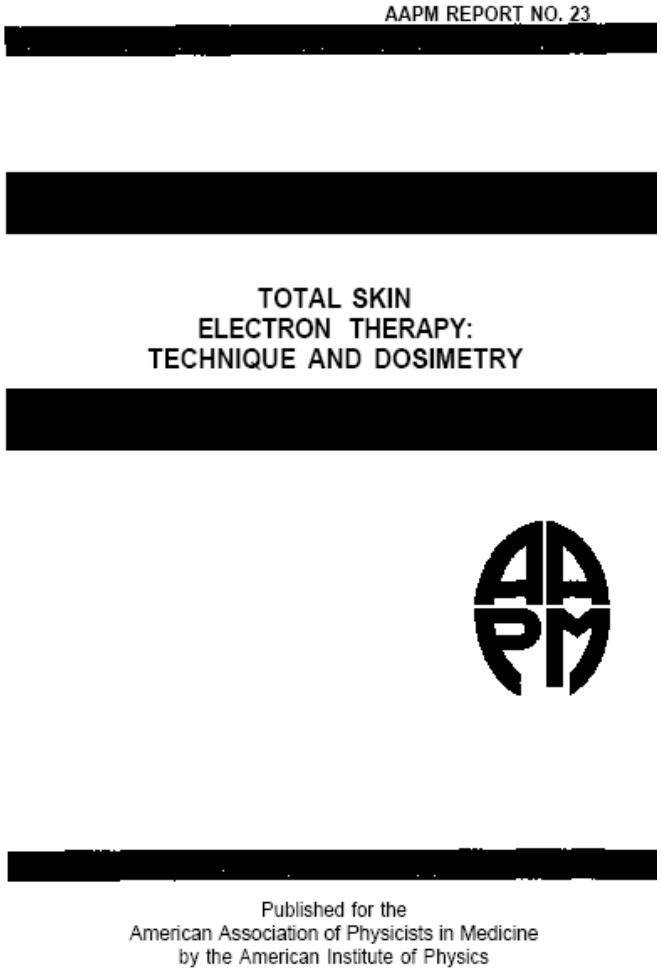
**Table II.** Expected adverse effects with total skin electron radiation

- Mild erythema in some normal regions of skin with greater skin reaction in areas of prior ultraviolet exposure; the lesions of MF become erythematous, then pigmented
- Complete, temporary scalp alopecia (100%)
- Temporary nail stasis (100%)
- Some edema of hands and feet (<50%)
- Minor nosebleeds (<10%)
- Blisters on fingers and feet (<5%)
- Self-limiting anhidrosis, minor parotiditis, and gynecomastia in males (<3% each)
- Corneal tears from internal eye shields (<1%)
- Chronic nail dystrophy, chronic xerosis, partial but permanent alopecia of the scalp, and fingertip dysesthesias that persist for more than a year (<1% each)
- Acute or late mortality attributable to TSEB (0%)

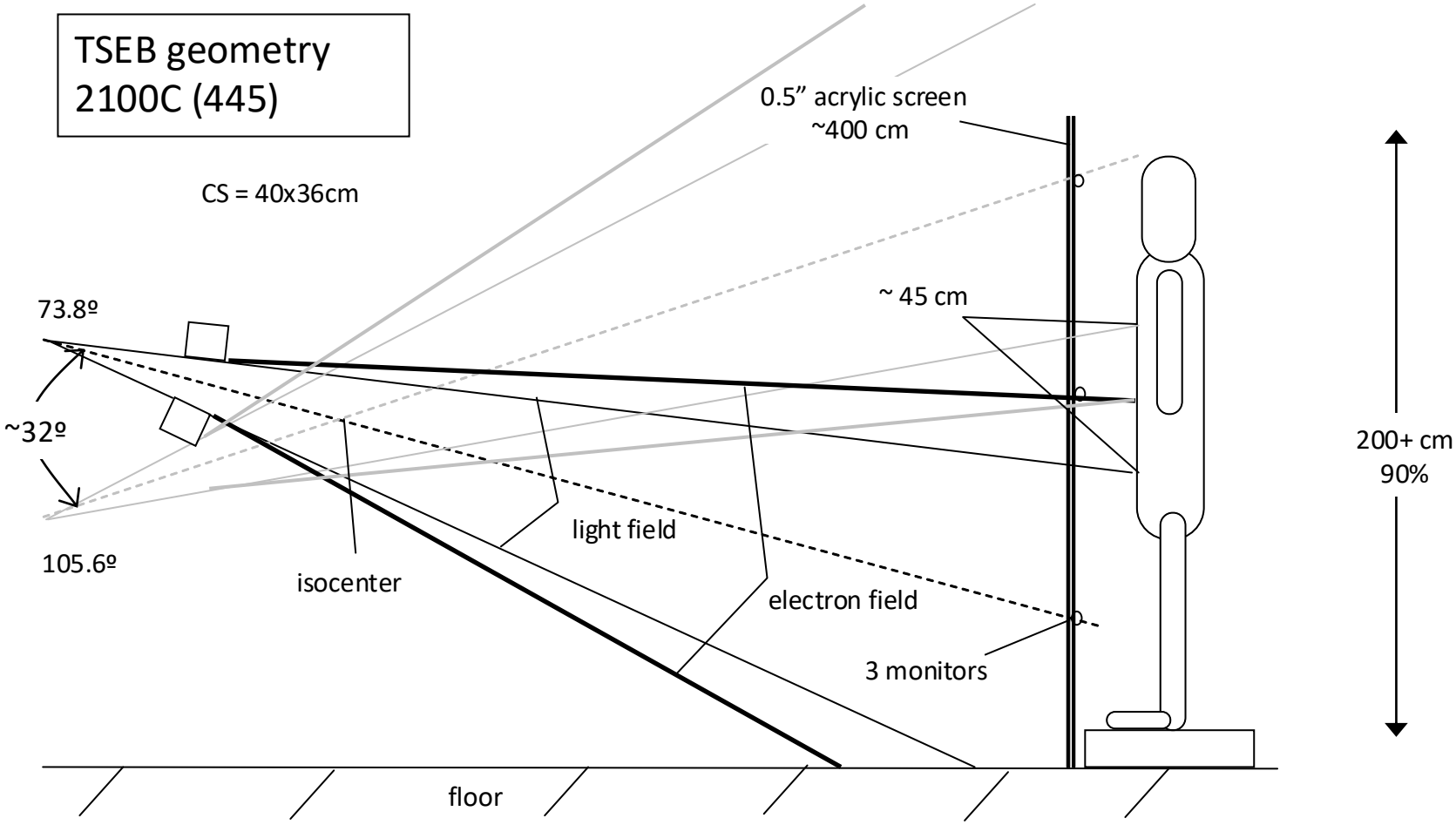
J Am Acad Dermatol 47: 364-370; 2002

# Six dual-field irradiation technique

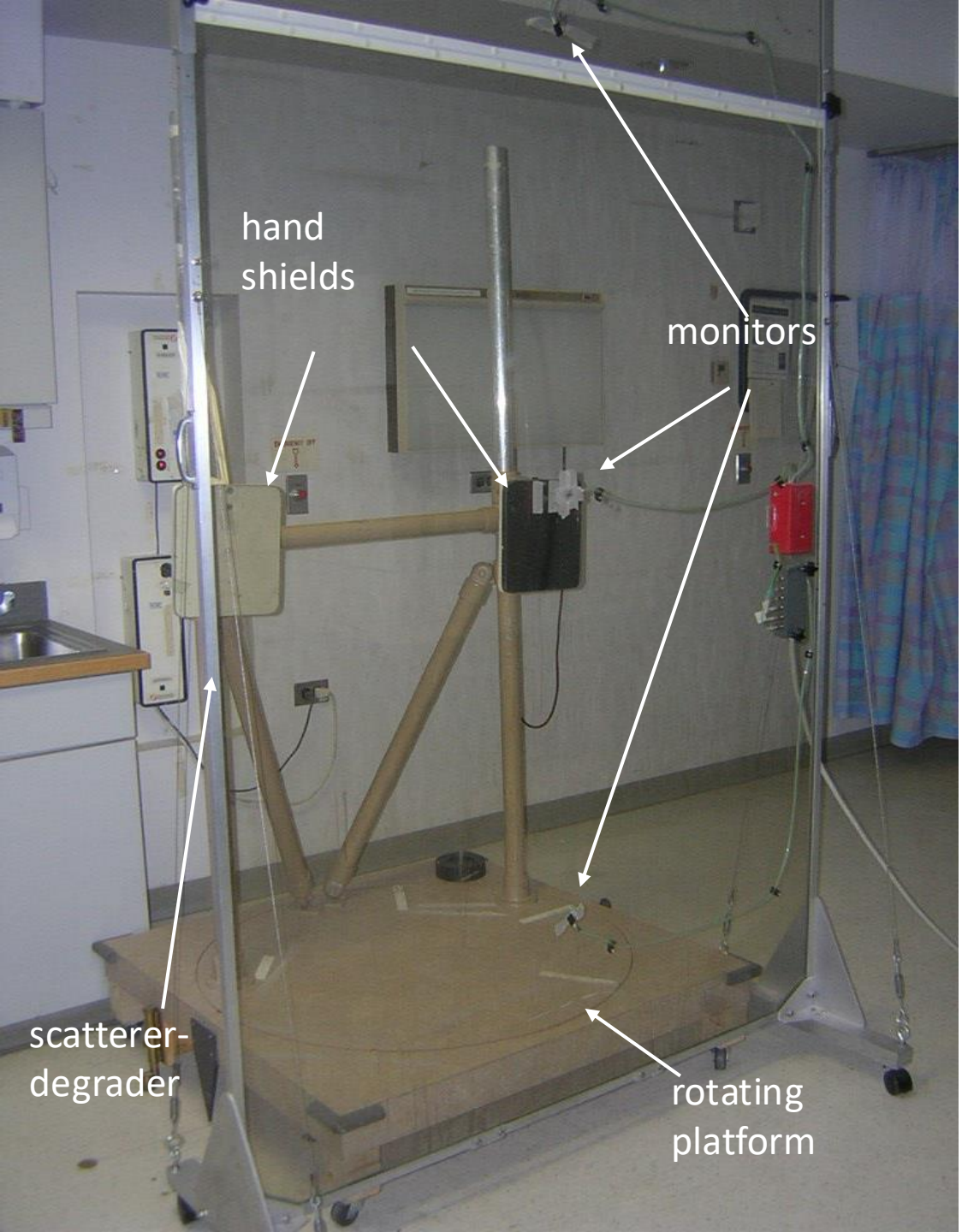
- Modified “Stanford technique” used at MSKCC
- Technique requirements:
  - Treat entire skin surface (200 x 80 cm)
  - Treat limited depth (<1 cm)
  - Deliver uniform doses
  - Minimize x-ray contamination (<3%)
  - Minimize treatment time (use high dose rate)



# Six dual-field geometry on 445




Courtesy T. LoSasso




# TSEB stand

Courtesy T. LoSasso

# “Problem areas” in TSEB

Regions at risk for dose > prescription (to be shielded)

- eyes, over or under lids
  (note: if placed under lids, backscatter ~ 50%)
- hands and feet (especially nails)
- ears and nose

Regions at risk for dose < prescription (may need boost)

- soles of feet
- perineum
- dorsal surface of penis
- inframammary folds
- top of head
- ear canal

Courtesy T. LoSasso

# Acute Effects of Radiation on Skin

- Erythema
  - Depends on dose, field size, fractionation, beam quality
- Dry desquamation (peeling)
- Moist desquamation
  - Epidermal basal cell layer eradication causes exposure of dermis and oozing from surface
  - Epidermal regrowth occurs at periphery of field first, and in epithelial cells around hair follicles
- Erosions
- Epilation
- Response depends on patient phenotype (individual sensitivity), anatomic site, total dose, dose rate, fractionation, ionization density, vascular supply

# Management of Acute Reactions

- Avoid trauma to skin (shaving, scratching, sun exposure)
- Clean with mild soap and pat dry
- Avoid creams/cleansers with harsh chemicals (alcohol)
- Mild potency steroids (1% hydrocortisone, 0.025% triamcinilone) minimizes erythema, dry desquamation, pruritis
- Dilute hydrogen peroxide, 1% aqueous gentian violet can dry moist desquamation and prevent infection
- 1% silver sulfadiazene cream promotes healing of moist desquamation

# Chronic Effects of Radiation on Skin

- Telangiectasias
- Hyperpigmentation (melanocyte stimulation)
- Hypopigmentation (melanocyte destruction)
- Alopecia
- Subcutaneous fibrosis
- Xeroderma (sebaceous and sweat gland destruction)
- Soft tissue necrosis (5%)
- Secondary malignancies

# Management of Chronic Reactions

- Apply gentle moisturizing creams
- Avoid trauma to skin (new skin is thin, atrophic)
  - Mechanical
  - Chemical
  - Radiation (UV or ionizing)

# Patient Reported Outcomes of RT

- 47 elderly patient treated with RT for BCC
- 12/47 alive 10 years after RT
- Asked about cosmetic result
  - Excellent/Very Good/Good/Mediocre/Poor
  - 6/12 (50%) rated it Excellent
  - 3/12 (25%) rated it Very Good
  - 3/12 (25%) rated it Good

Cooper JS. Patients' perceptions of their cosmetic appearance more than ten years after radiotherapy for basal cell carcinoma. Radiation Medicine 1998.

# Secondary Malignancies after Skin RT

- Lindelof and Ekland reviewed 14,410 patients treated with radiation (Grenz) rays for benign skin diseases using Swedish Cancer Registry
- Average follow-up was 15 years
- 0.4% developed a non-BCC skin cancer
  - 1 of these 58 patients developed a tumor in the irradiated field
- Felt risk of secondary skin cancer was low if:
  1. "No area of the skin is subjected to more than 100 Gy in a lifetime
  2. The dose is fractionated (1 fraction/week for 4-6 weeks), with 6 months between treatments
  3. Dose of Grenz rays is tailored to the skin disease in question and treated area."

# The more you read, the more things you will know
# The more that you learn, the more places you'll go

-Dr Seuss (I Can Read with My Eyes Shut!)

Suggested Reading:


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