PowerPoint Presentation for Transplant Physicians

- This presentation was designed to be given by a health-care professional to an audience of transplant physicians
- The presenter should feel free to modify the slides and the presentation to fit the needs of the audience
- The presenter should use discretion as to whether any images or other materials in the presentation are suitable for any particular audience
- Explanations and elements of narration can be found in the notes section

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Skin Cancer in Organ Transplant Patients: Challenges and Opportunities

Supported by an unrestricted educational grant from Connetics Corporation

connetics®

AT-RISC ALLIANCE

After Transplantation – Reduce Incidence of Skin Cancer

AT-RISC Alliance

TRIO

INTERNATIONAL TRANSPLANT NURSES SOCIETY

ITSCC
INTERNATIONAL TRANSPLANT SKIN CANCER COLLABORATIVE

AT-RISC
ALLIANCE

After Transplantation–
Reduce Incidence of Skin Cancer

AT-RISC
ALLIANCE
After Transplantation–
Reduce Incidence of Skin Cancer

Skin Cancer Facts: the AT-RISC Fact Sheet

- Skin cancer is a serious problem for transplant patients
  - Up to 70% of long term patients will develop
- Immunosuppression and sun damage cause skin cancer
- Skin cancer can significantly decrease transplant recipients' quality of life
  - Some patients may develop > 100 skin cancers per year
- Skin cancer may even cause death
  - After the fourth year post-transplant, 27% of patients in high risk areas die of skin cancer

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Skin Cancer Facts: the AT-RISC Fact Sheet

- Sun protection is the best strategy to prevent skin cancer
- Early diagnosis of skin cancer can save lives
- Sun protection practices are currently inadequate
  - Only 54% of transplant recipients remember receiving skin cancer education
  - Only 40% of transplant recipients regularly use sunscreen

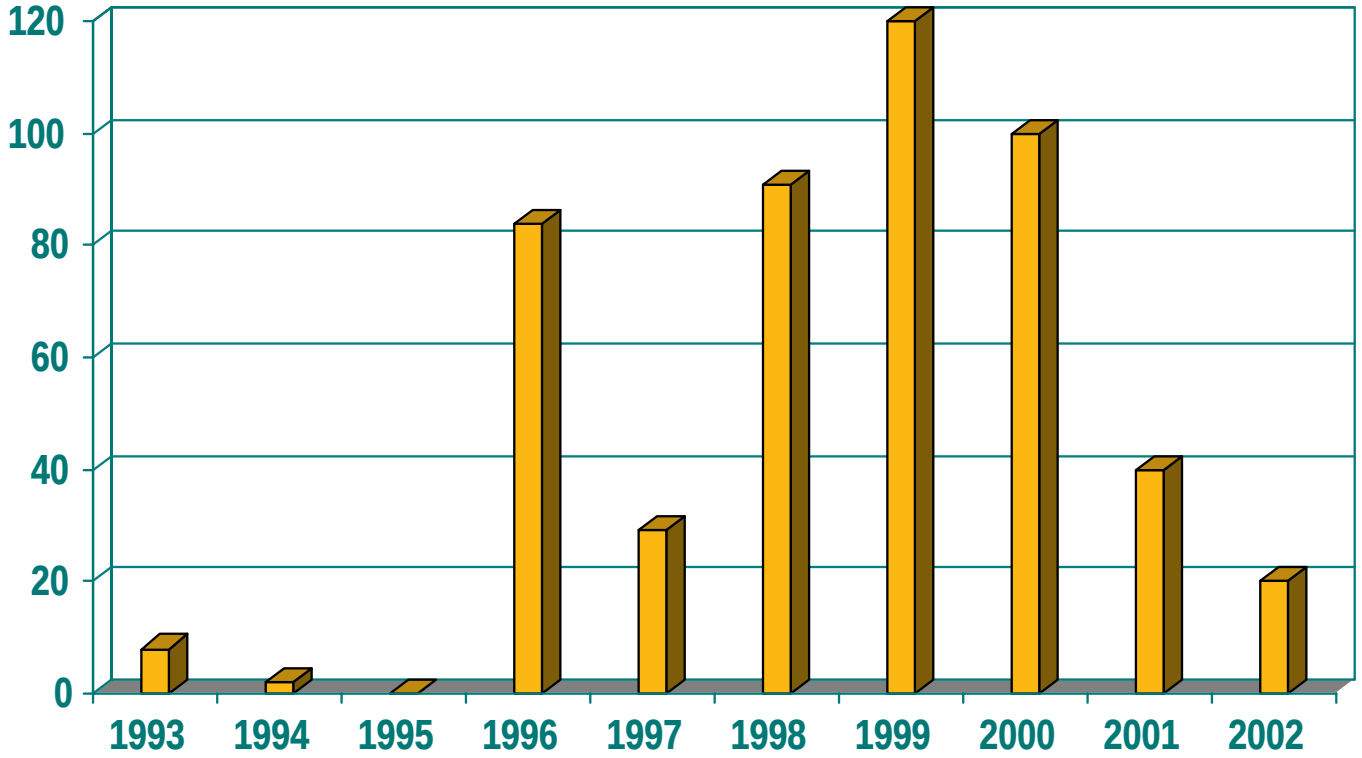
AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

How Bad Can This Be?

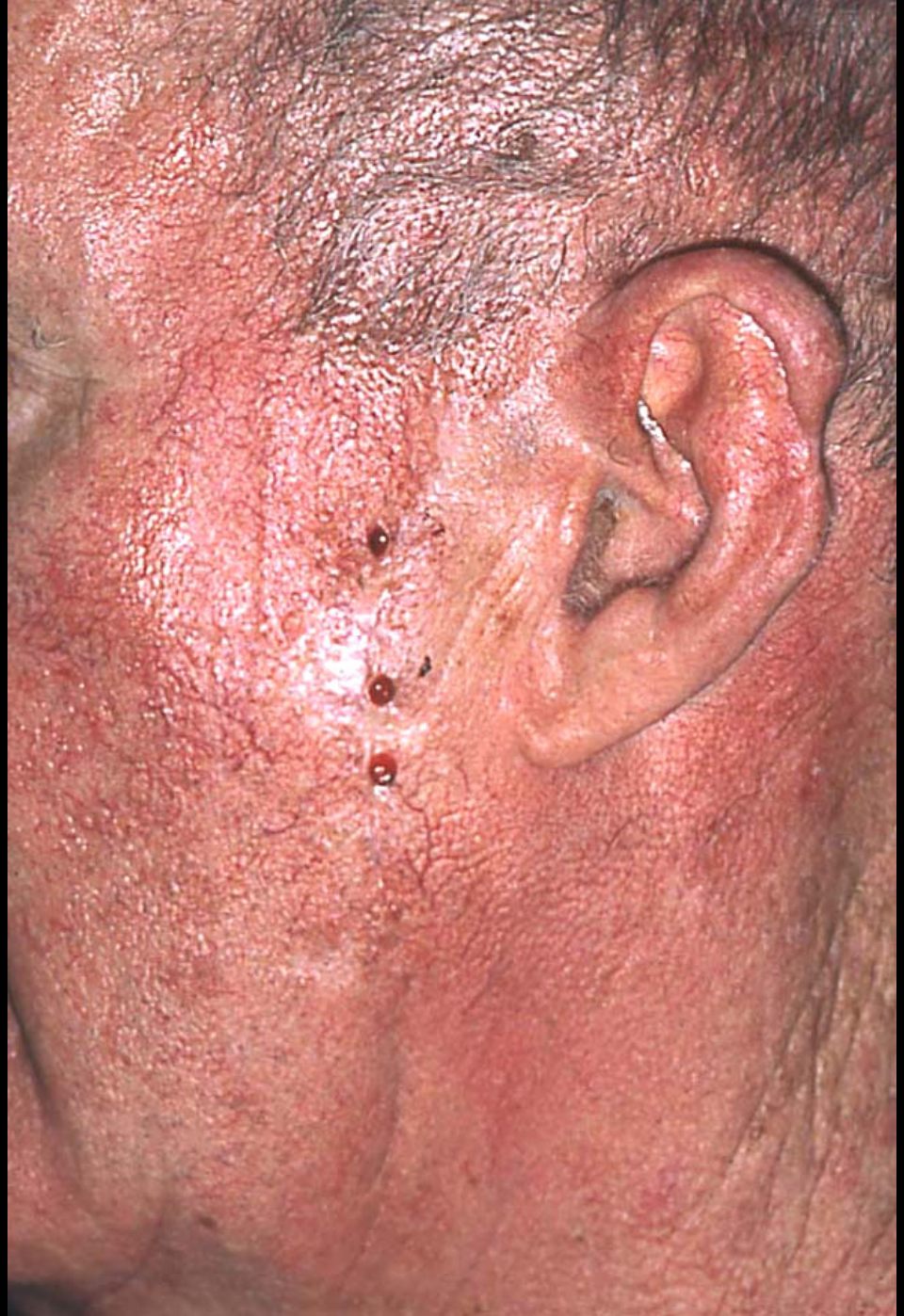
AT-RISC ALLIANCE

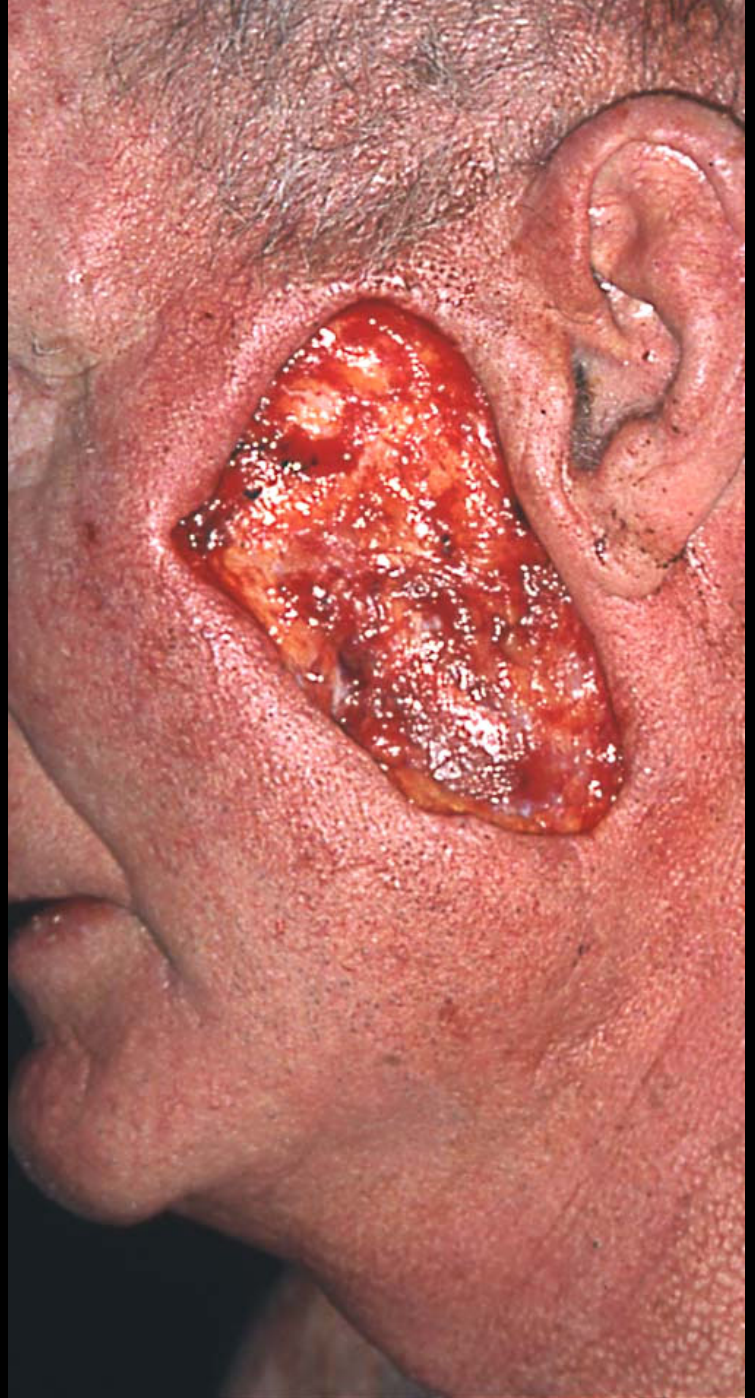
After Transplantation–
Reduce Incidence of Skin Cancer

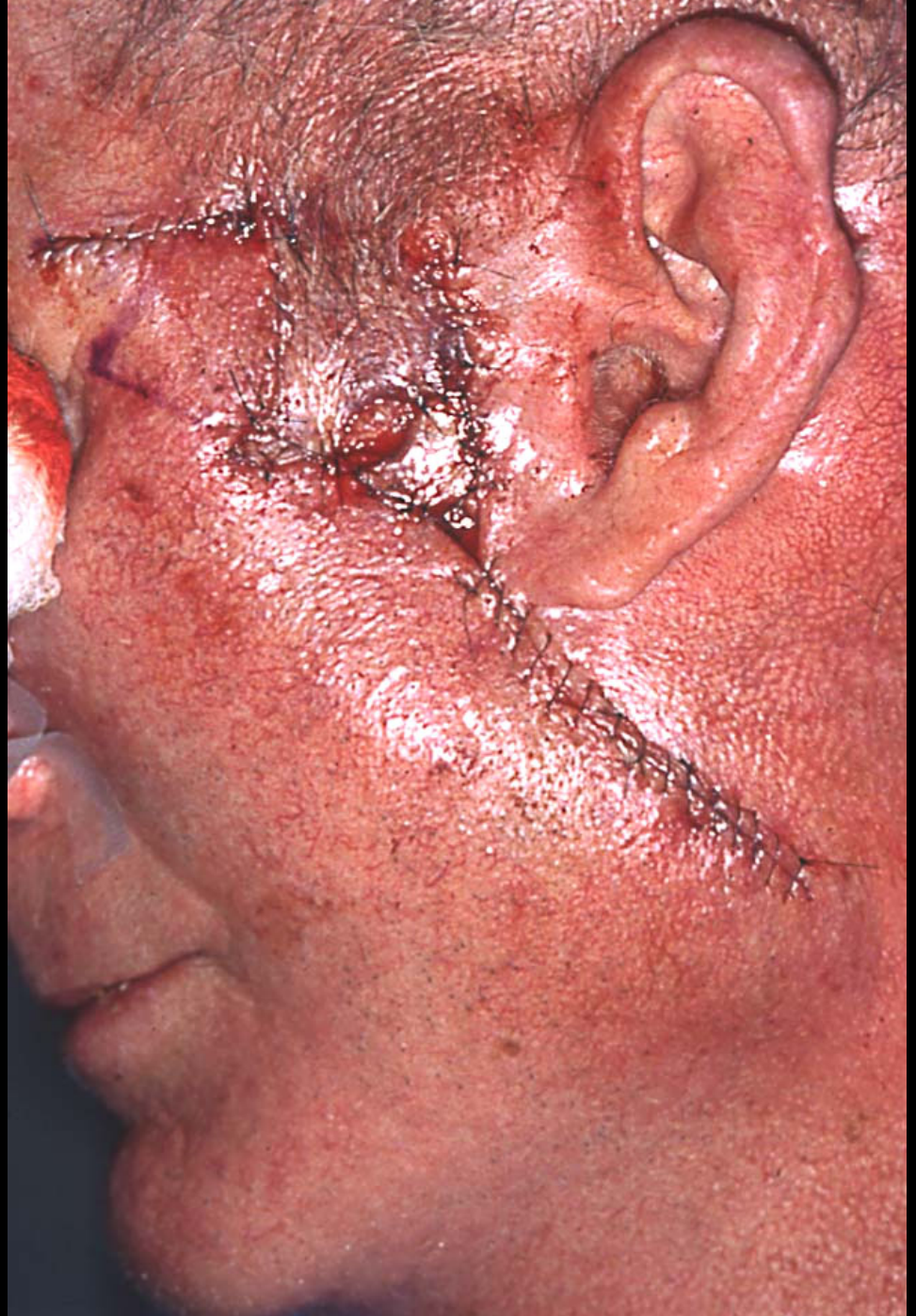
73 Year-old Outdoorsman s/p Cardiac Transplant 1993



AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer



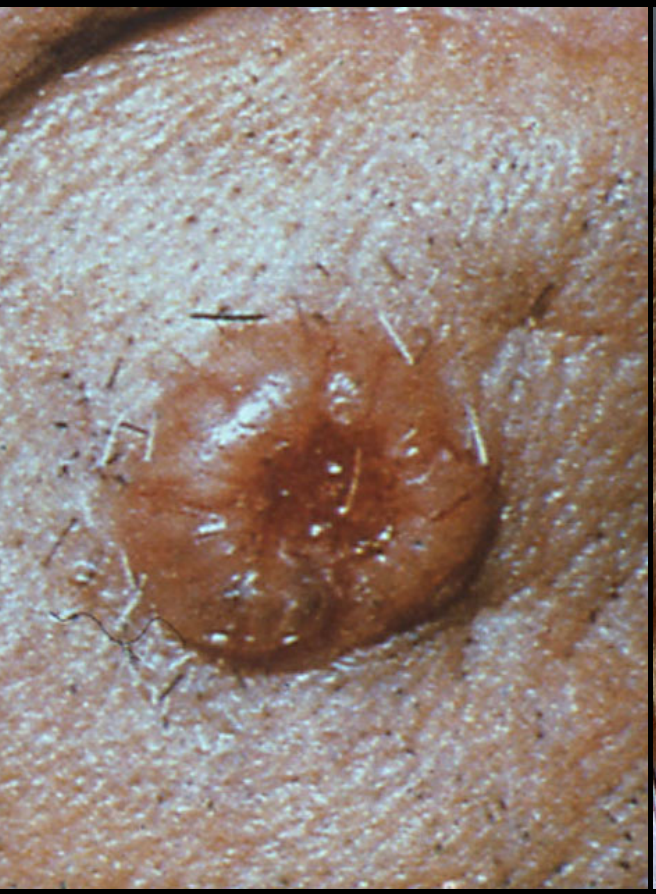


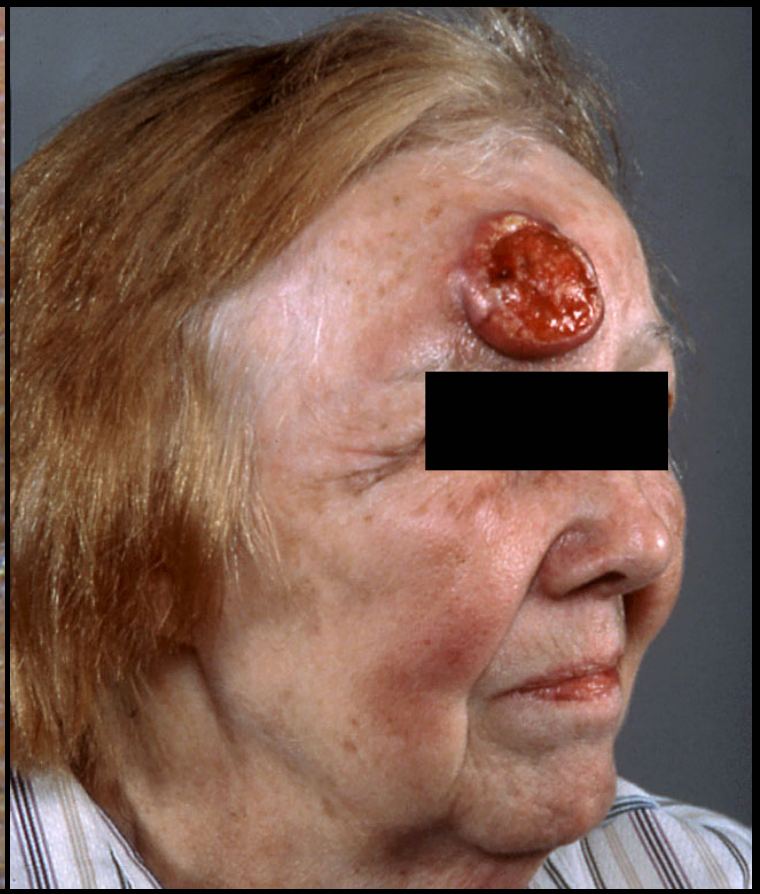


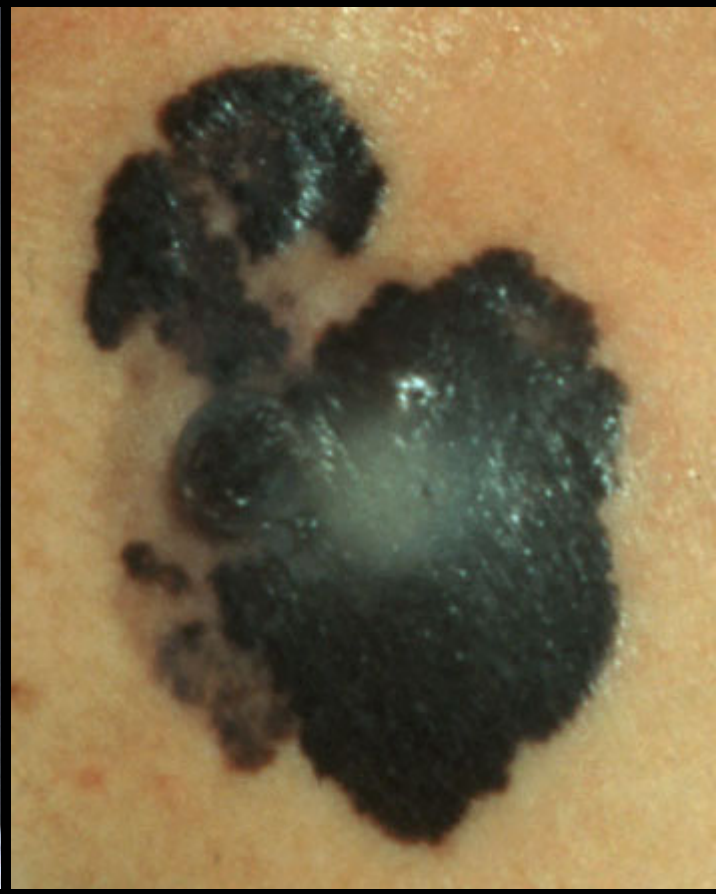
Skin Cancer Essentials

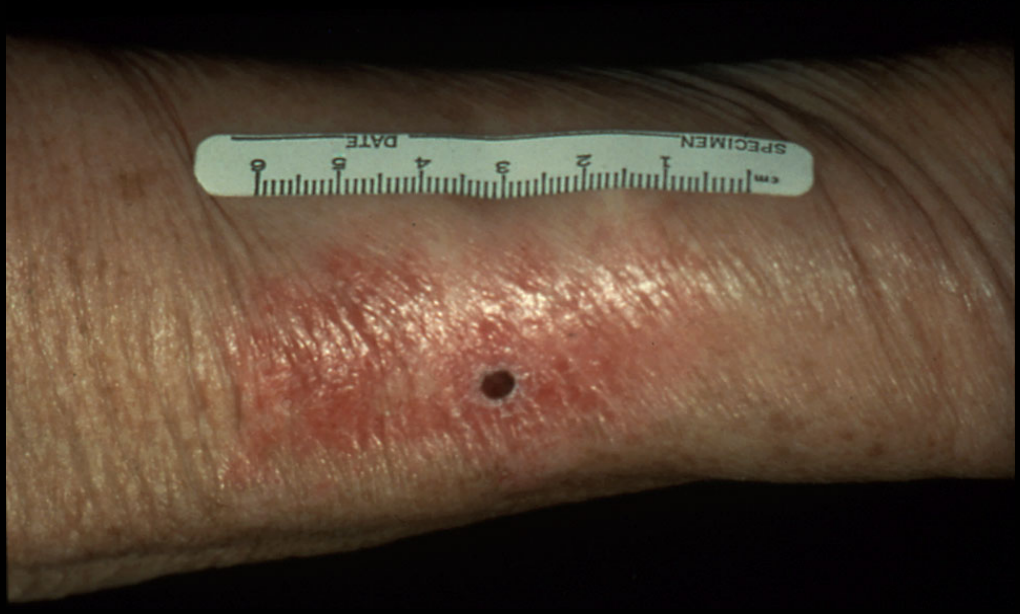
- Basal Cell Carcinoma
- Squamous Cell Carcinoma
- Melanoma
- Rare carcinomas

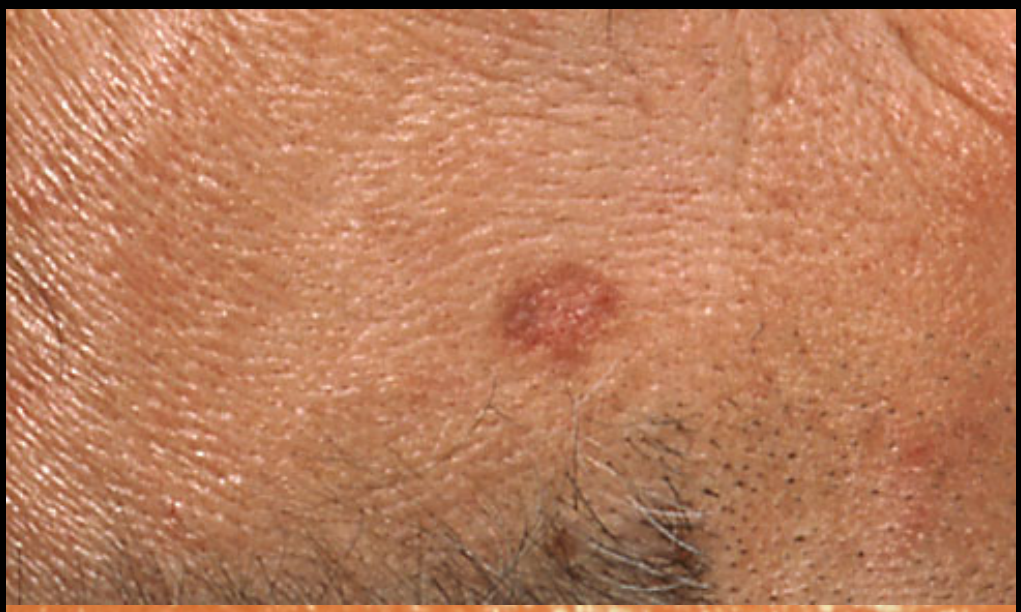
AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

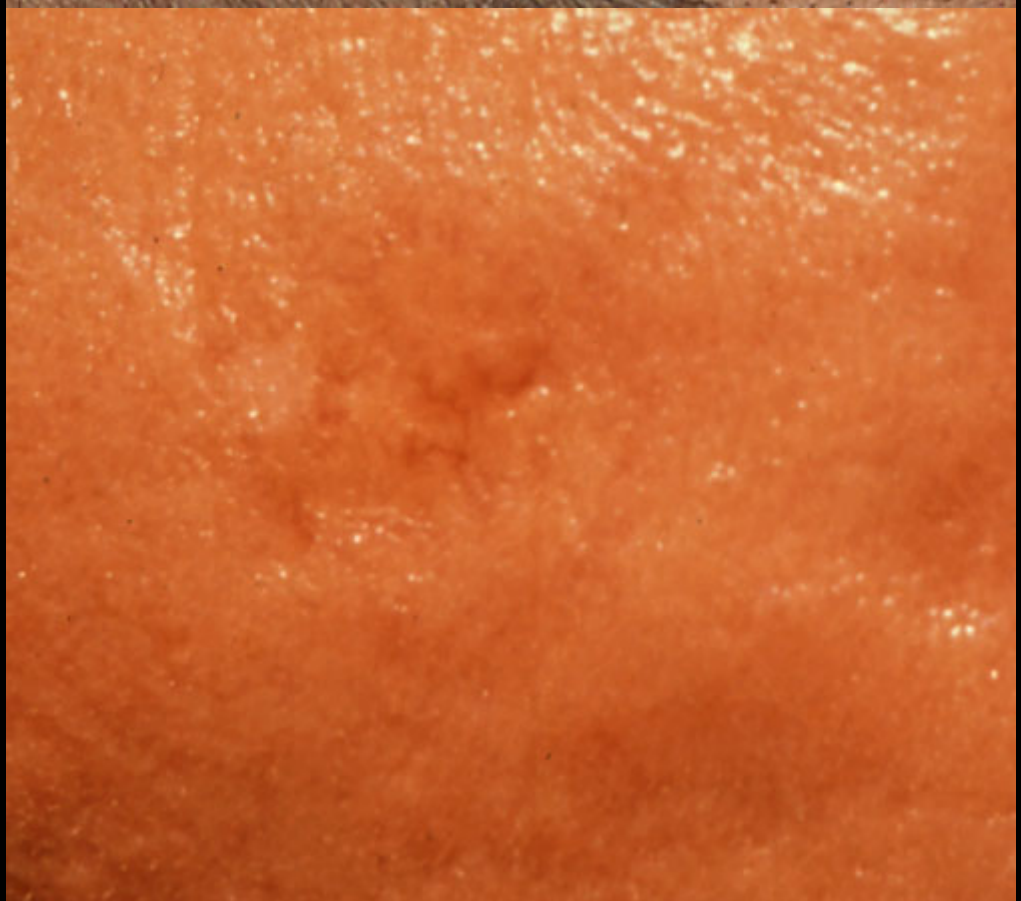







SPECIMEN
DATE
cm
1
2
3
4
5
6



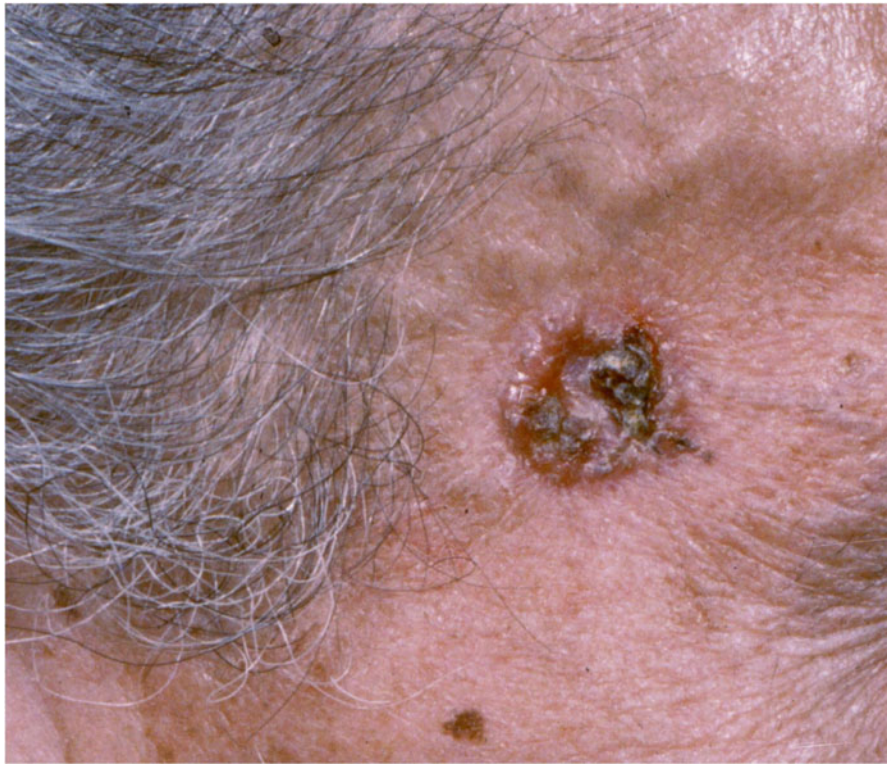


Basal Cell Carcinoma

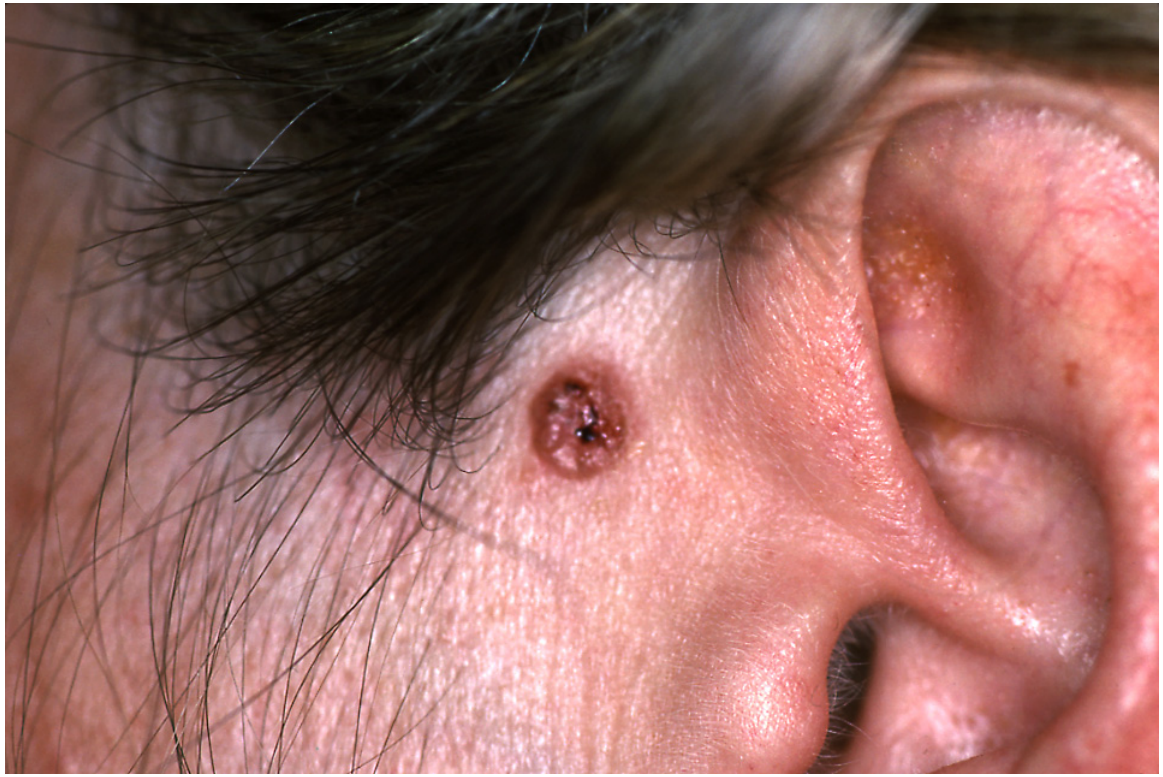
- 1,000,000/year in U.S. in photodamaged adults
- Incidence doubles every 25 years
- Local destruction, rare metastasis
- Electrodessication and Curettage, Excision, Radiation
- Mohs Micrographic Surgery
- Clinical types
  - Nodular
  - Superficial
  - Morpheaform

Features of Nodular (Classic) BCC

- Most often on the face, ears and other sun-exposed areas
- Papule with rolled borders
- Pearly sheen
- Blood vessels at the edges
- Central ulceration
- NON-HEALING SORE

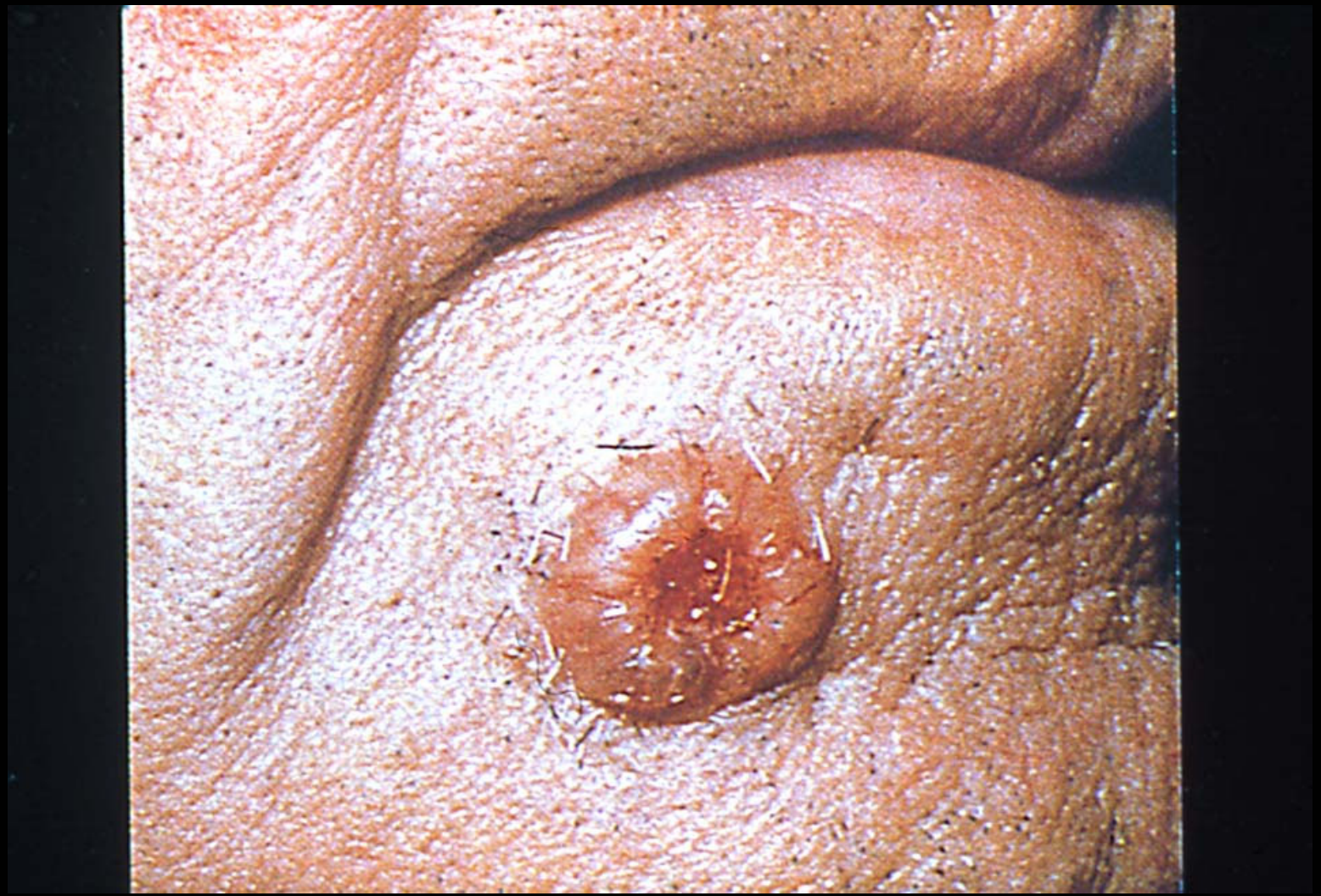


AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer



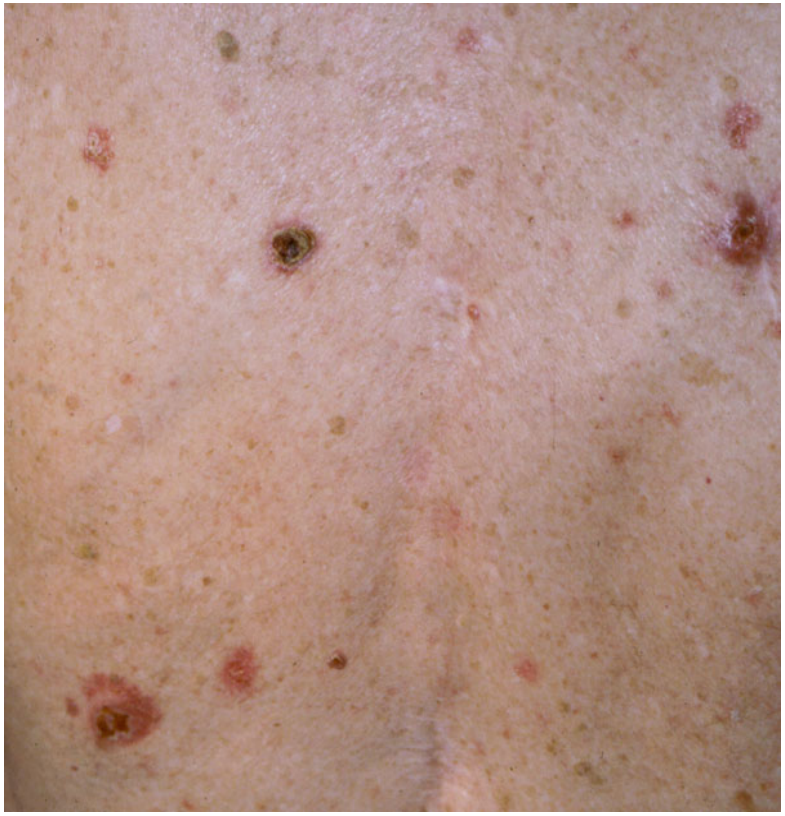
- Basal Cell Carcinoma-nodular

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

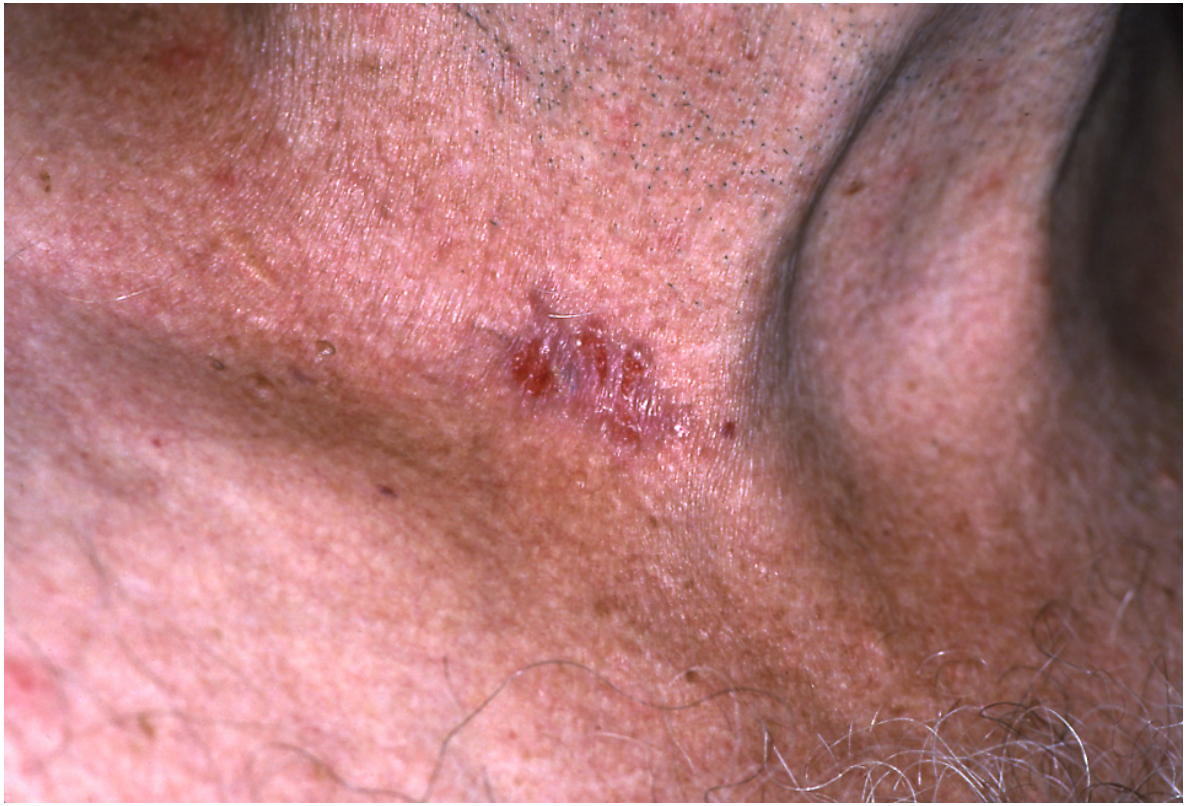


Features of Superficial BCC

- Most common on shoulders, chest, back and arms
- Area of redness, often with scale
- May have brown color at the border
- Slow growing

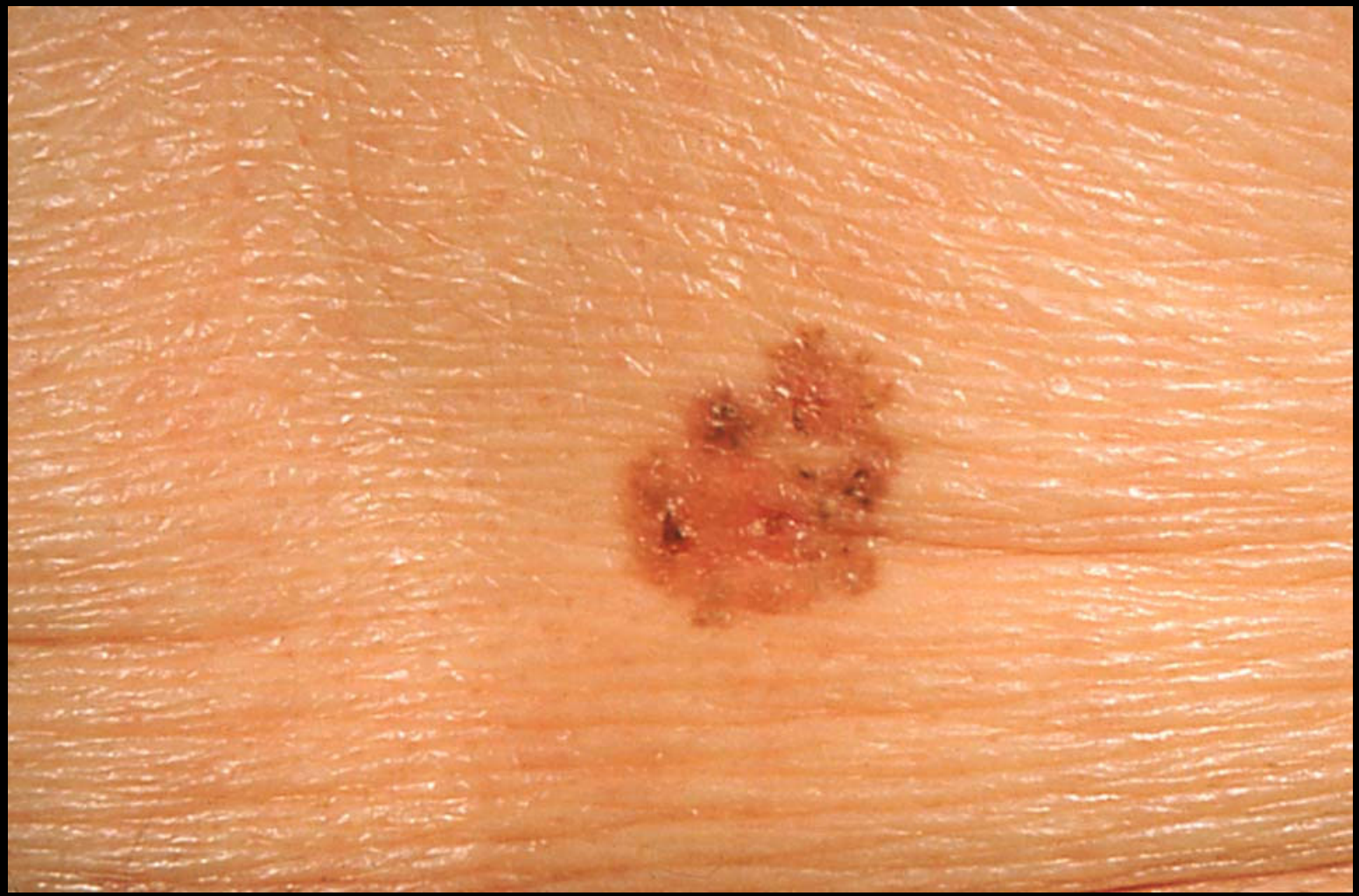


AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer



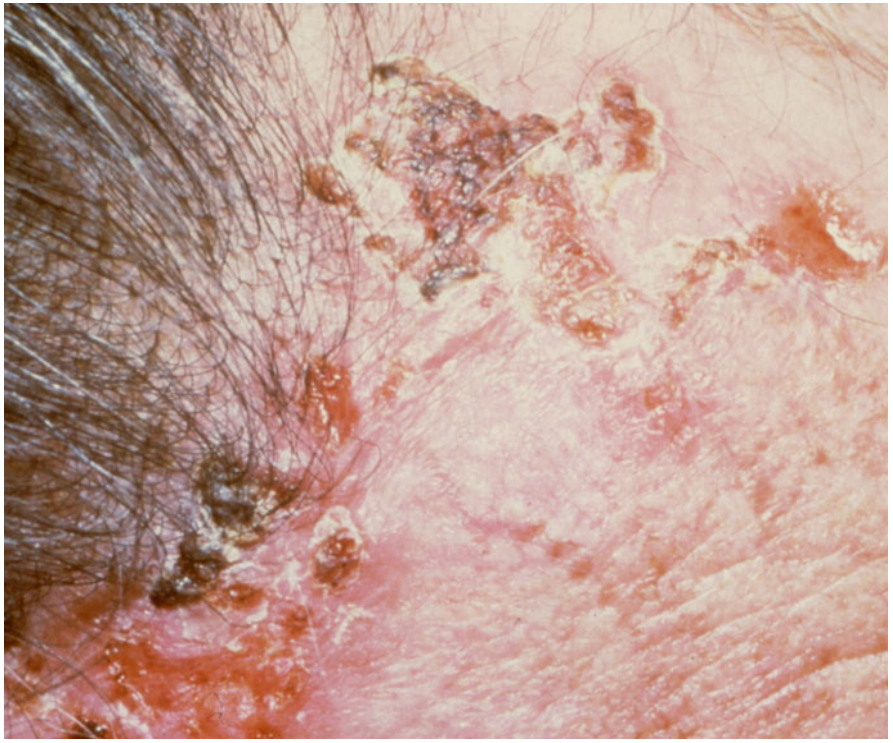
- Basal Cell Carcinoma-superficial

AT-RISC ALLIANCE
After Transplantation–
Reduce Incidence of Skin Cancer

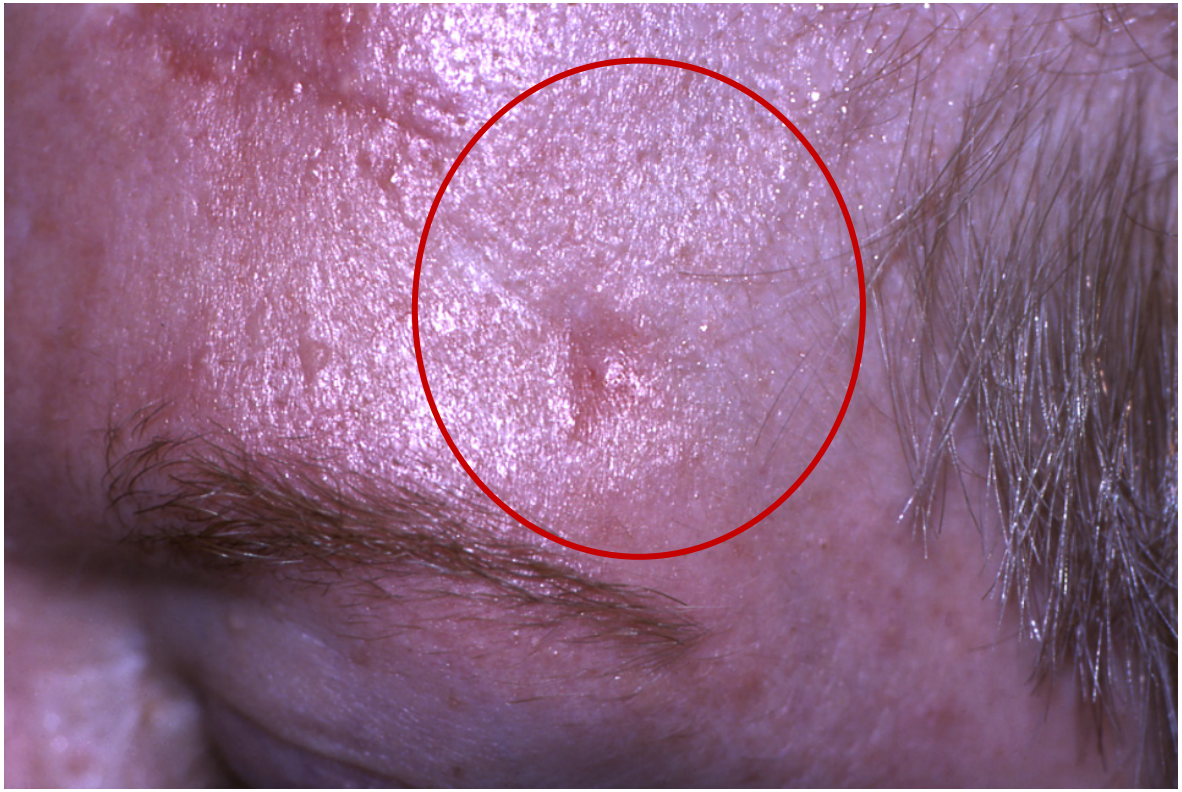


Features of Morpheaform BCC

- Most often on the face
- May look like a scar with poorly defined borders and a shiny, taut surface
- May ulcerate
- Usually more aggressive
- Often cosmetically destructive

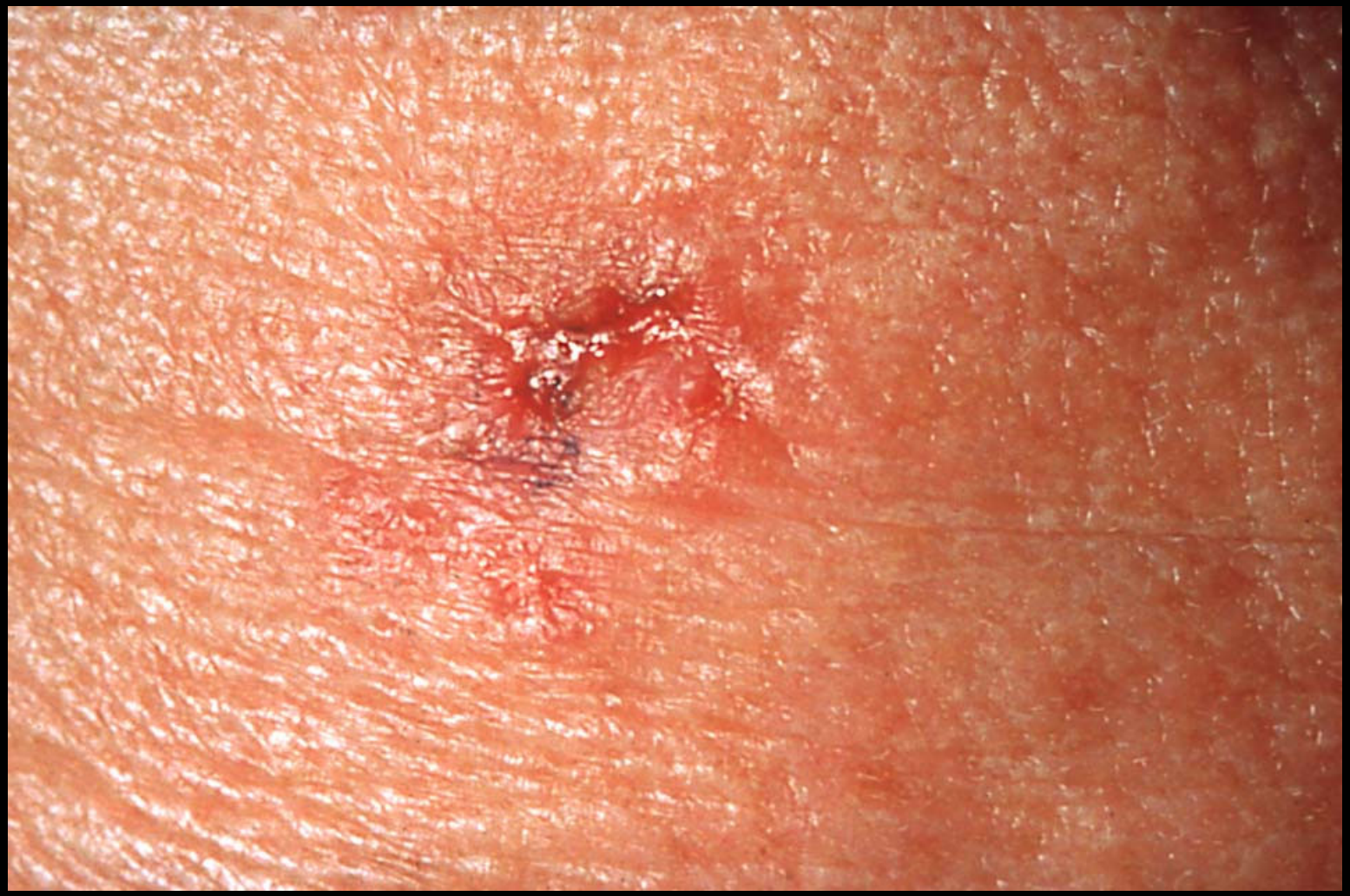


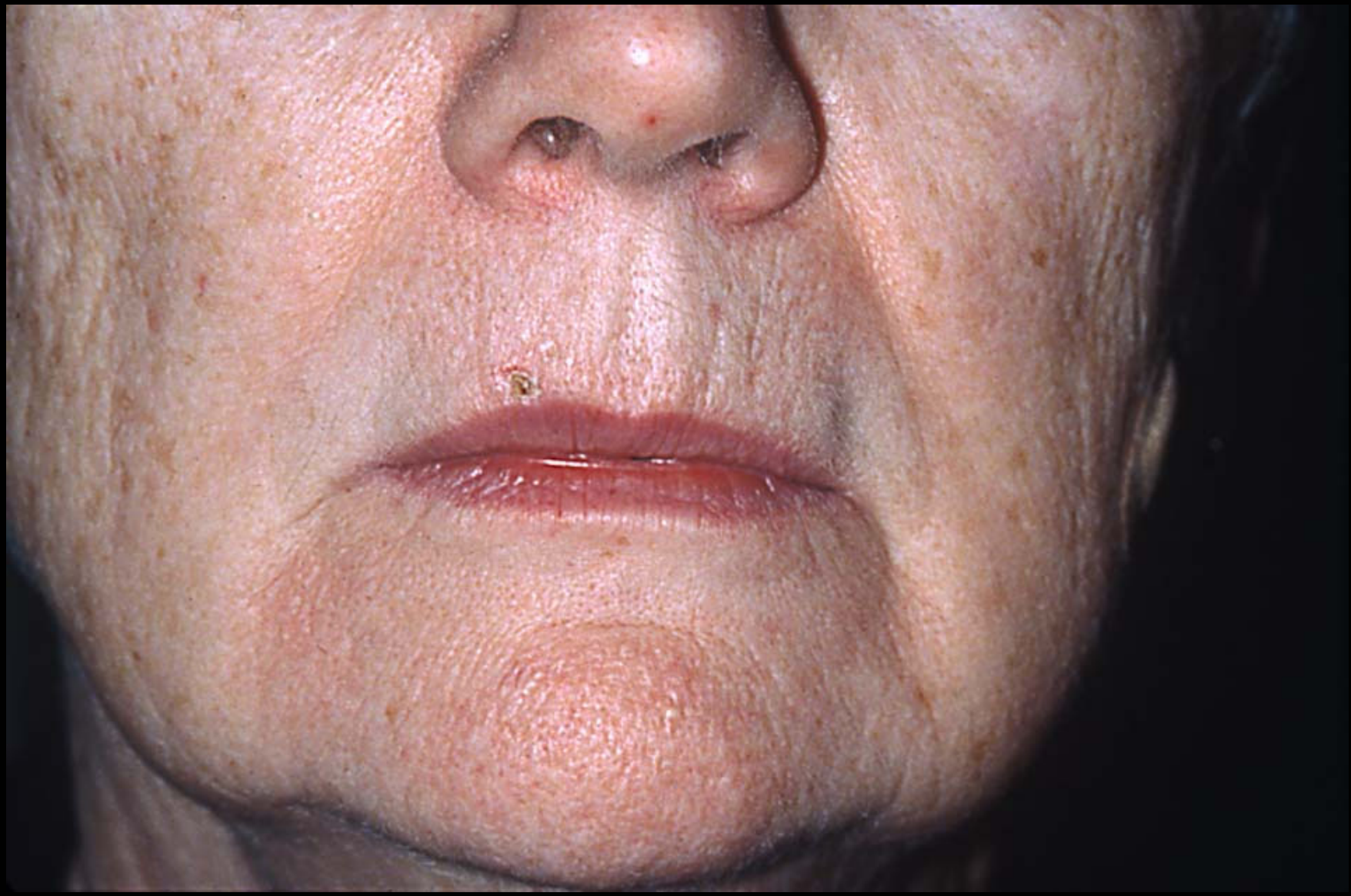
AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

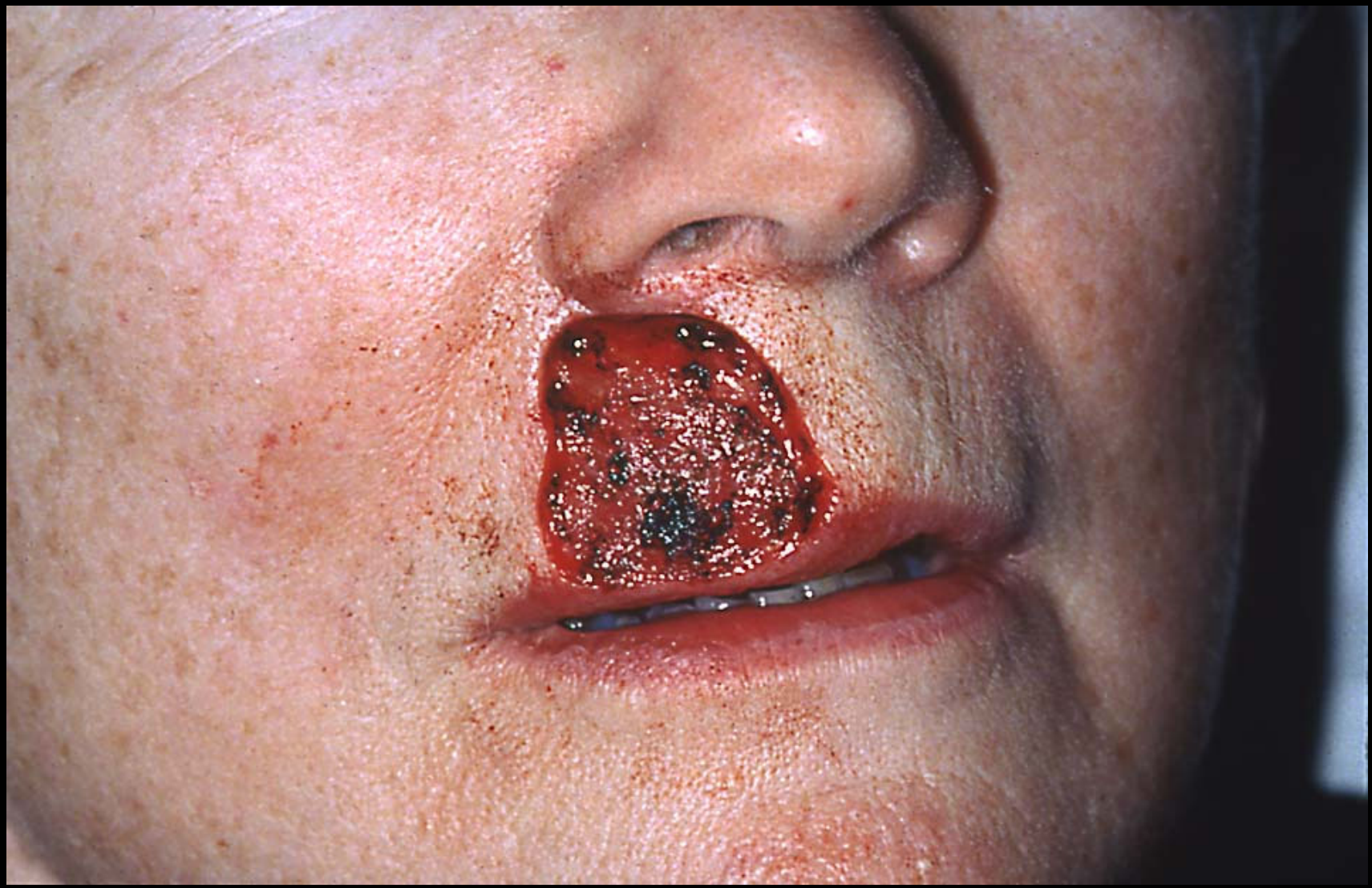


- Basal cell carcinoma-morpheaform type

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

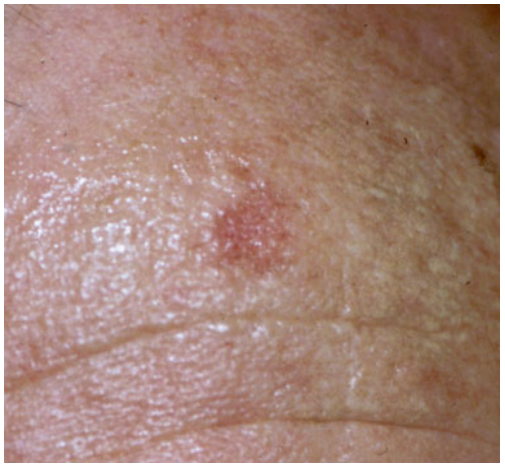


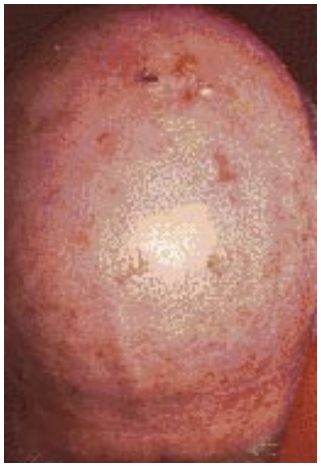




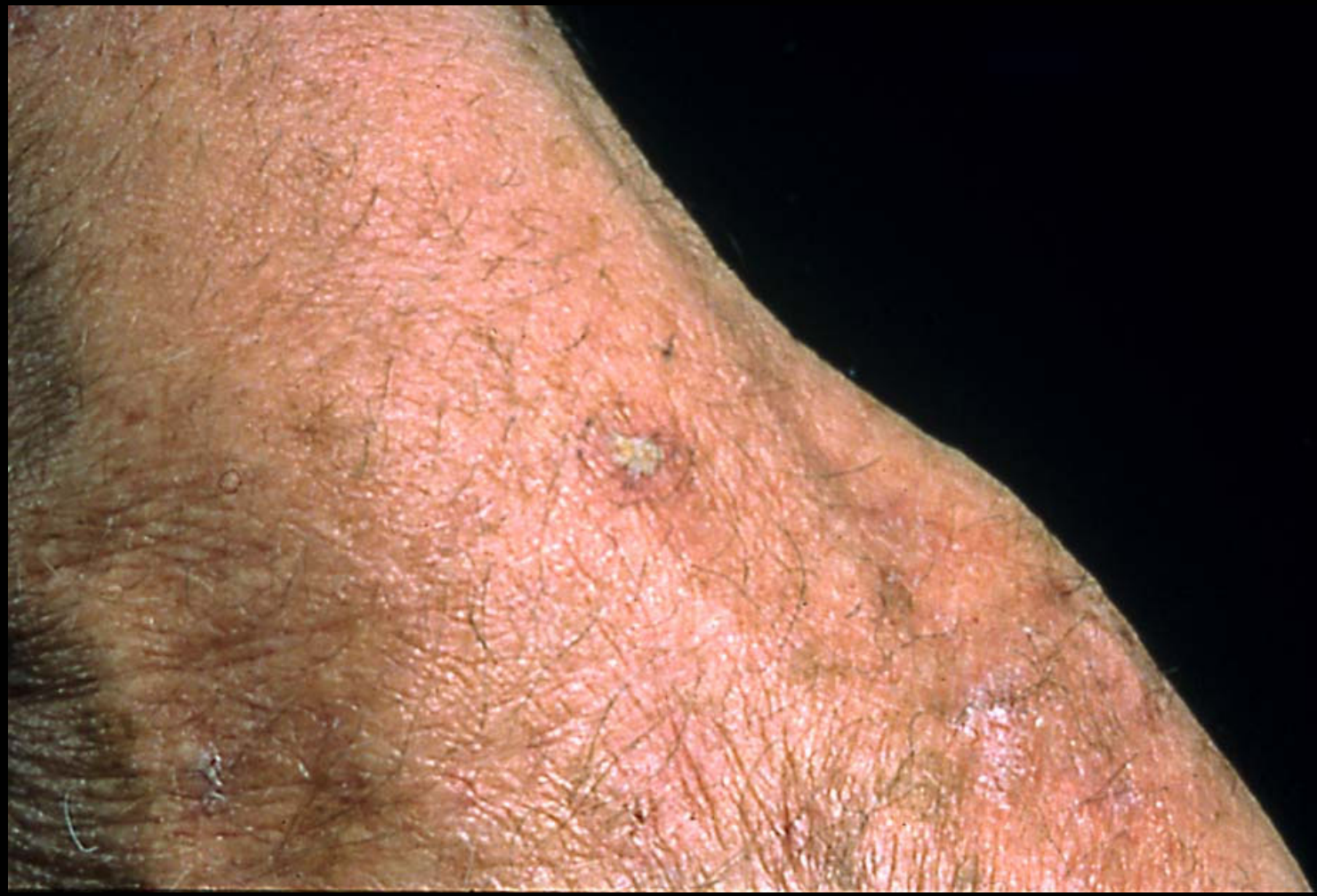
Actinic Keratosis (a.k.a. the First Stage of SCC)

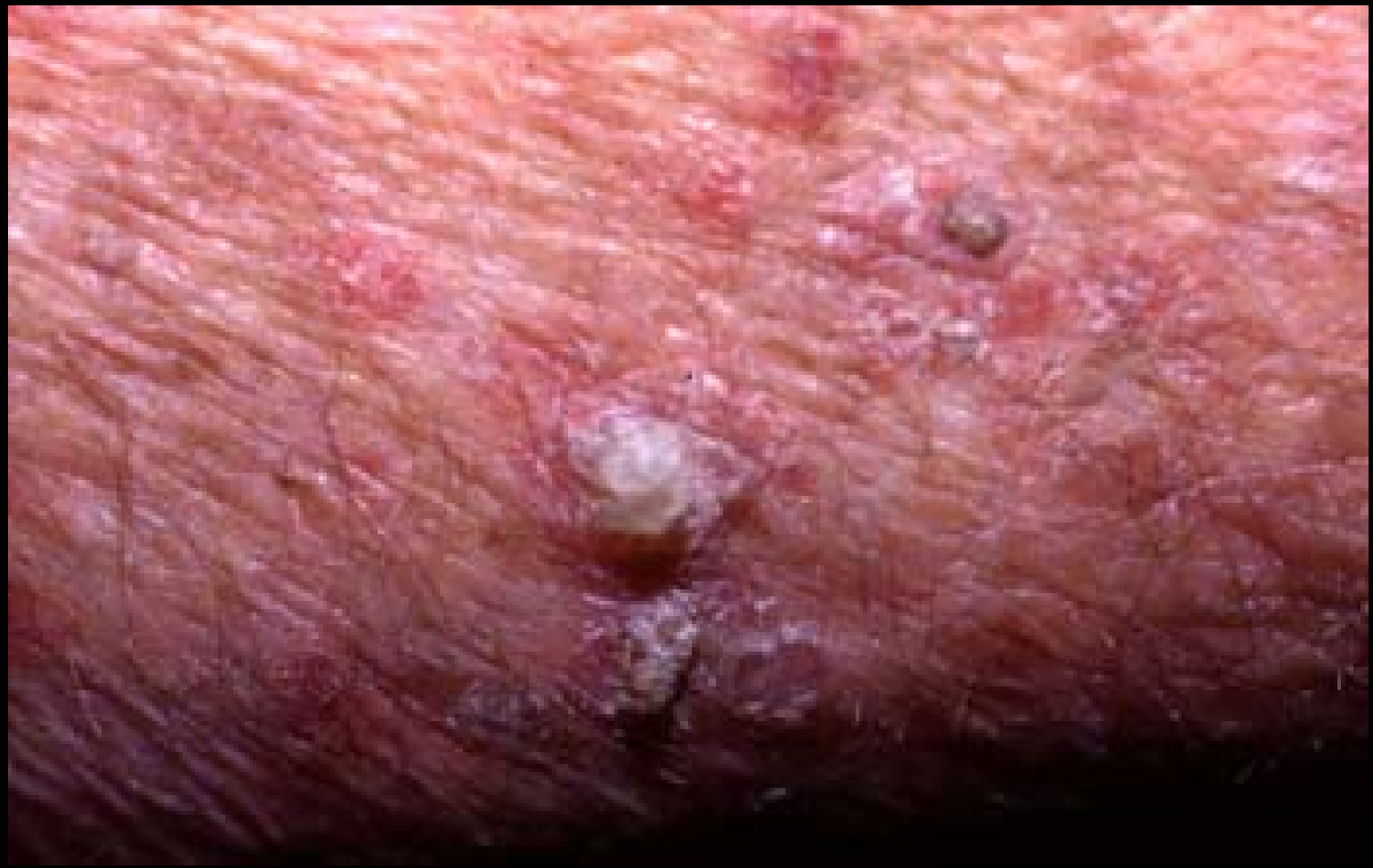
- Rough, scaly lesion on a red, irritated base
- May shed to leave red base--then recur
- May be more easily felt than seen
- Individuals often have multiple lesions

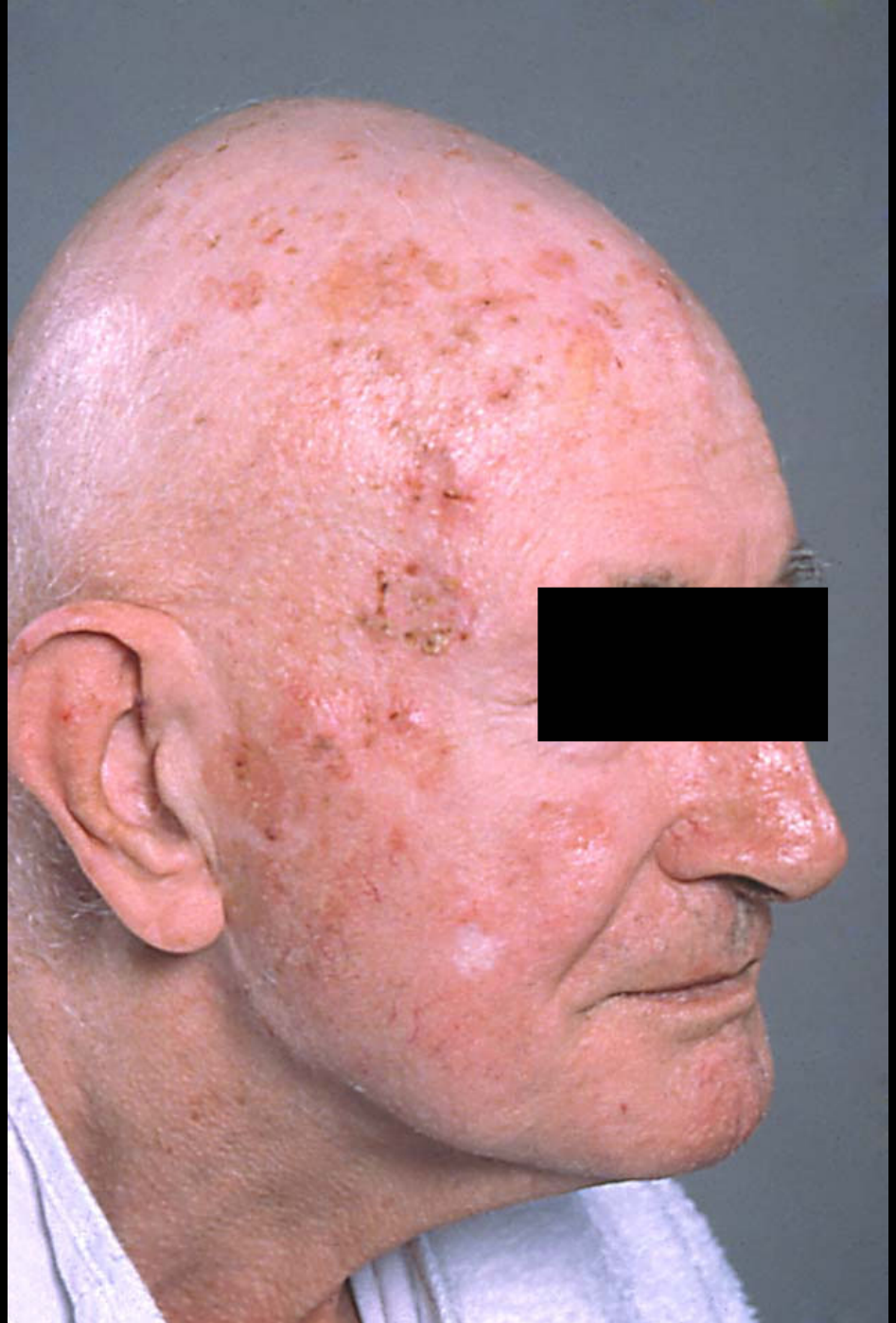




AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer







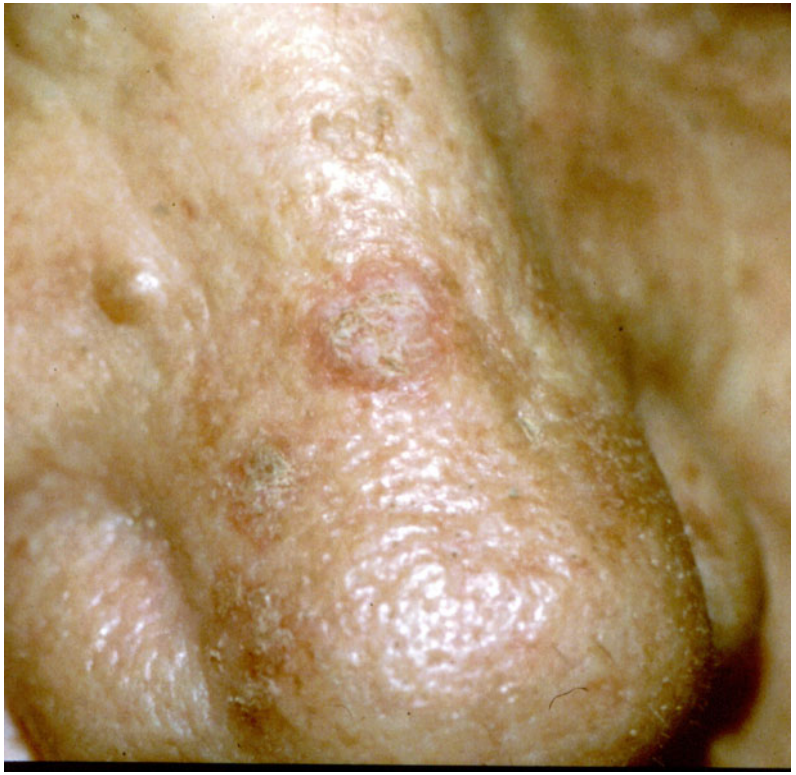
Squamous Cell Carcinoma (SCC)

- Second most common skin cancer in general population
- Most frequent cancer in transplant patients
- 300,000/year in the U.S.
- Location: 75% on head/neck or hands
- Risk of metastasis in general population: 0.5-5%
  - Increased for organ transplant patients

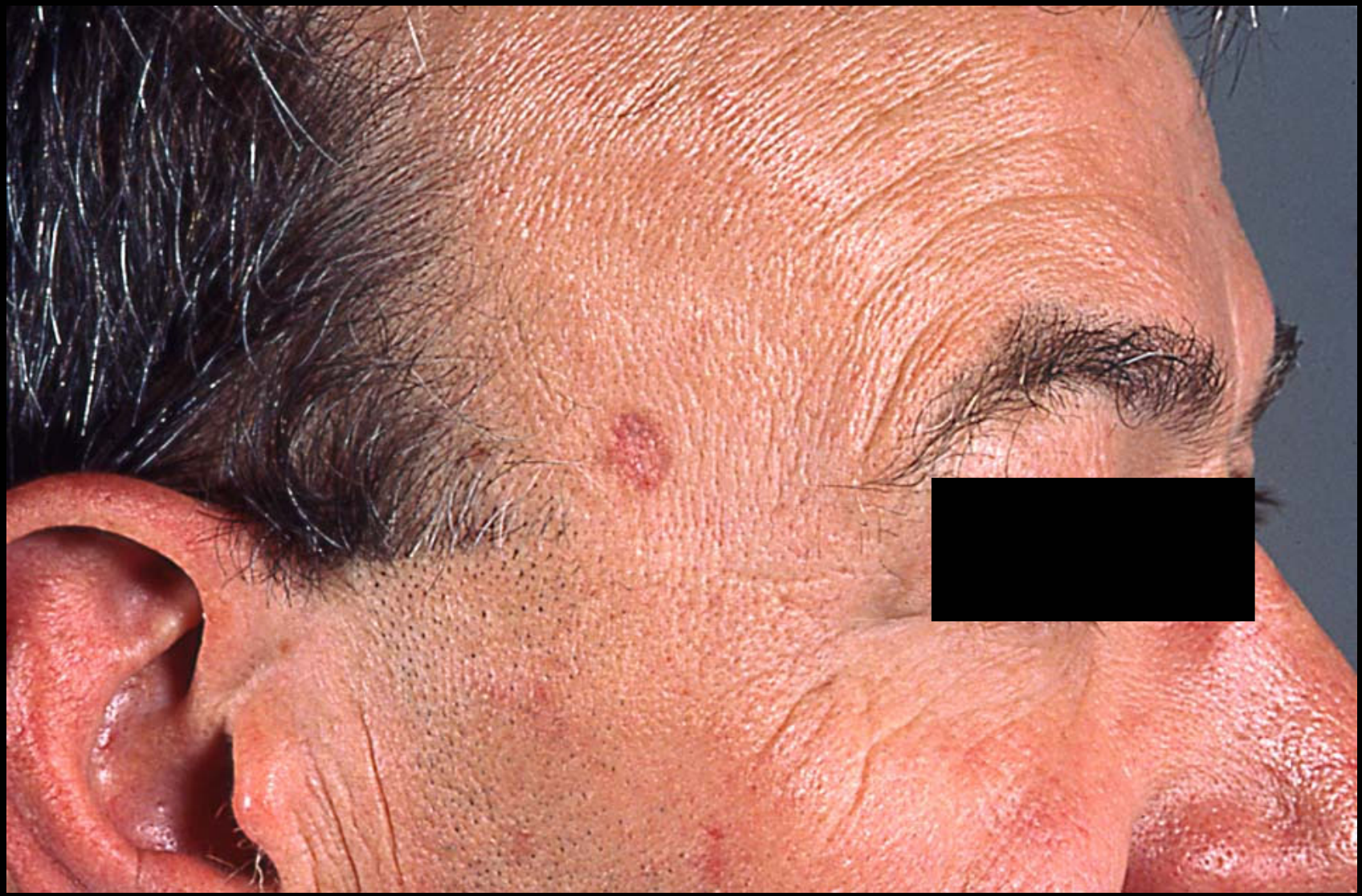
AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

SCC

- As the lesion progresses from the appearance of an AK
- Red, scaly patch
- With or without crusting
- May develop a nodule

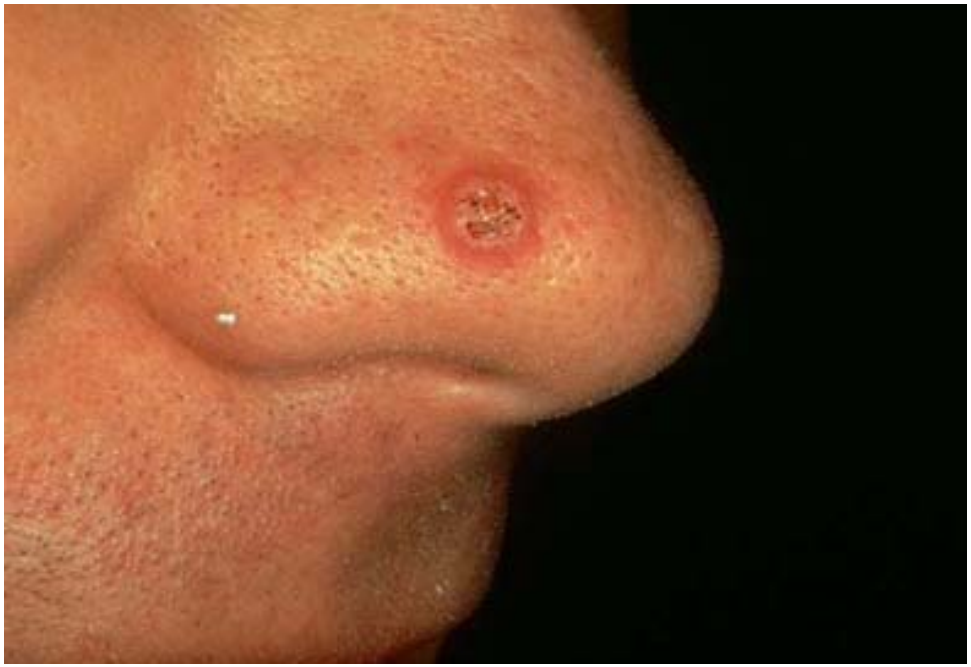


AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

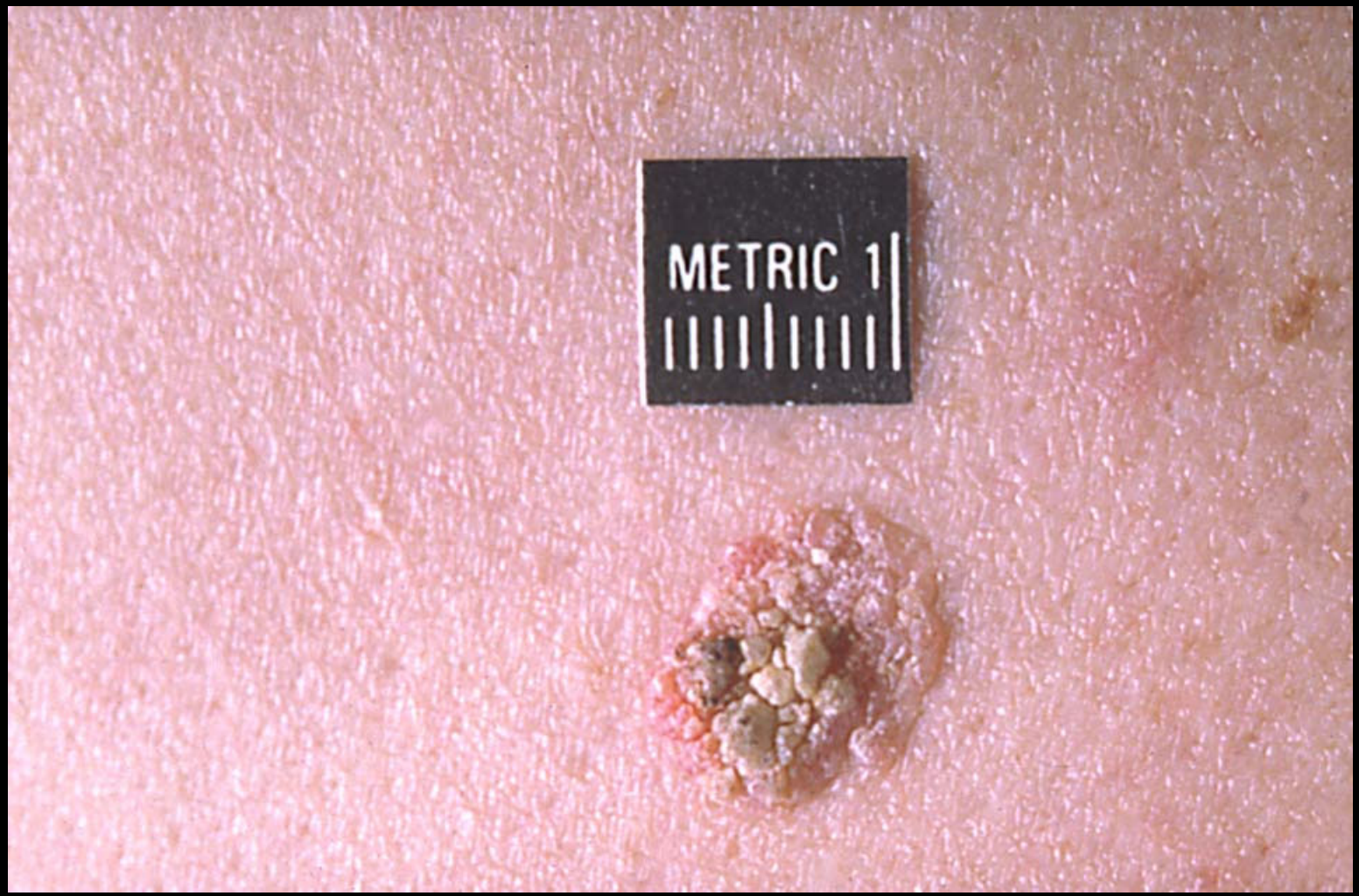


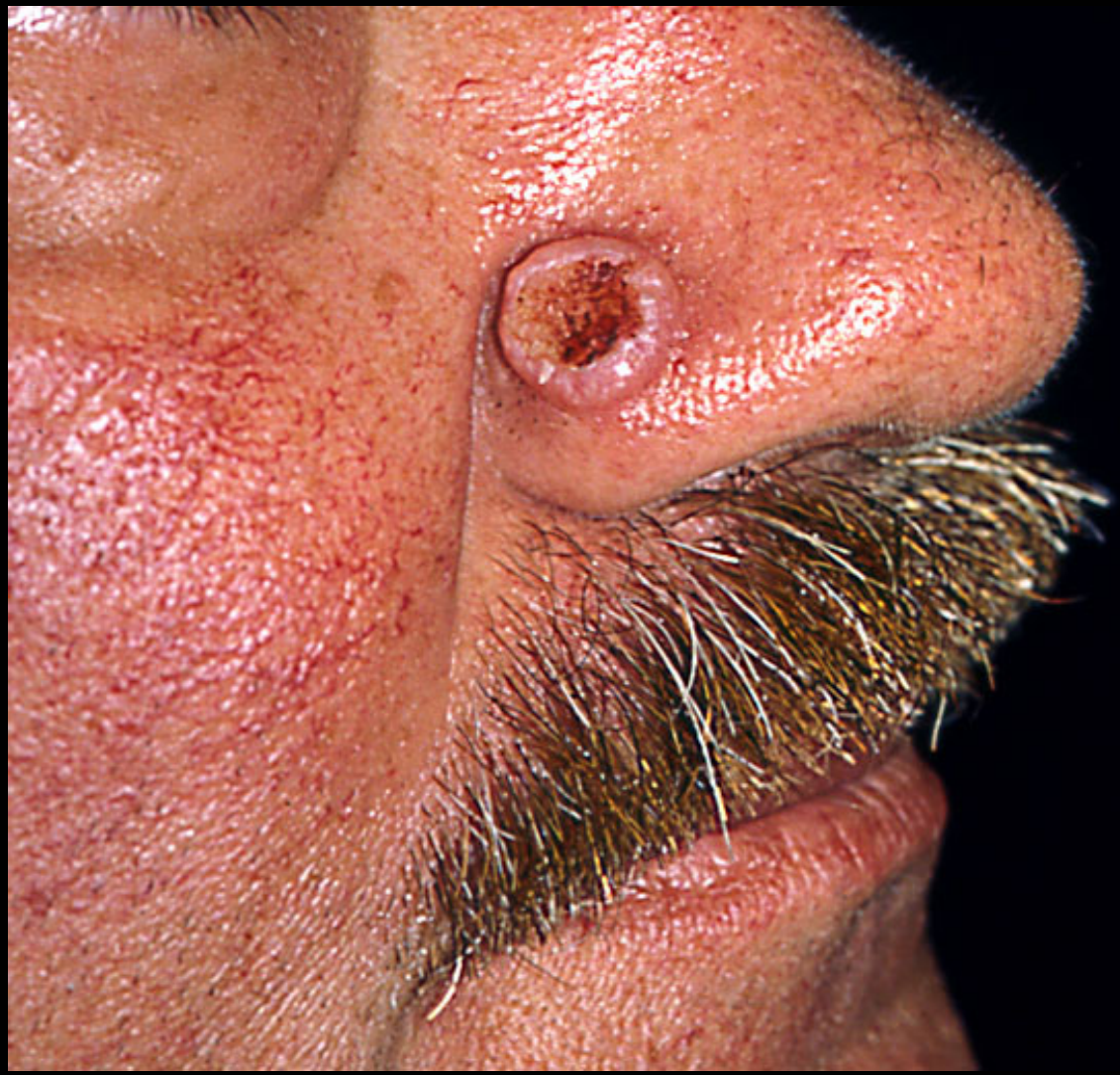
SCC

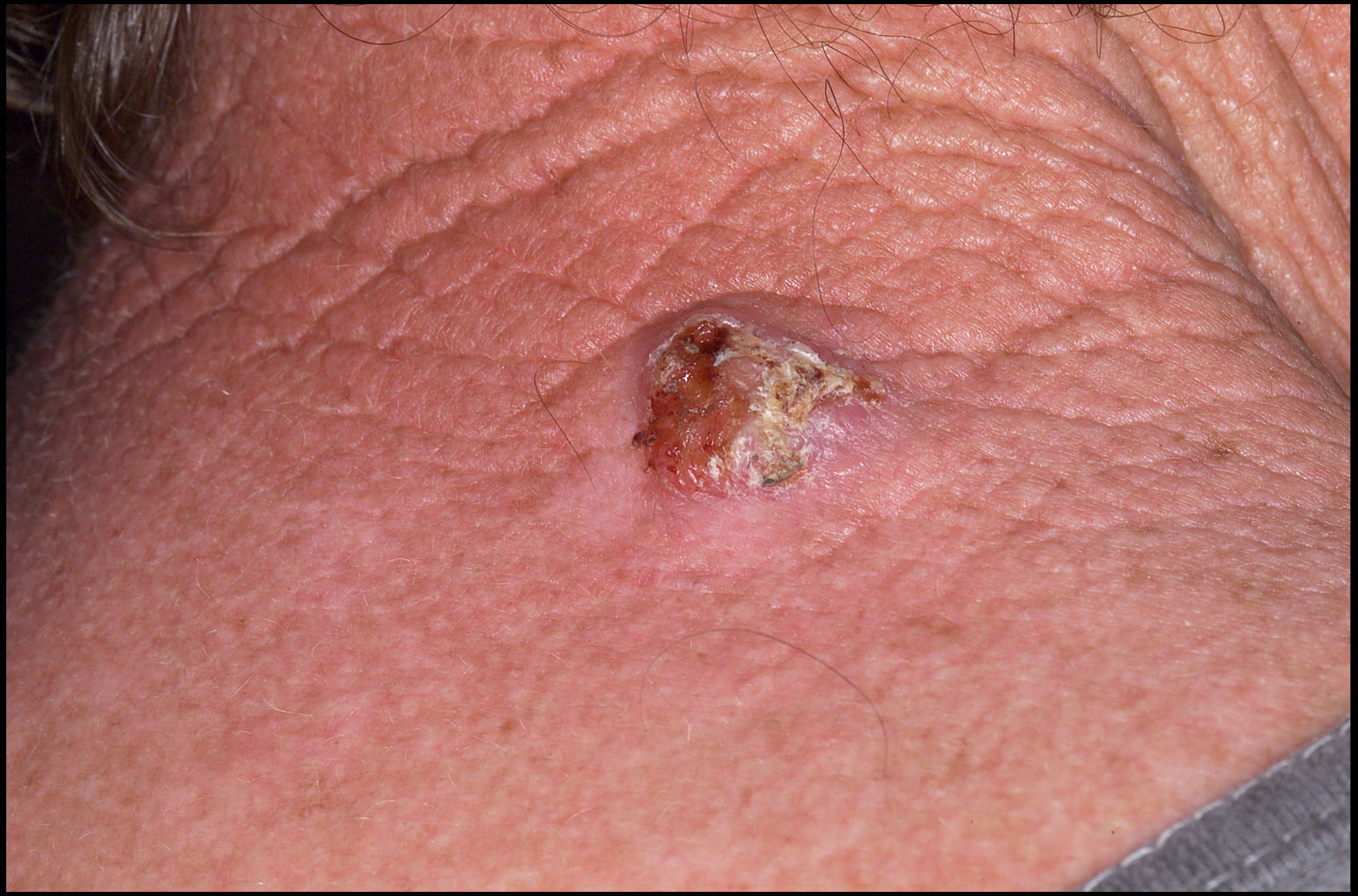
- As the lesion progresses from the appearance of an AK
- Red, scaly patch
- With or without crusting
- May develop a nodule

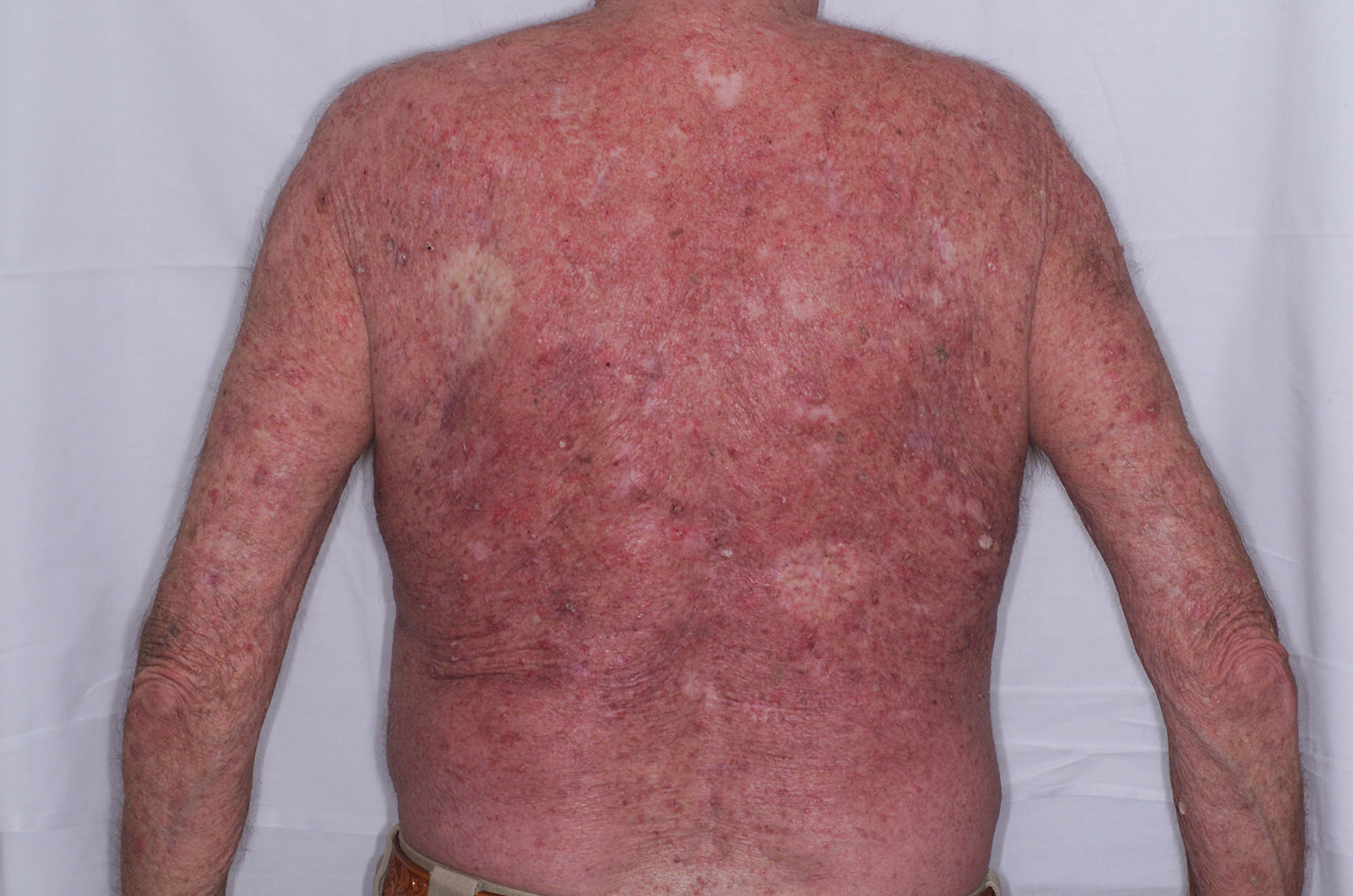


AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer


METRIC 1



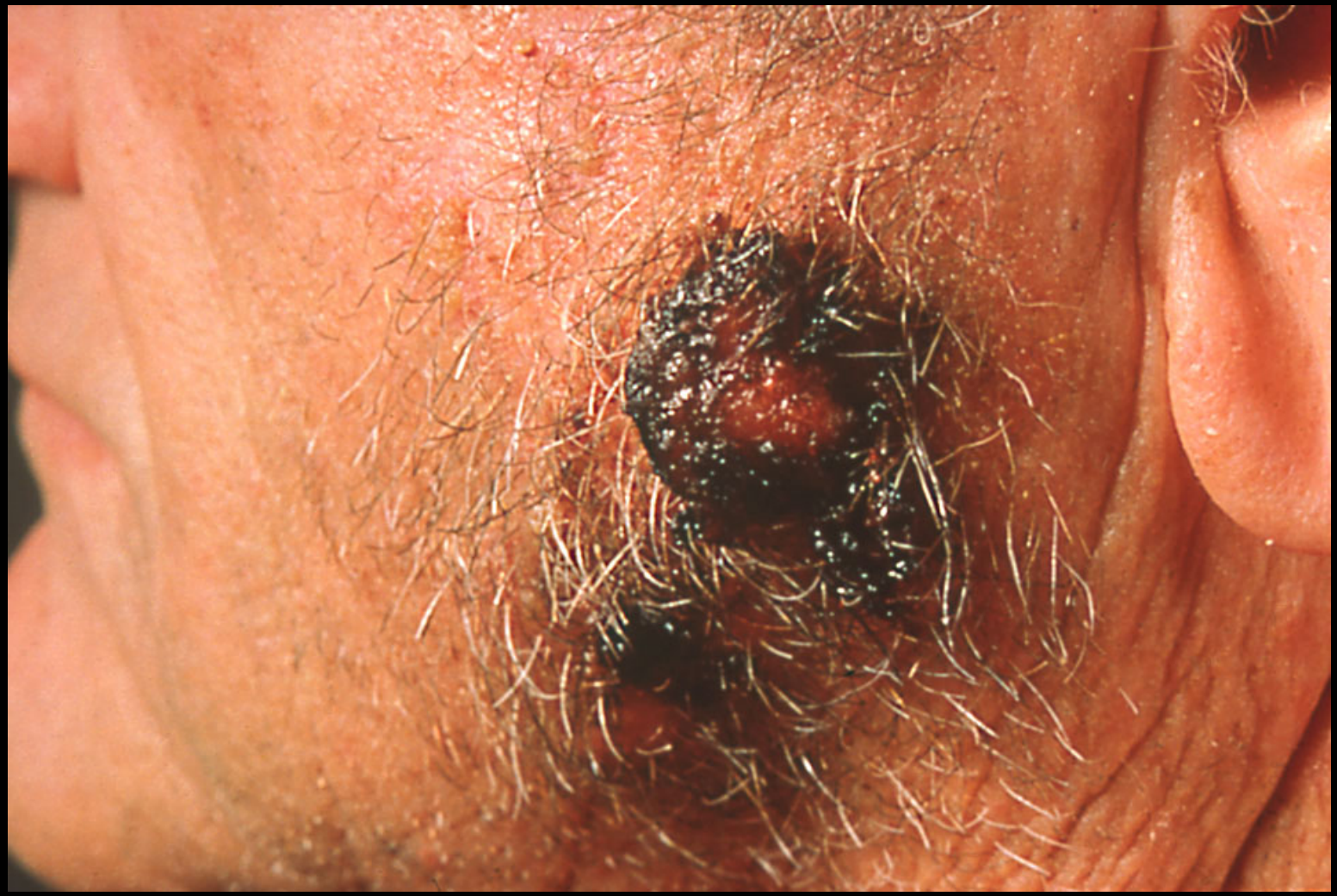


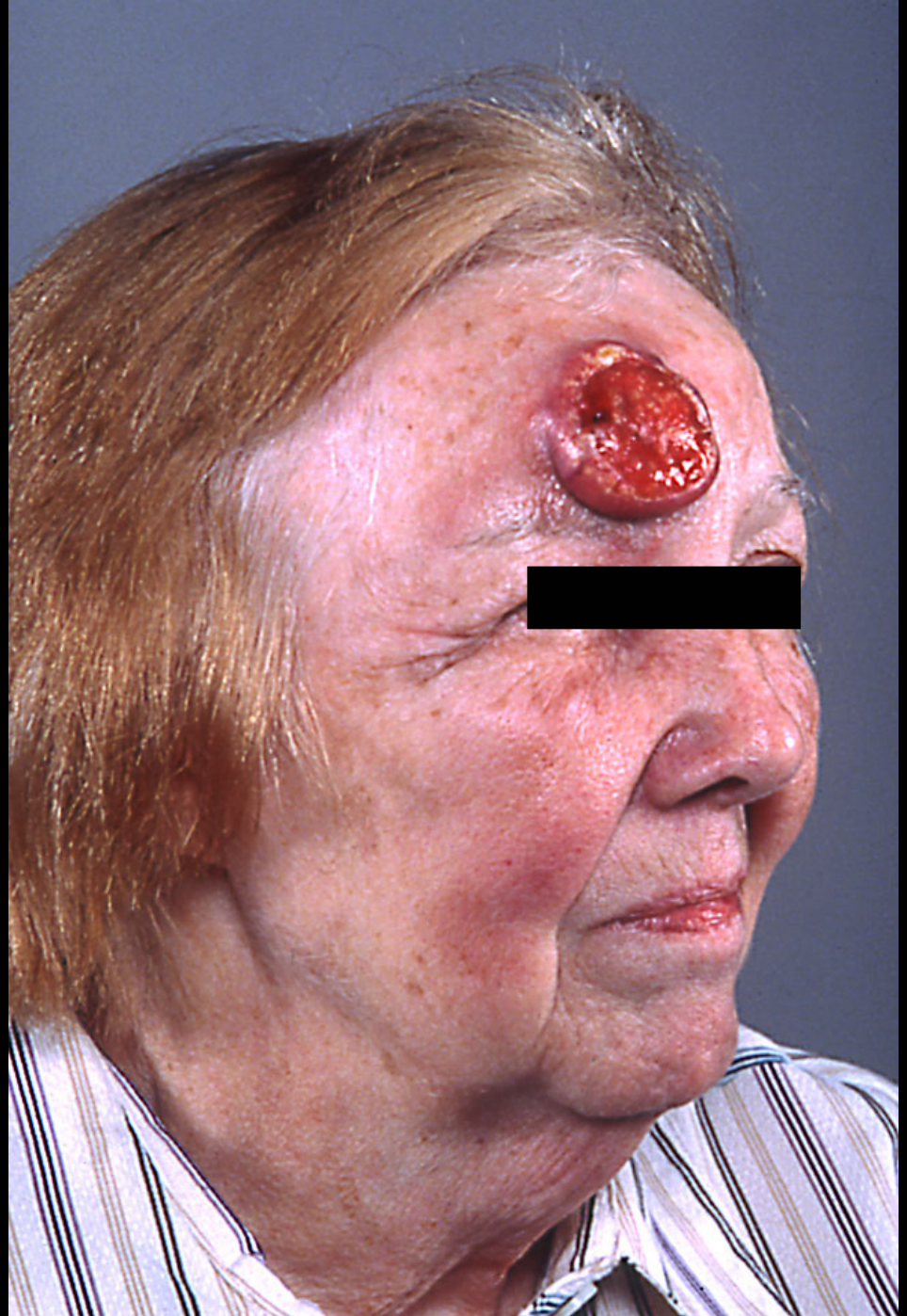


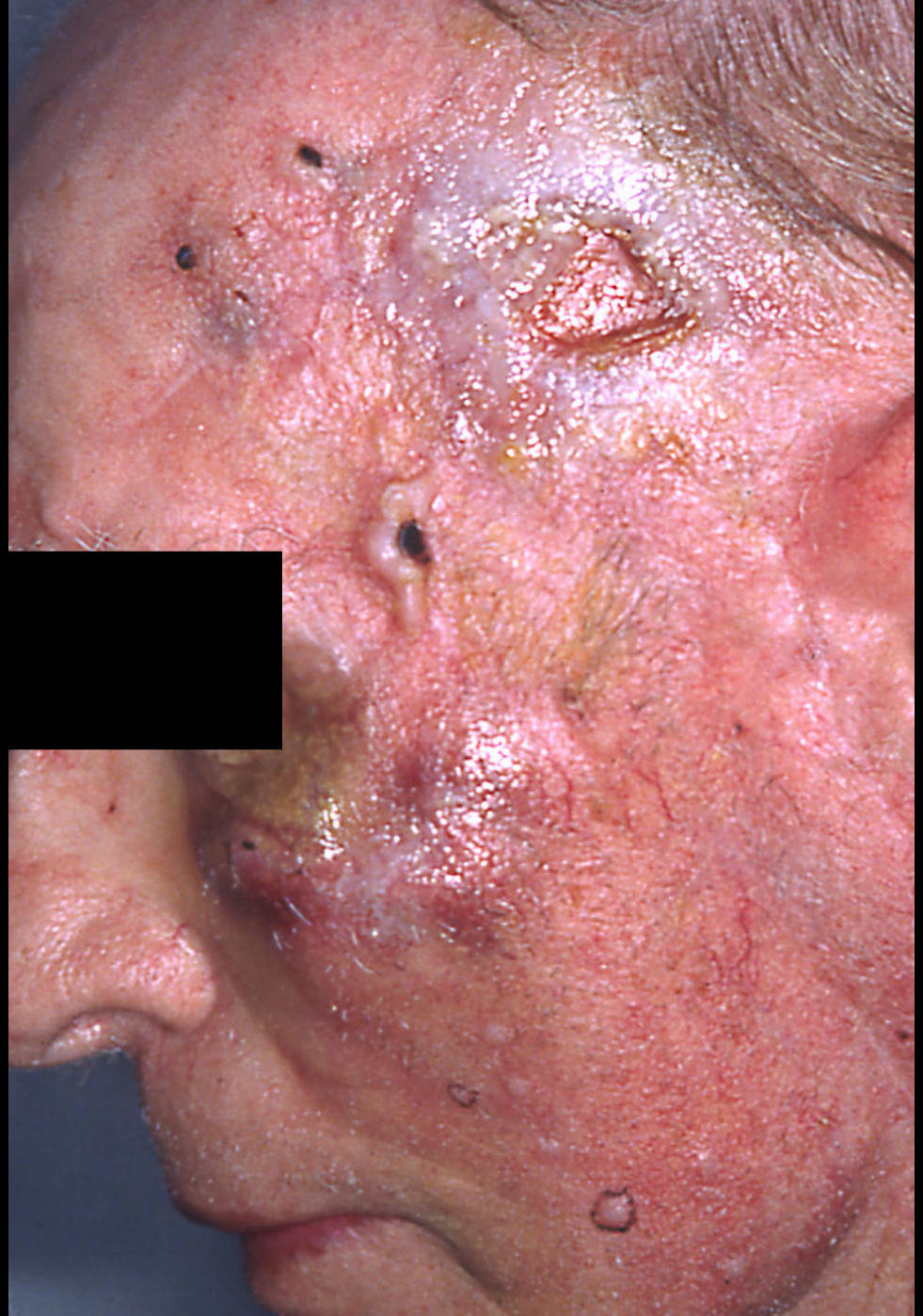
Recognizing the High-risk SCC

- Multiple, rapid recurrences
- High risk location:forehead/temple/ear/lip
- Large size
- Aggressive growth
- Poor differentiation
- Transformation to poor differentiation
- Deep invasion (>4-6 mm), especially fat, muscle, cartilage, bone, nerve
- Perineural invasion

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer



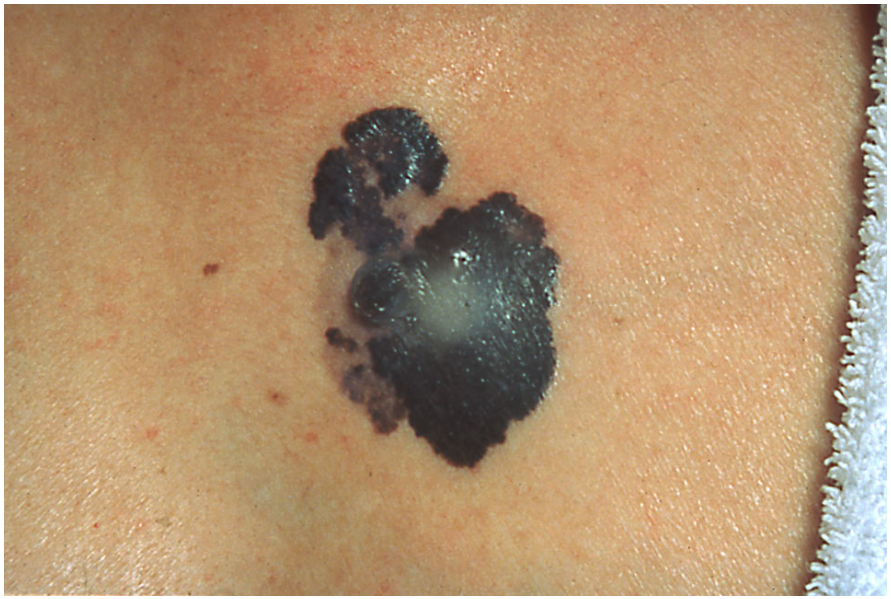




Malignant Melanoma

- 59,000 cases of invasive melanoma last year in U.S.
- Incidence doubles every 15 years
- Changing or new pigmented lesion
- Prognosis based on thickness
- 15% mortality; 7,770 deaths
- Surgery
  - Wide local excision
  - Sentinel lymph node biopsy

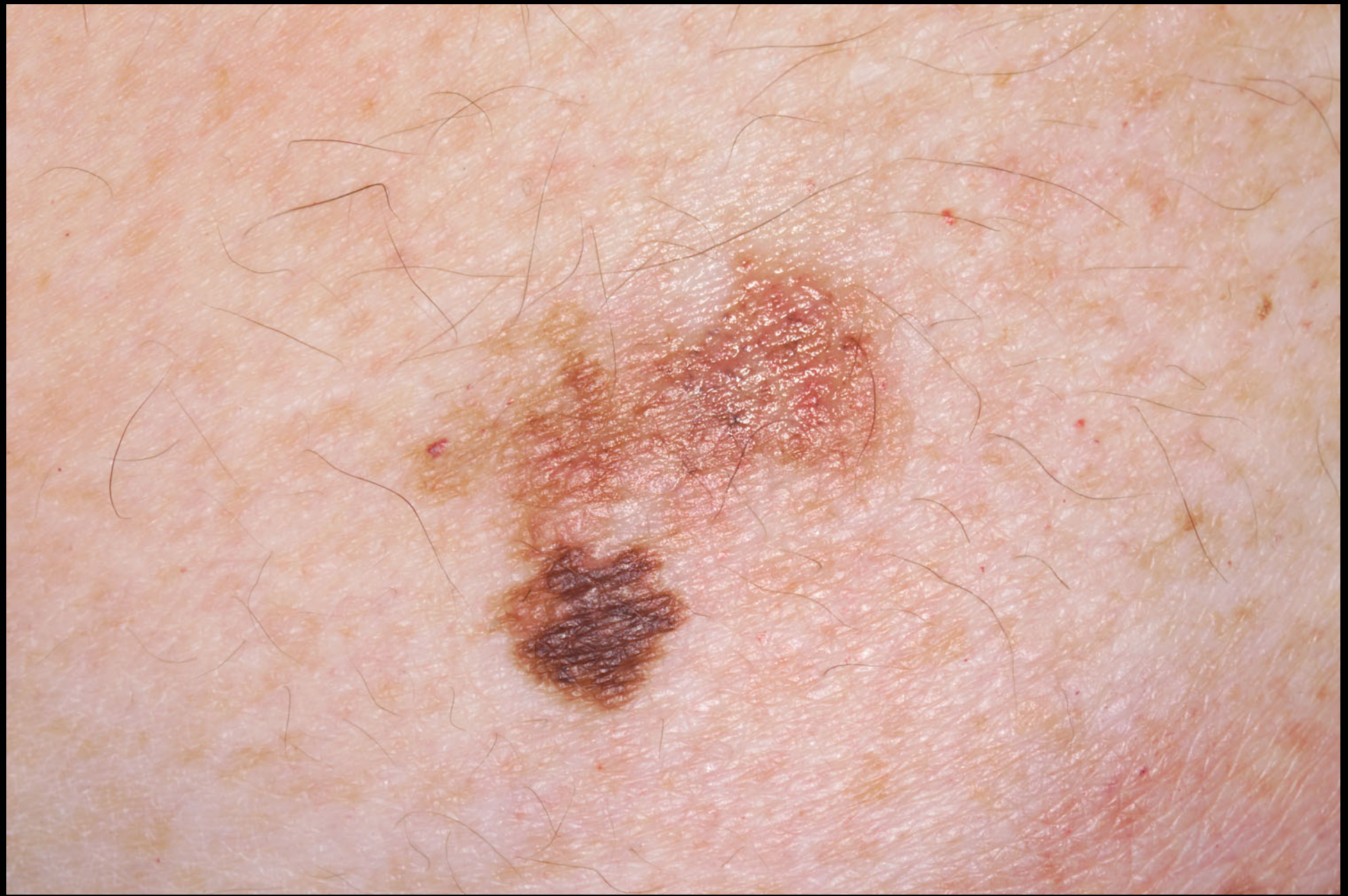
AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

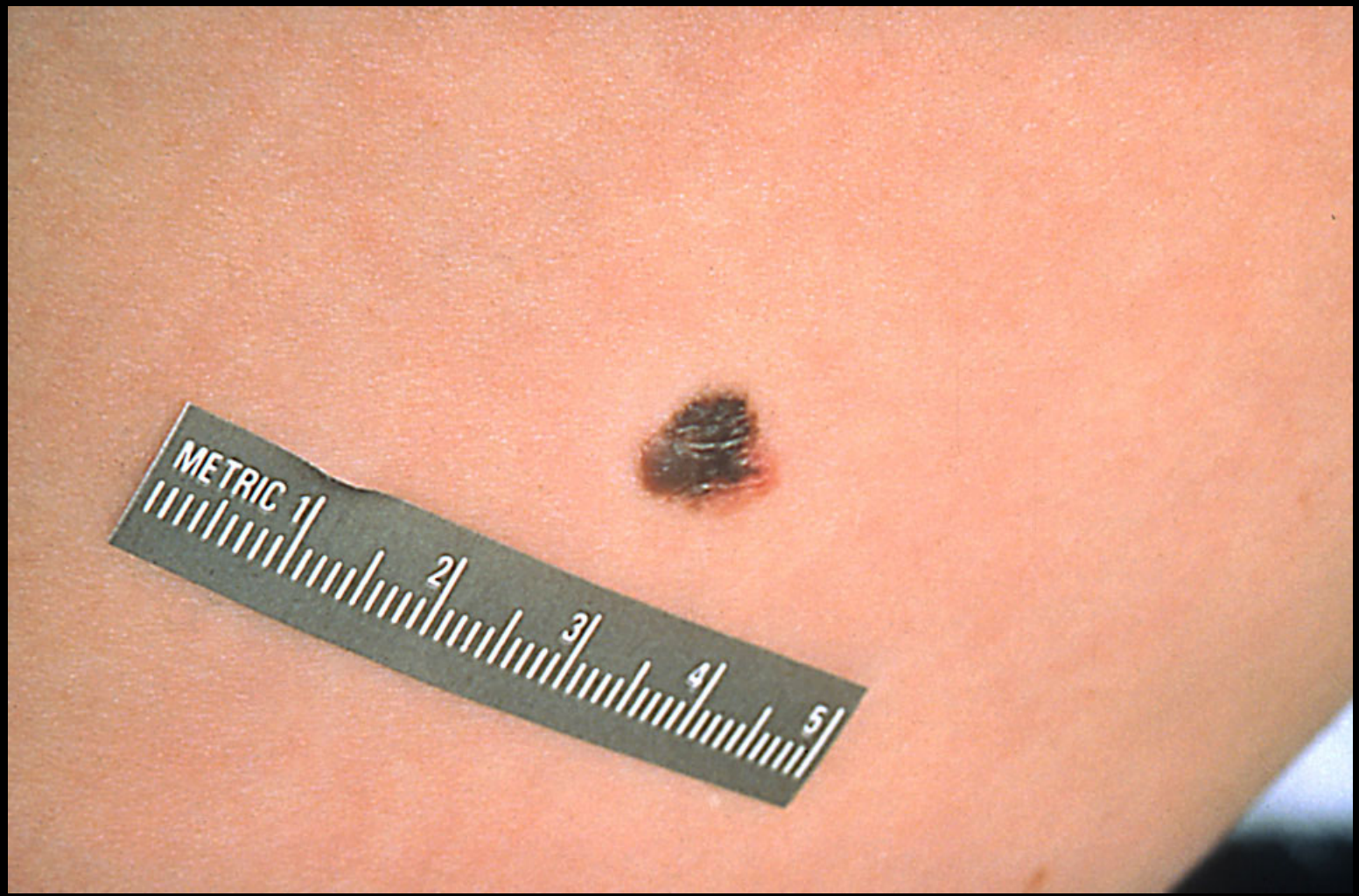


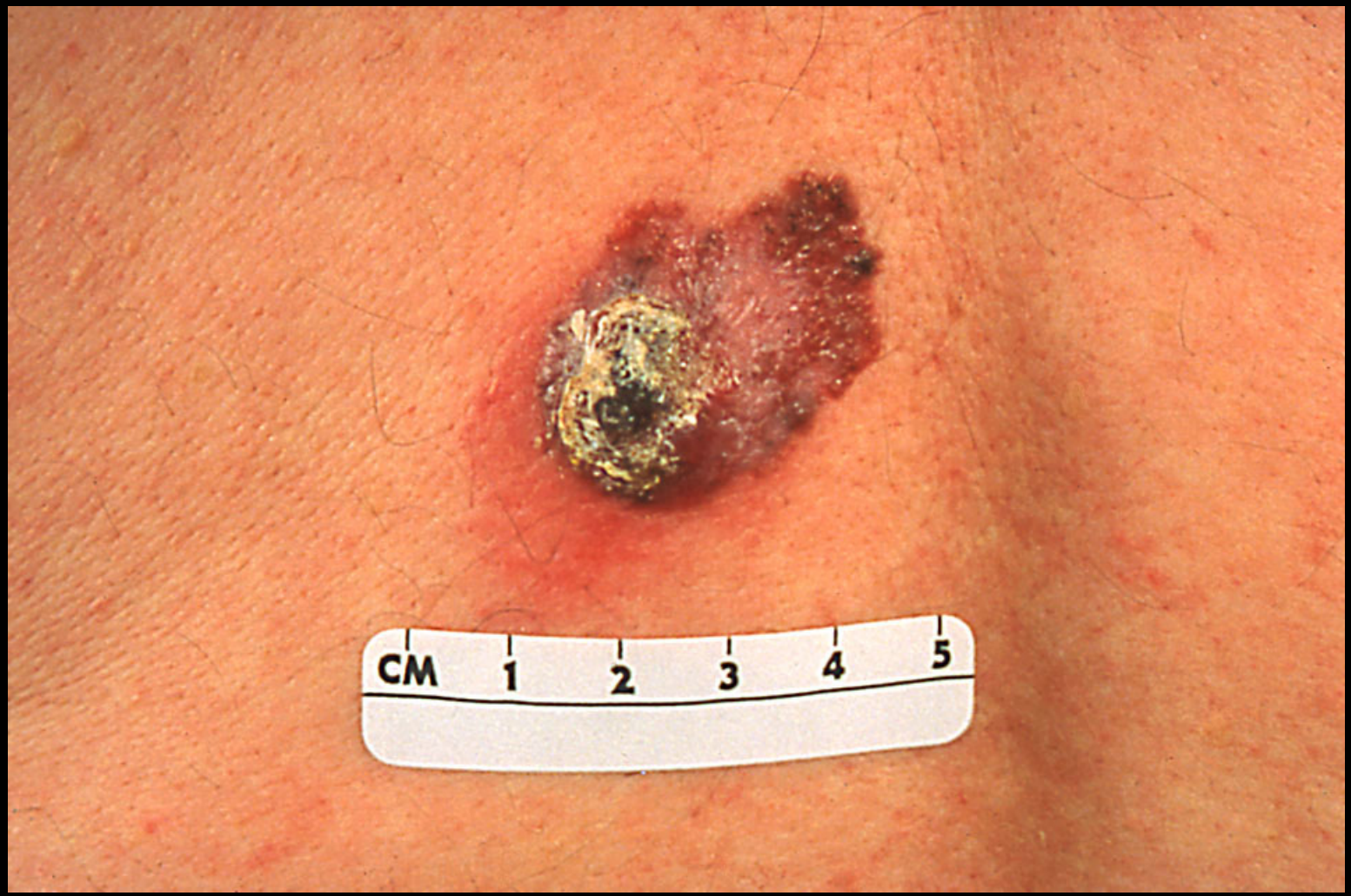
Melanoma

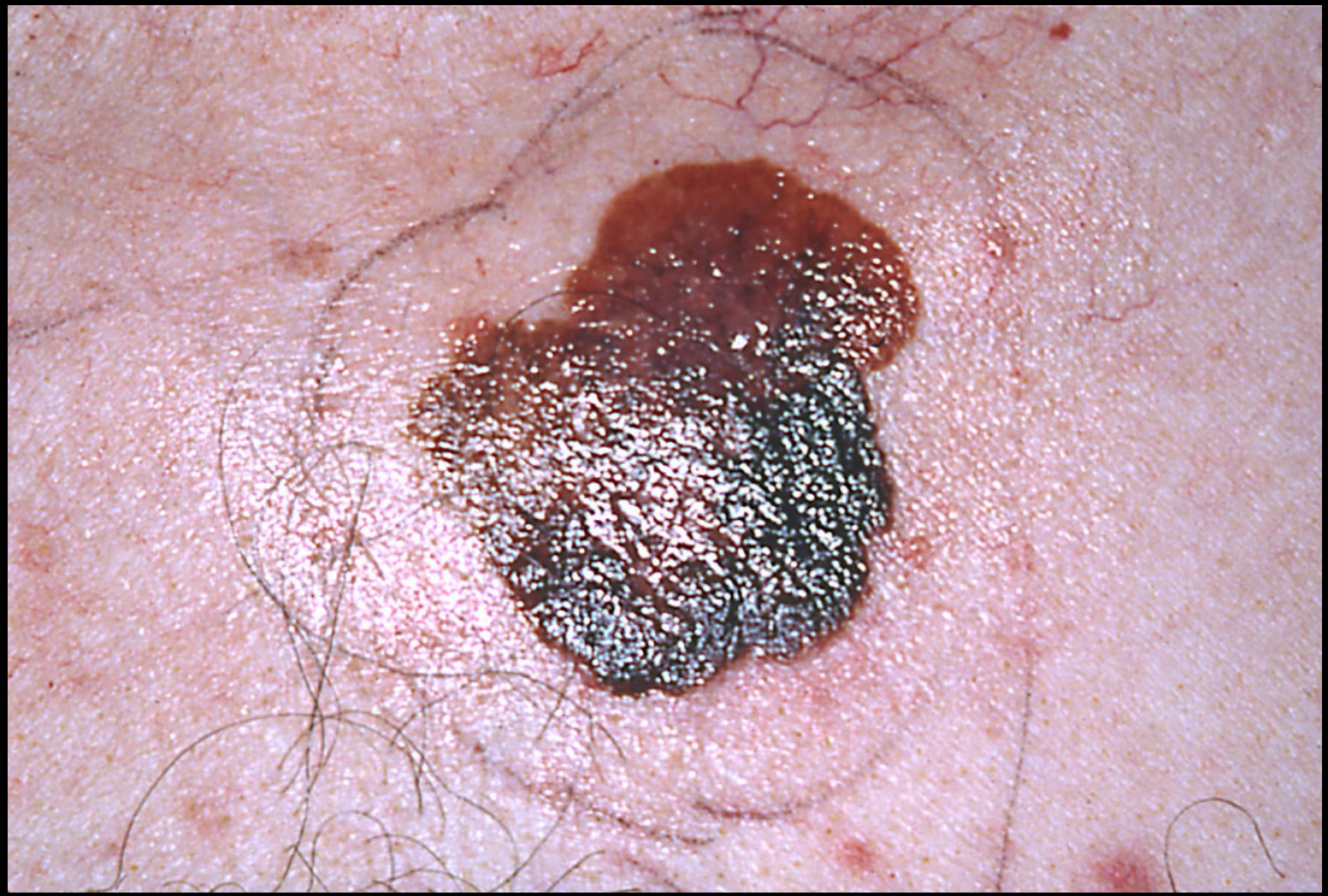
- Assymetry
- Irregular Border
- Variations in Color
- Diameter >6mm
- Evolving (changing)

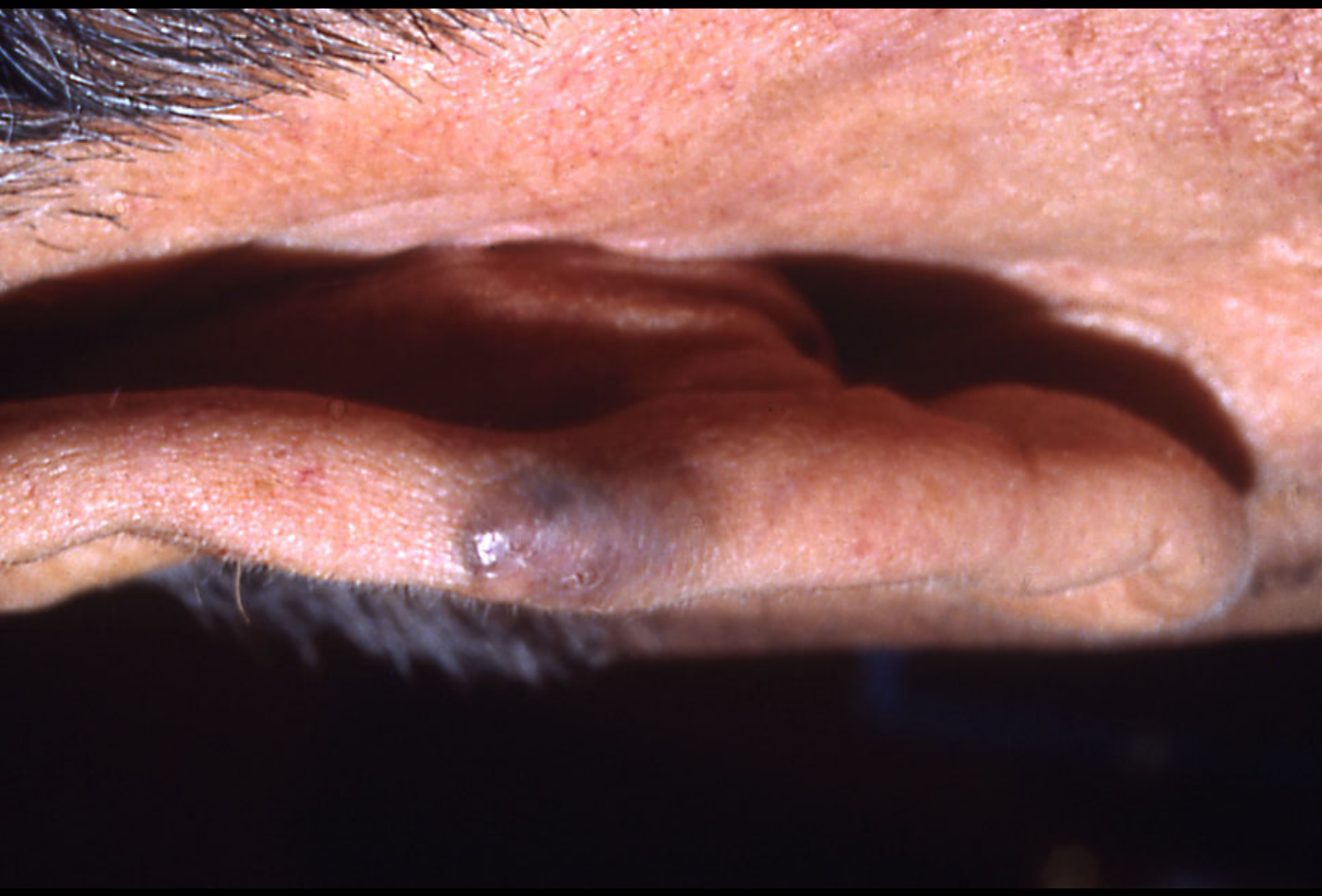
AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

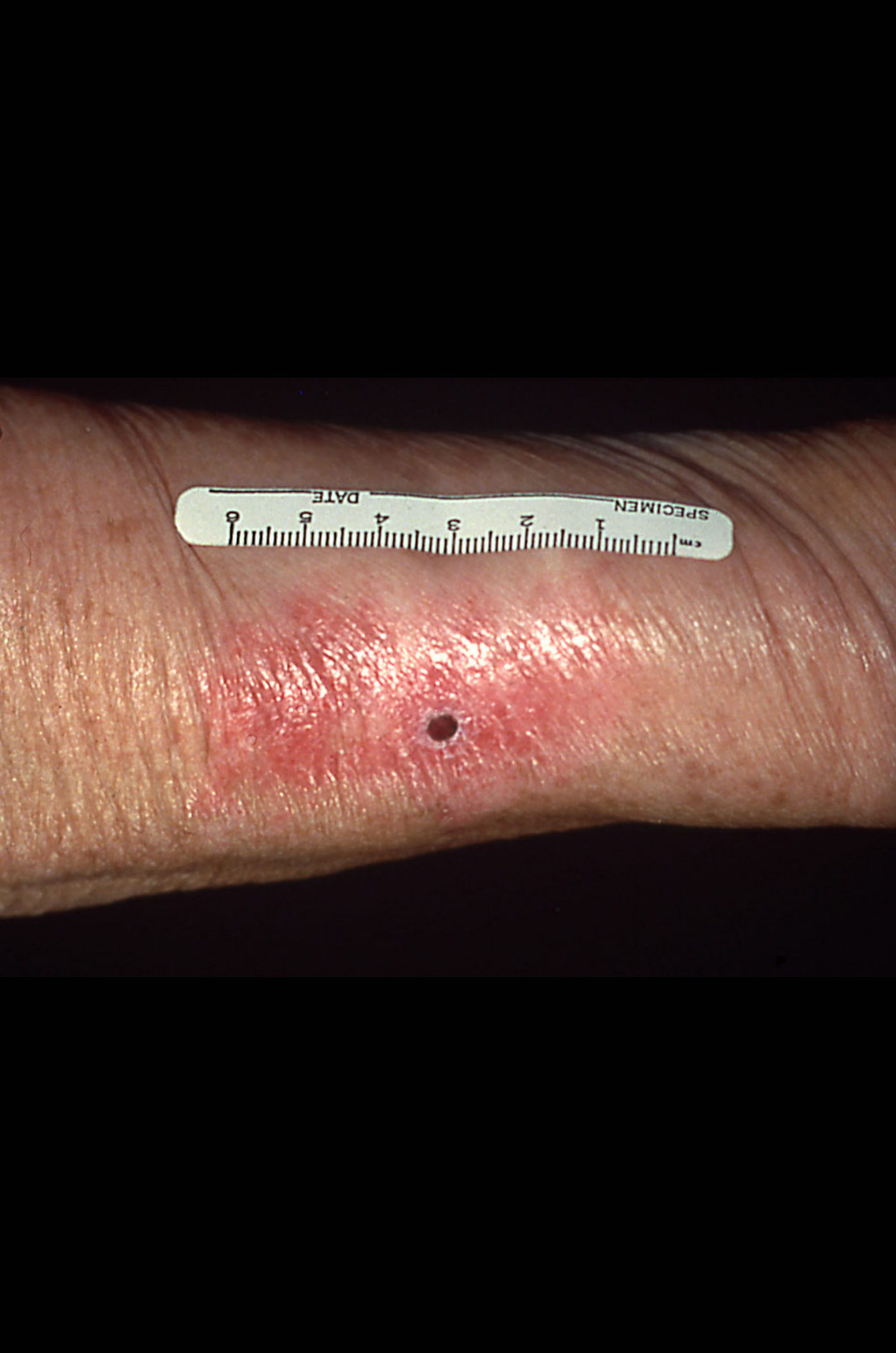


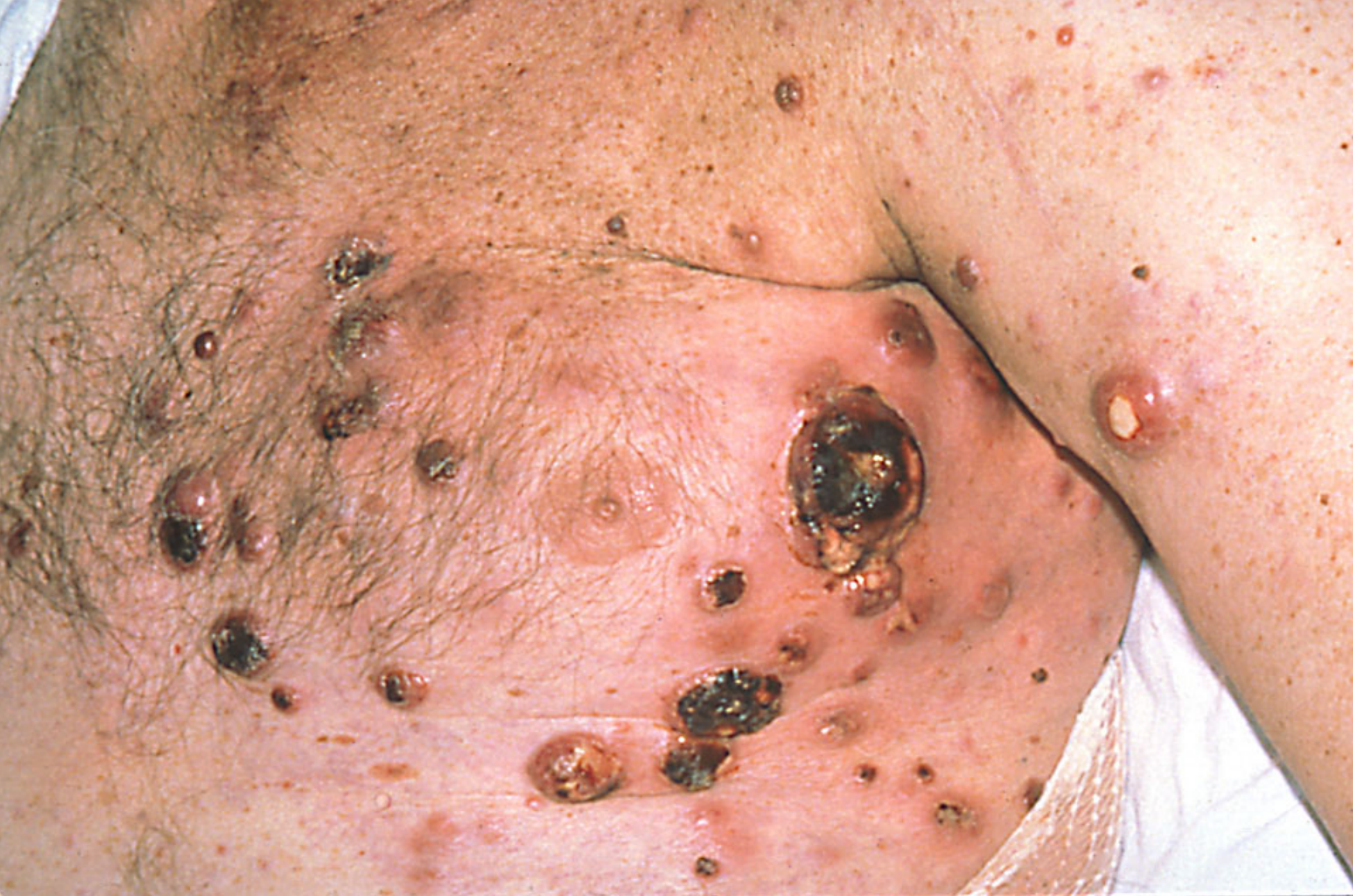

METRIC
1
2
3
4
5


CM
1
2
3
4
5






DATE
SPECIMEN
1
2
3
4
5
6
cm

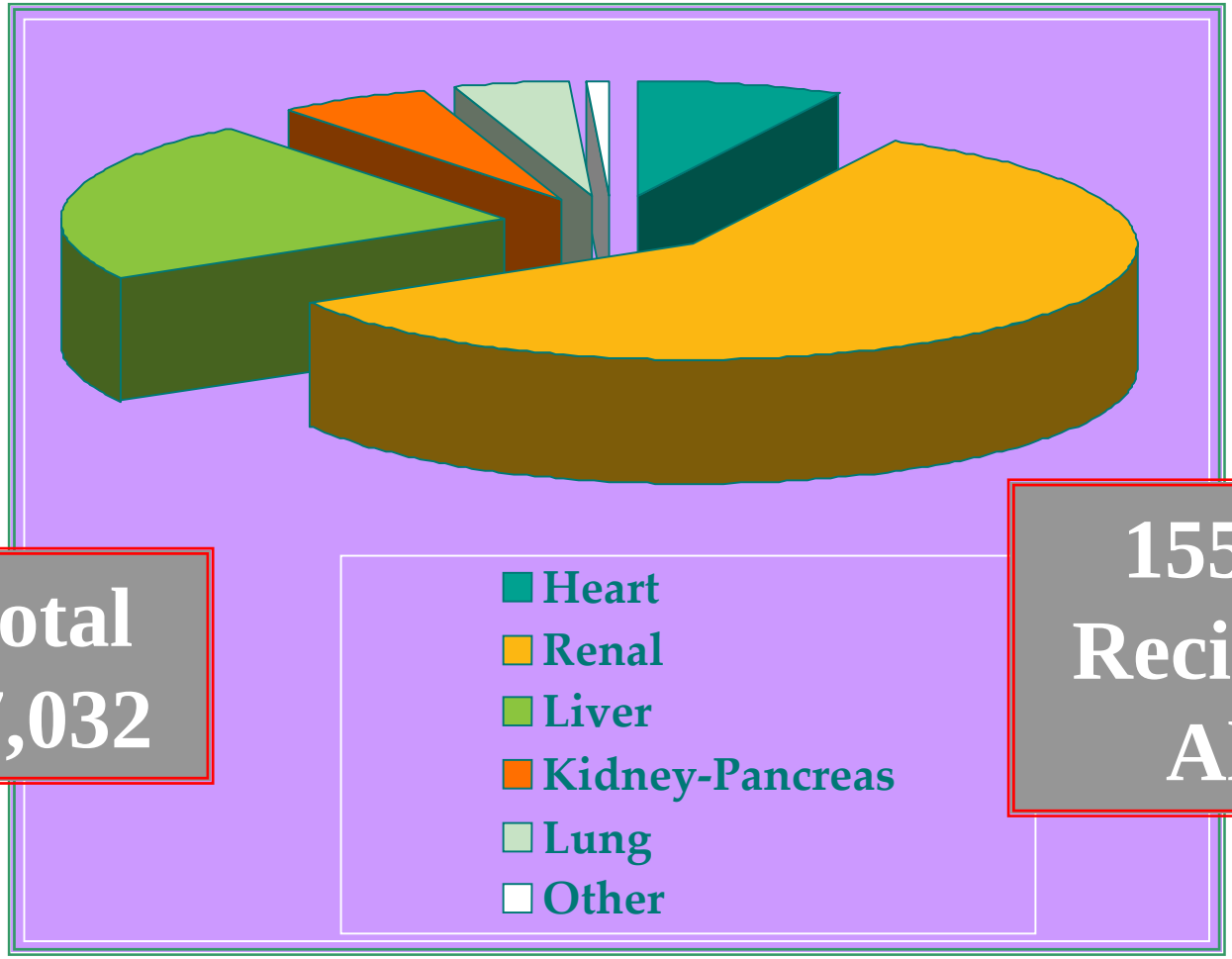


The State of Transplantation in the U.S. - UNOS Data

- Over 28,000 organ transplants per year (74,000 worldwide)
- 155,000 organ recipients currently alive in U.S.
- Over 90,000 people awaiting transplants
- More than 7,000 die waiting each year
- Organ donation numbers increasing only slightly
- Organ scarcity is major problem

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

U.S. Organ Transplants in 2004



Total 27,032

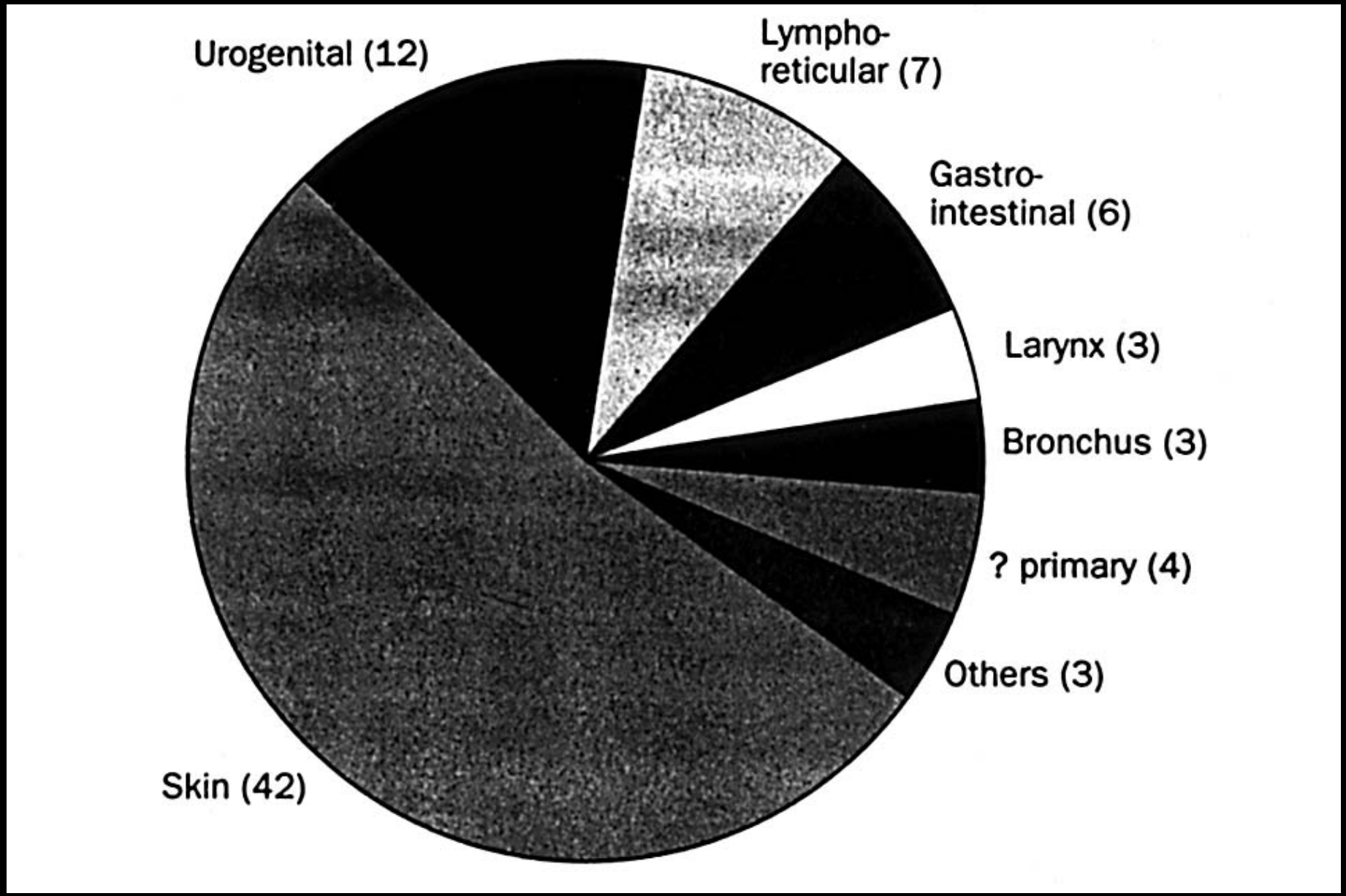
155,000 Recipients Alive

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

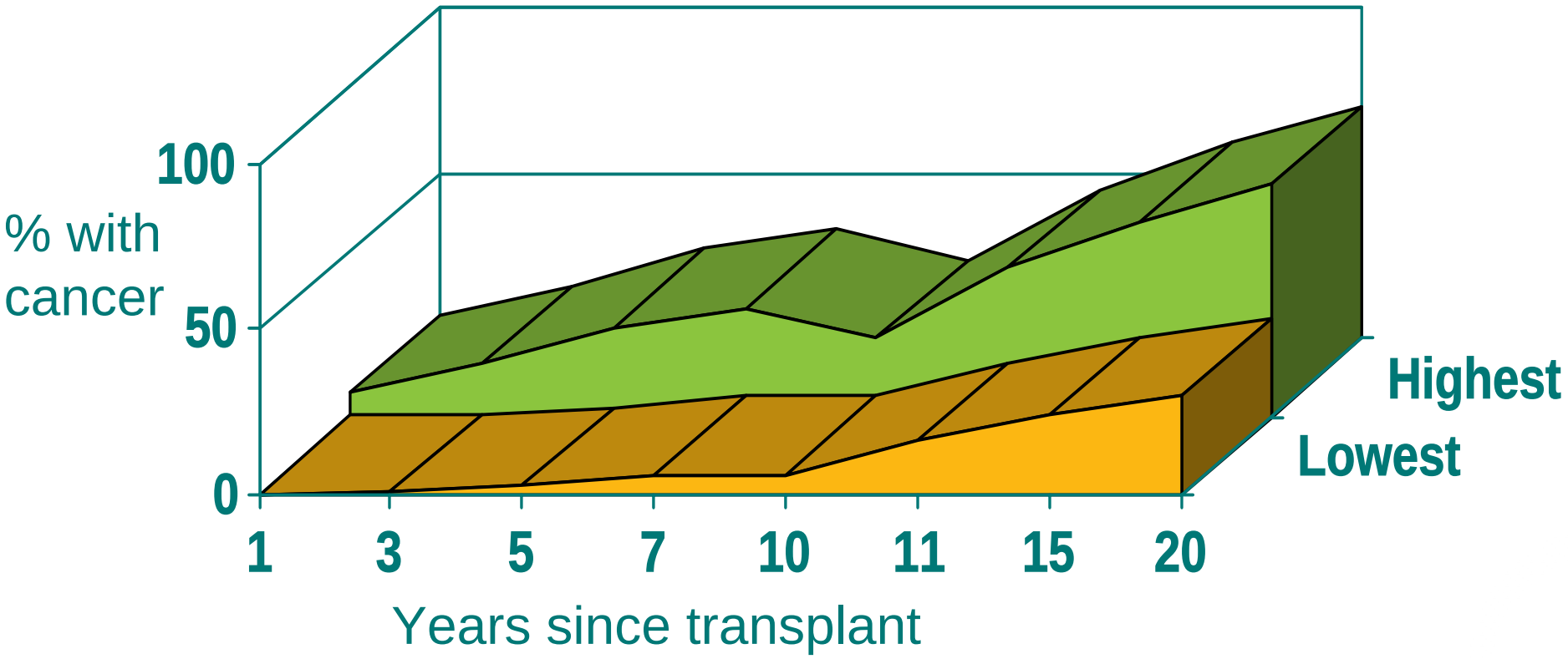
Skin Cancer in Transplant Patients - Clinical Characteristics

- Skin cancer is most common post-transplant malignancy
- Ranges from minor inconvenience to major morbidity to lethal
- Increased risk of metastasis and death

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer


Urogenital (12)
Lympho-
reticular (7)
Gastro-
intestinal (6)
Larynx (3)
Bronchus (3)
? primary (4)
Others (3)
Skin (42)

Prevalence of Skin Cancer in Transplant Patients: High and Low Estimates



AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Population-Based Standard Incidence Ratios of Skin Cancer in Transplant Patients

• Squamous Cell Carcinoma	• 65-fold increase
• SCC of lip	• 20 to 38-fold increase
• Basal Cell Carcinoma	• 10-fold increase
• Melanoma	• 1.6 to 3.4-fold increase
• Kaposi's Sarcoma	• 84-fold increase

Ref: Jensen JAAD 1999;40:17 Hartevelt Transplantation 1990;49:506; Lindelof BJD 2000;143;513

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Other Cutaneous Neoplasms in Organ Transplant Patients

- Melanoma
- Kaposi's sarcoma
- Angiosarcoma
- Merkel cell carcinoma
- Verrucous carcinoma
- Atypical fibroxanthoma
- Leiomyosarcoma
- Cutaneous T-cell lymphoma
- Cutaneous B-cell lymphoma

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Risk Factors for Skin Cancer

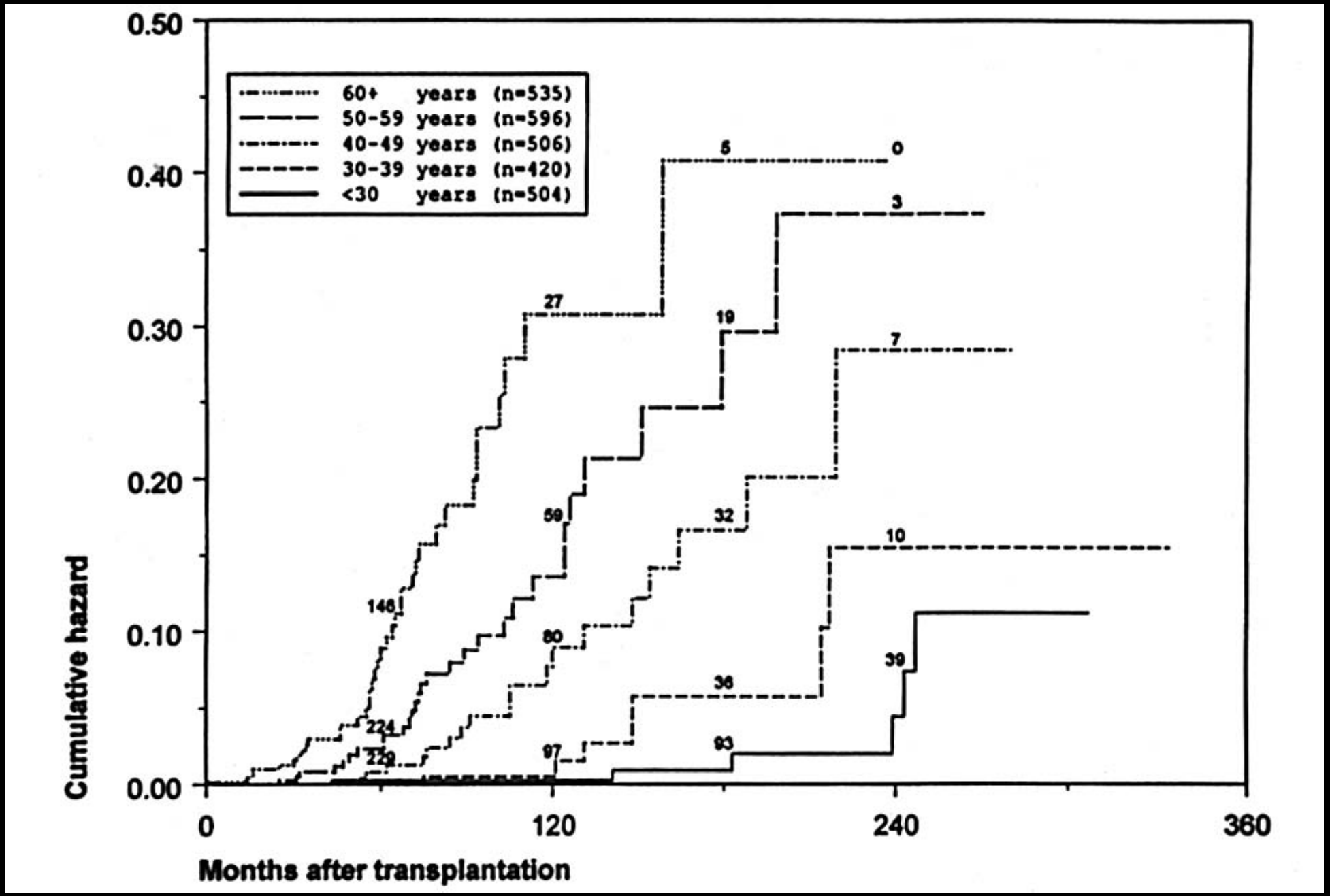
	General Population	Transplant Population
Increasing age	++	++++
Fair skin, light hair, light eyes	++	++++
Sun exposure	++	++++
History of previous skin cancer	50% risk of 2nd cancer	>70% risk of 2nd skin cancer

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Additional Risk Factors for Skin Cancer in Organ Transplant Patients

• Duration of immunosuppression	• Longer = more
• Intensity of immunosuppression	• Stronger = more
• HPV infection	• Present = more
• CD4 lymphocytopenia	• Lower = more

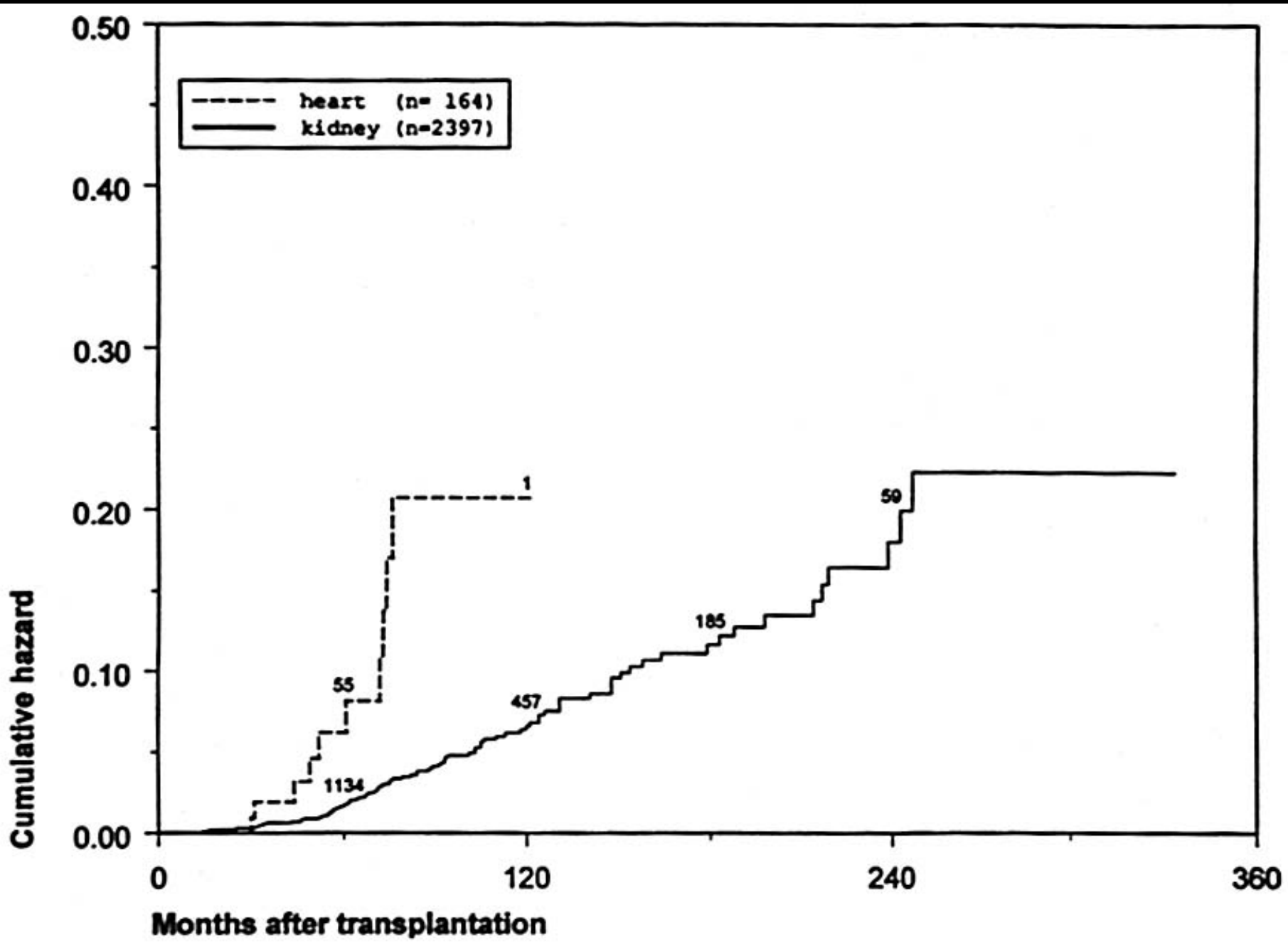
AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer


60+ years (n=535)
50-59 years (n=596)
40-49 years (n=506)
30-39 years (n=420)
<30 years (n=504)
0.50
0.40
0.30
0.20
0.10
0.00
Cumulative hazard
0
120
240
360
Months after transplantation
5
0
3
27
19
7
59
32
10
148
80
39
36
224
97
93
229

Skin Cancer in Different Types of Transplants

- Cardiac transplants have a 2.9-fold higher risk of SCC compared to renal transplants
  - Cardiac transplants older
  - Immunosuppression more intense
- Skin cancer is less common in liver transplants than renal or cardiac

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer


heart (n= 164)
kidney (n=2397)
0.50
0.40
0.30
0.20
0.10
0.00
Cumulative hazard
0
120
240
360
Months after transplantation
1
55
1134
457
185
59

The State of Immunosuppression

- Intense regimen to prevent acute rejection
- Tapered regimen to prevent chronic rejection
- Improved survival rates in cyclosporine era
- Stable survival since cyclosporine

The State of Immunosuppression

- Multi-agent, intense immunosuppression
- Highly variable regimens
  - Rapamycin
  - Deoxyspergualin
  - Leflunomide
  - Mizoribine
  - Brequinar
  - Immunomodulating antibodies
    - Anti-CD40 and CTLA4-Ig
    - Anti- LFA-1
    - Anti-IL-2 receptor antibody
    - Anti-ICAM-1 antibody

Which Agent is Worst?

- Animal data
  - Azathioprine > Cyclosporine > steroids
- Human data
  - Minor differences between agents
  - 3 agents > 2 agents > one agent
  - Overall intensity of immunosuppression most important

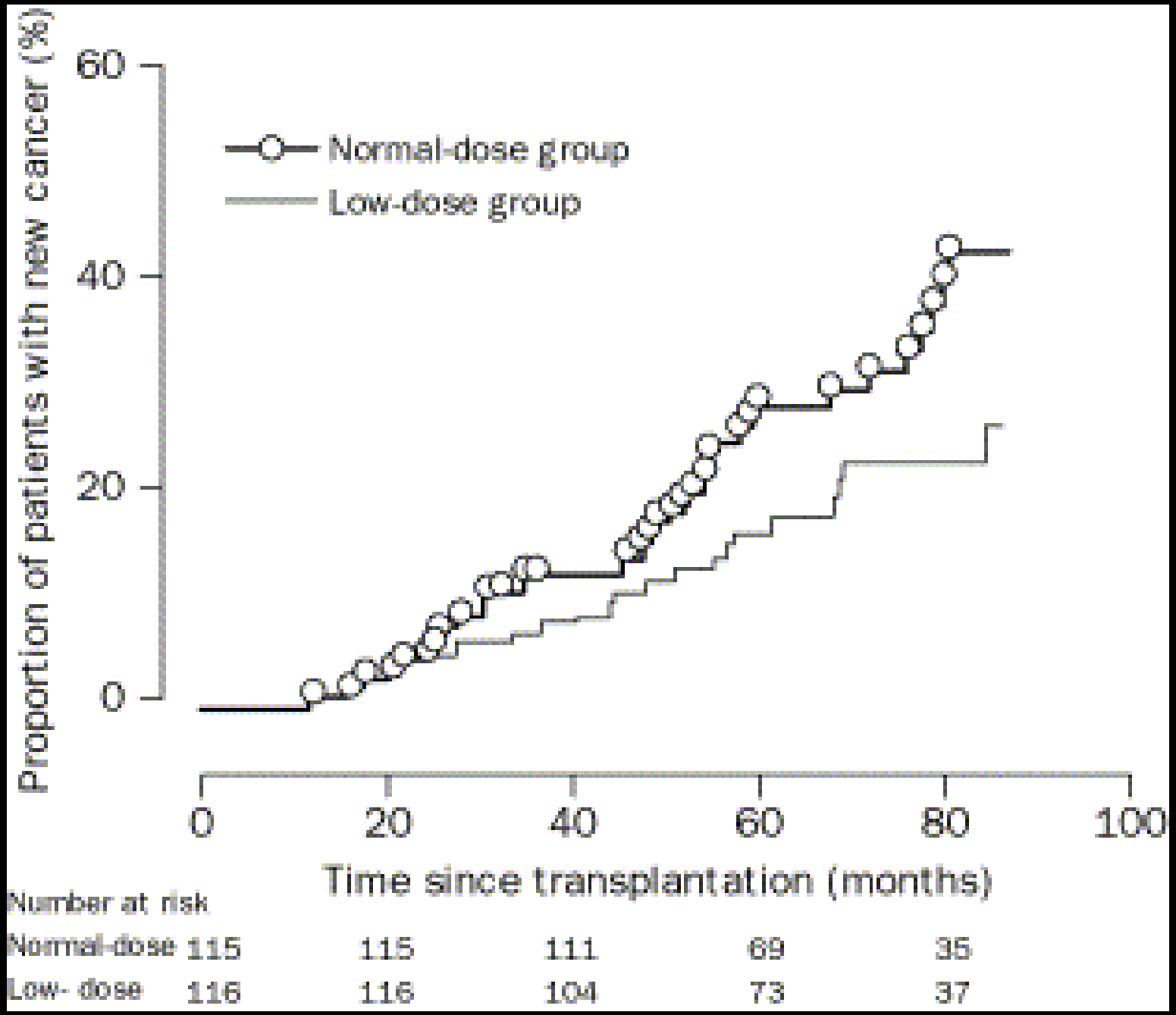
Ref: Jensen JAAD 1999;40:177/ Penn Transplant Proc 1991;23:1191; Fortina Arch Dermatol 2004;140:1079.

Low Dose Versus Normal Dose Cyclosporine A

- Trough levels of CyA 75-125 vs 150-250
- More rejection episodes
- Fewer skin cancers
- Fewer overall cancers (solid tumors and lymphoma)
- Same overall and graft survival

Ref: Dantal. Lancet 1998;351:623.

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer


Proportion of patients with new cancer (%)
60
40
20
0
Normal-dose group
Low-dose group
0
20
40
60
80
100
Time since transplantation (months)
Number at risk
Normal-dose 115 115 111 69 35
Low- dose 116 116 104 73 37

Changing Regimens: Medications One Year s/p Renal Transplant

1992

- Steroids: 100%
- Cyclosporine: 96%
- Tacrolimus: 3%
- Rapamycin: 0%
- CellCept: 1%
- Imuran: > 90%

2000

- Steroids: 97%
- Cyclosporine: 53%
- Tacrolimus: 52%
- Rapamycin: 16%
- CellCept: 80%
- Imuran: < 10%

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Newer Immunosuppressants and Skin Cancer (Liver Data)

- CyA + Aza worse than Tac + MMF (p=0.014)
- CyA + MMF worse than Tac + MMF (p=0.042)
- Tac + Aza worse than Tac + MMF (p=0.013)

Ref: UNOS Tumor Transplant Database

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Don’t Forget About Steroids

- Karagas et al.
  - Systemic steroids vs controls
    - 2.31-fold increase in SCC
    - 1.49-fold increase in BCC
    - 2.68-fold increase in NHL

Ref: Karagas et al Br J Cancer 2001;85:683-6;
Sorenson HT et al J Natl Cancer Inst 2004;96:709-11.

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Newer Immunosuppressants and Skin Cancer

- Steroids seem to play a lesser role in the development of skin cancers

Substitution of immunosuppressive agents

- Mycophenolate mofetil for azathioprine
- Tacrolimus for cyclosporine
  - » For both-- an improvement if it allows for easier dosing and lower levels of immunosuppression

AT-RISC ALLIANCE
After Transplantation– Reduce Incidence of Skin Cancer

Transplant Oncology: Rapamycin

- May be different than other immunosuppressants with regards to skin cancer
- Anti-angiogenic, anti-neoplastic properties

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Rapamycin and Skin Cancer

- 1.9% incidence of skin cancer/5 yr mean
  - 7% historical controls/5 yr mean
  - 1.5% in general population (SEER data)/5 yr

    Kahan BD, Knight R, Schoenberg L, Pobielski J, Kerman RH, Mahalati K, Yakupoglu Y, Aki FT, Katz S, Van Buren CT. Ten years of sirolimus therapy for human renal transplantation: the University of Texas at Houston experience. Transplant Proc 2003;35(Supp 3A):25S-34S.
- Randomized trial started in Lieden

AT-RISC ALLIANCE
After Transplantation– Reduce Incidence of Skin Cancer

Rapamycin and Skin Cancer

- Pooled (5) rapamycin studies - 2 year data
  - Skin cancer incidence
    - CyA 6.9%
    - CyA + Aza 4.3%
    - CyA + Rapa (low dose) 2.0% $p < 0.01$
    - CyA + Rapa (high dose) 2.8% $p<0.05$
    - Rapa vs CyA: 0% vs 1.3% (NS trend)
    - Rapa + CyA withdrawal vs Rapa + CyA: 2.3 vs 5.1% (NS trend)

Ref: Mathew Clin Transplan 2004;18:446-9.

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Rapamycin and Non-skin Cancer

- UNOS Transplant Tumor Database
- 33,249 renal transplant patients
- 1996-2001
- De novo solid tumors
  - m-TOR inhibitors 0%
  - Combination 0.47%
  - Calcineurin inhibitors 1%
- RR = 0.44 (p=0.0092)

Kauffman et al. Transplantation 2005;80:883-9.

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Rejection Versus Cancer

PREVENT REJECTION

- More drugs
- Less rejection
- Higher graft survival
- More skin cancer

PREVENT CANCER

- Fewer drugs
- Less skin cancer
- Higher survival from skin cancer
- Increased QOL
- ? More rejection

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

The Hope

- Donor specific tolerance

AT-RISC ALLIANCE
After Transplantation–
Reduce Incidence of Skin Cancer

A Model of Accelerated Carcinogenesis

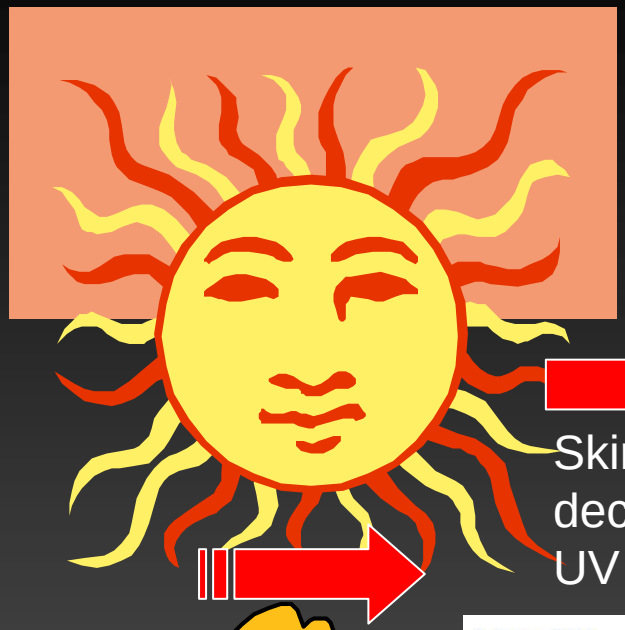
- Multi-hit theory - p53, ras, fos, patched
- Non-immunosuppressed lag time = 10 - 40 years
- Accelerated immunosuppressed lag time = 1 - 10 years

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Cofactors in Accelerated Carcinogenesis

- Carcinogenic drugs
- Carcinopermissive drugs
- Decreased immune surveillance/eradication
- Decreased antigen presentation
- HPV
- Ultraviolet radiation -> carcinogen/immunosuppressant

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer



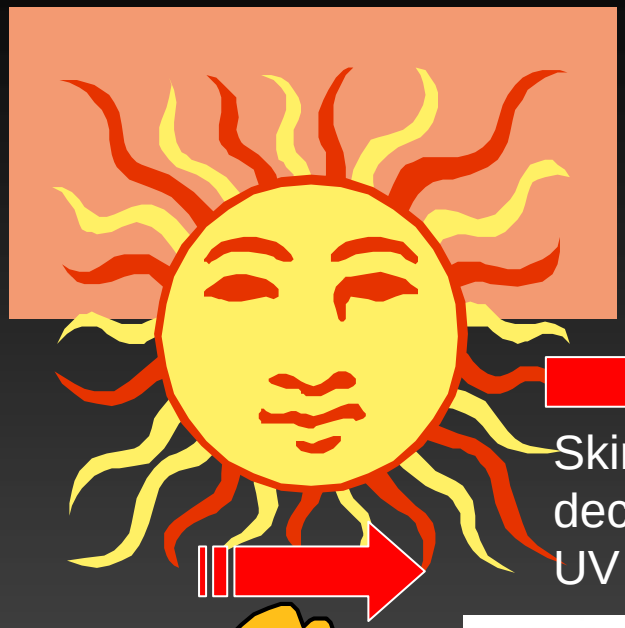
Cells with mutations removed by cellular immunity

Skin immunity decreased by UV

Mutations, p53 and others

Most mutations destroyed but a few cancers develop

Corrected by DNA repair mechanisms



Cells with mutations removed by cellular immunity

Skin immunity decreased by UV

Cellular DNA

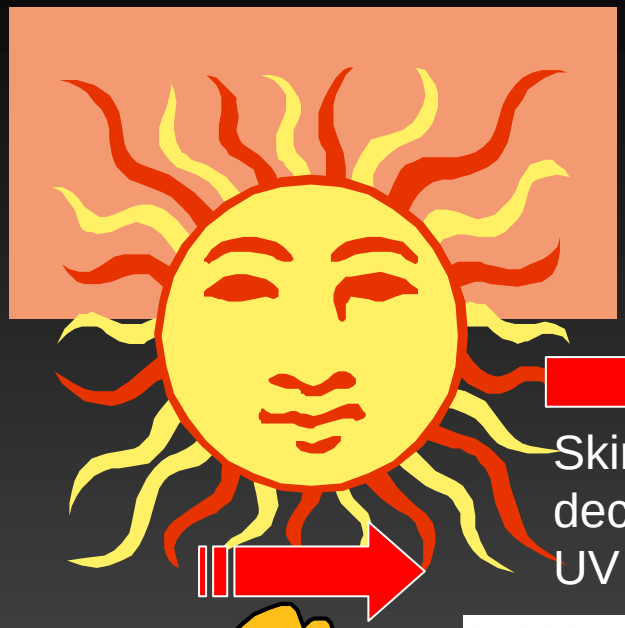
Mutations, p53 and others

+ HPV to perpetuate the mutation

+ HPV effect on p53 products

Corrected by DNA repair mechanisms

Most mutations destroyed but a few cancers develop



Cells with mutations removed by cellular immunity

Skin immunity decreased by UV

Immunosuppression

+ Proliferative effects of medications

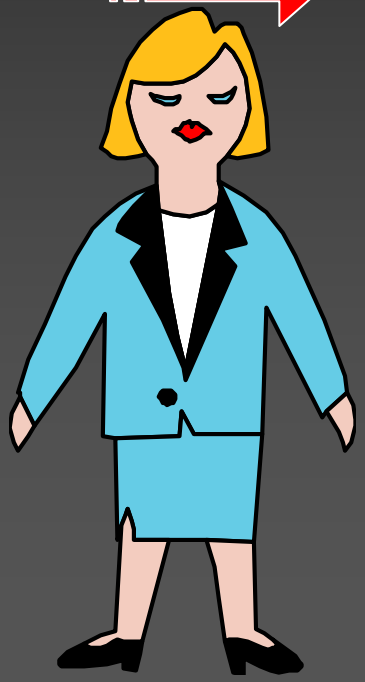
Mutations, p53 and others

+ HPV to perpetuate the mutation

Many cancers develop

+ HPV effect on p53 products

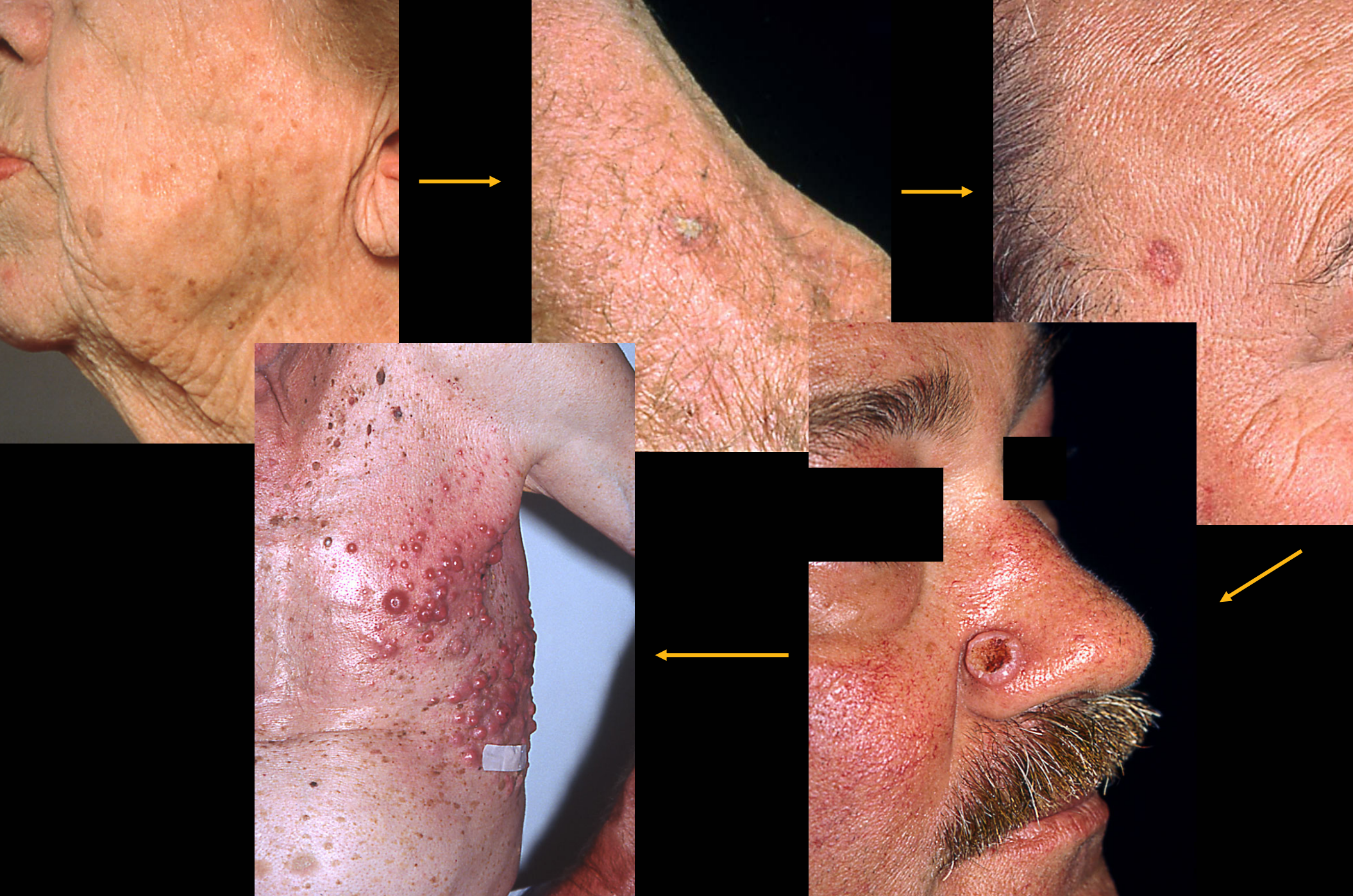
Corrected by DNA repair mechanisms



Accelerated Carcinogenesis: the Life Cycle of Dysplasia

- Actinic damage
- Actinic Keratosis
- Squamous Cell Carcinoma in-situ
- Invasive Squamous Cell Carcinoma
- Metastatic Squamous Cell Carcinoma

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

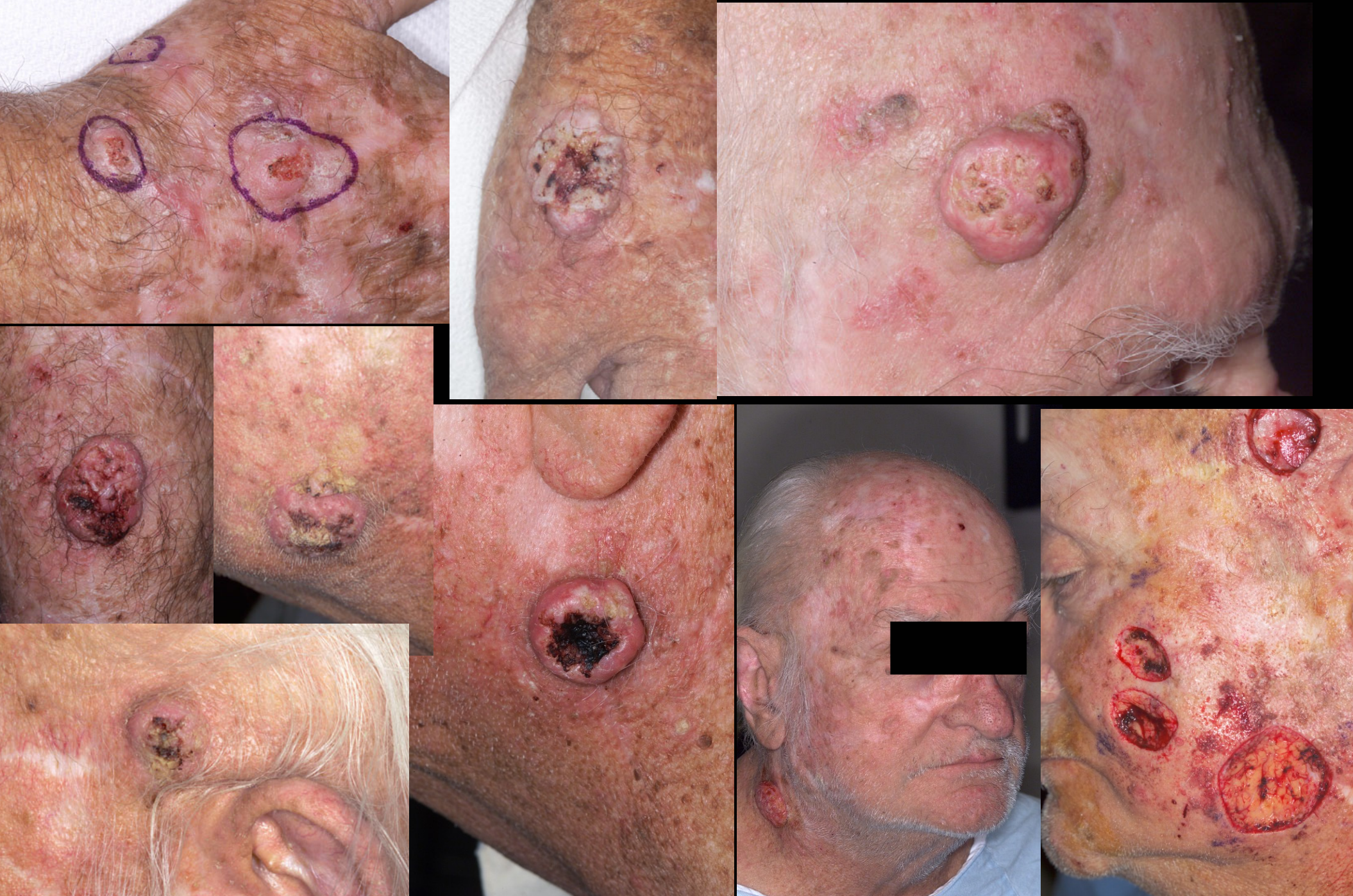


High Volume SCC

- Mean annual incidence = 28%
- Mean number SCC = 1.85/year
- 12% > 5 SCC per year
- Occasional patients > 100 SCCs/ year
- High-risk for metastasis and death from SCC
- More likely with h/o skin cancer pre-Tx

(Ref: Am J Kidney Dis 2003;41;676)

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer



What Now?

AT-RISC ALLIANCE

After Transplantation–
Reduce Incidence of Skin Cancer

The Management of Skin Cancer in Transplant Patients - Basic Principles

- Sun protection
  - Limit outdoor activities 10 am - 3 pm
  - Broad spectrum (UVA/UVB) sunscreen SPF >30 and lip balm
  - Protective clothing and broad-brimmed hats
  - Avoid natural or artificial tanning

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

The Management of Skin Cancer in Transplant Patients - Basic Principles

- Education pre- and post-transplant
- Regular surveillance by dermatologist
  - Transplant dermatology clinic
- Monthly self skin exam
- Monthly self nodal exam with h/o SCC or MM
- Annual complete physical and history focused on metastatic potential

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Follow-up Interval For Skin And Nodal Exams

• No h/o skin cancer	q year
• h/o AKs	q 6 month
• h/o NMSC	q 6 month
• h/o multiple NMSC	q 4 month
• h/o dangerous SCC	q 3 month
• h/o metastatic SCC	q 2 month

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

The Management of Skin Cancer in Transplant Patients

- Aggressive treatment of Actinic Keratoses
  - Cryotherapy
  - 5-Fluorouracil cream
  - Topical retinoids
  - Photodynamic therapy
  - Topical NSAIDs
  - Immune response modifiers - imiquimod
- Chemoprophylaxis - systemic retinoids
- Reduce immunosuppression

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

A Word About Imiquimod

- Topically applied, non-specific immune modulator
- Approved for treatment of condyloma, actinic keratoses and some superficial BCCs
- Safety in organ transplant recipients--are there systemic effects?
  - Unpublished European safety study(relatively small numbers) showed no problems
  - No published reports of problems with graft rejection, many patients have been treated
- Efficacy in organ transplant recipients--can OTR's respond?
  - Early reports indicate: yes

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

The Management of Skin Cancer in Transplant Patients

- Individual tumors managed according to traditional principles, with increased diligence
- Mohs Micrographic Surgery
- Electrodesiccation and curettage
- Cryotherapy
- Excision
- Radiation

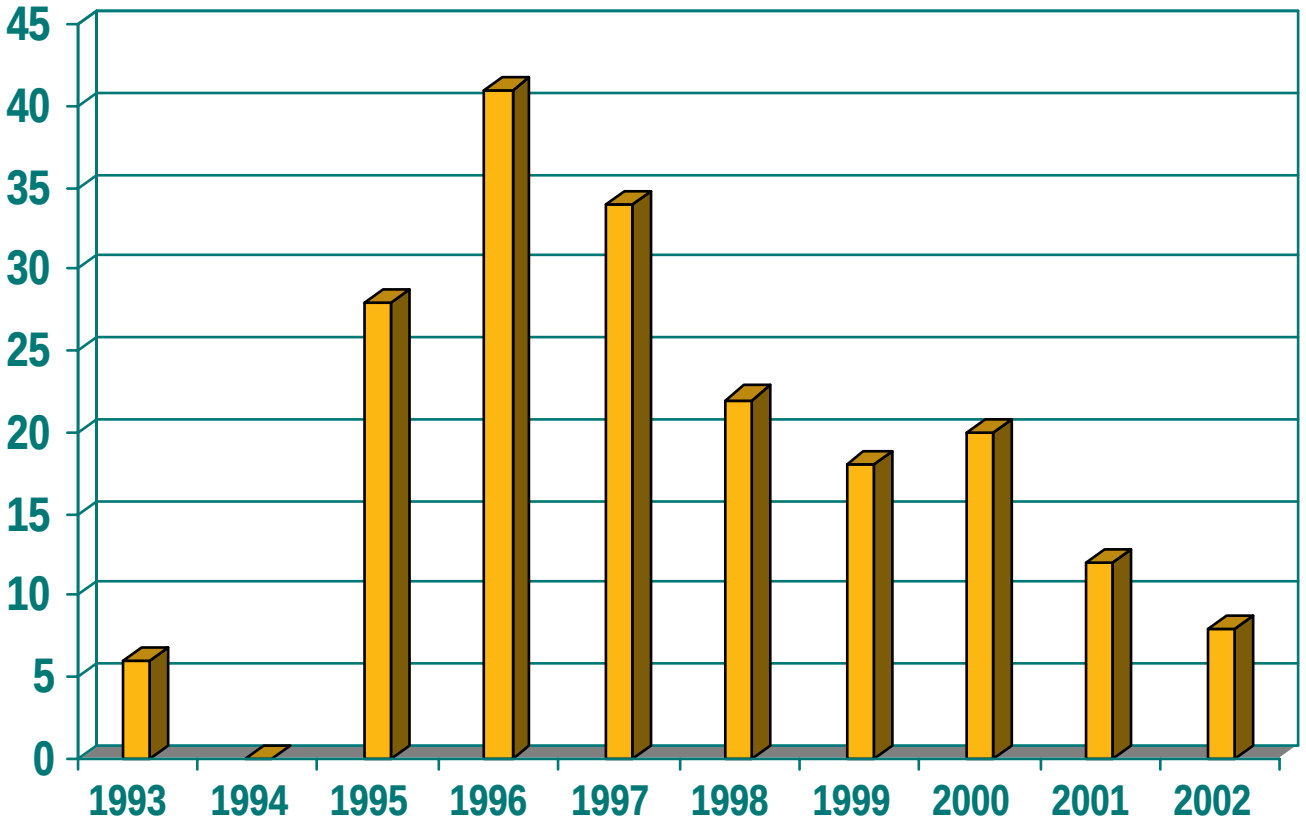
AT-RISC ALLIANCE
After Transplantation– Reduce Incidence of Skin Cancer

The Management of Skin Cancer in Transplant Patients - Basic Principles

- For highly susceptible patients, consider prophylactic topical
- Retinoids
- 5-fluorouracil
- Imiquimod
- Diclofenac

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

73 Year-old Man
s/p Renal Transplant 1992



AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Reduction of Immunosauppression for Severe Skin Cancer in Organ Transplant Recipients

AT-RISC
ALLIANCE

After Transplantation–
Reduce Incidence of Skin Cancer

Rationale For RI

- Restoration of effective anti-tumor immunity
- Restoration of effective immune surveillance
- Restoration of effective anti-viral immunity
- Decreased direct carcinogenic effect (CyA)
- Decreased photosensitization by azathioprine metabolites
- Others

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Evidence Supporting Reduction of Immunosuppression

- Dantal et al. RCT High vs low-dose CyA
  - Fewer NMSC, internal CA, more rejection, equivalent graft and patient survival
- Jensen et al. More NMSC with 3- vs 2-drug regimen
- Otley et al. 4/6 OTRs with decreased skin cancer after cessation of immunosuppression
- UNOS Transplant Tumor database - NMSC incidence -> cardiac > renal > liver; parallels intensity of immunosuppression

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

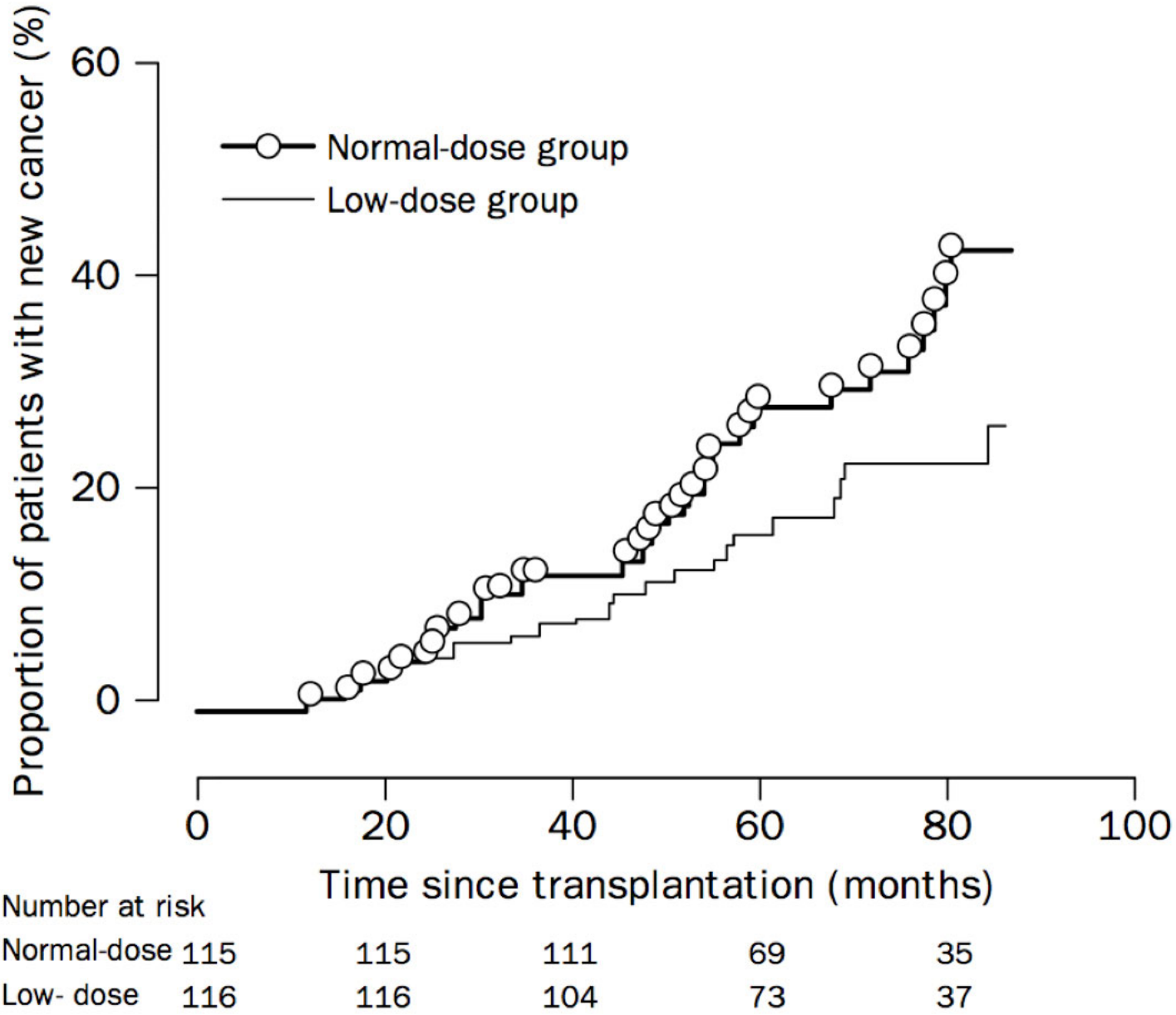
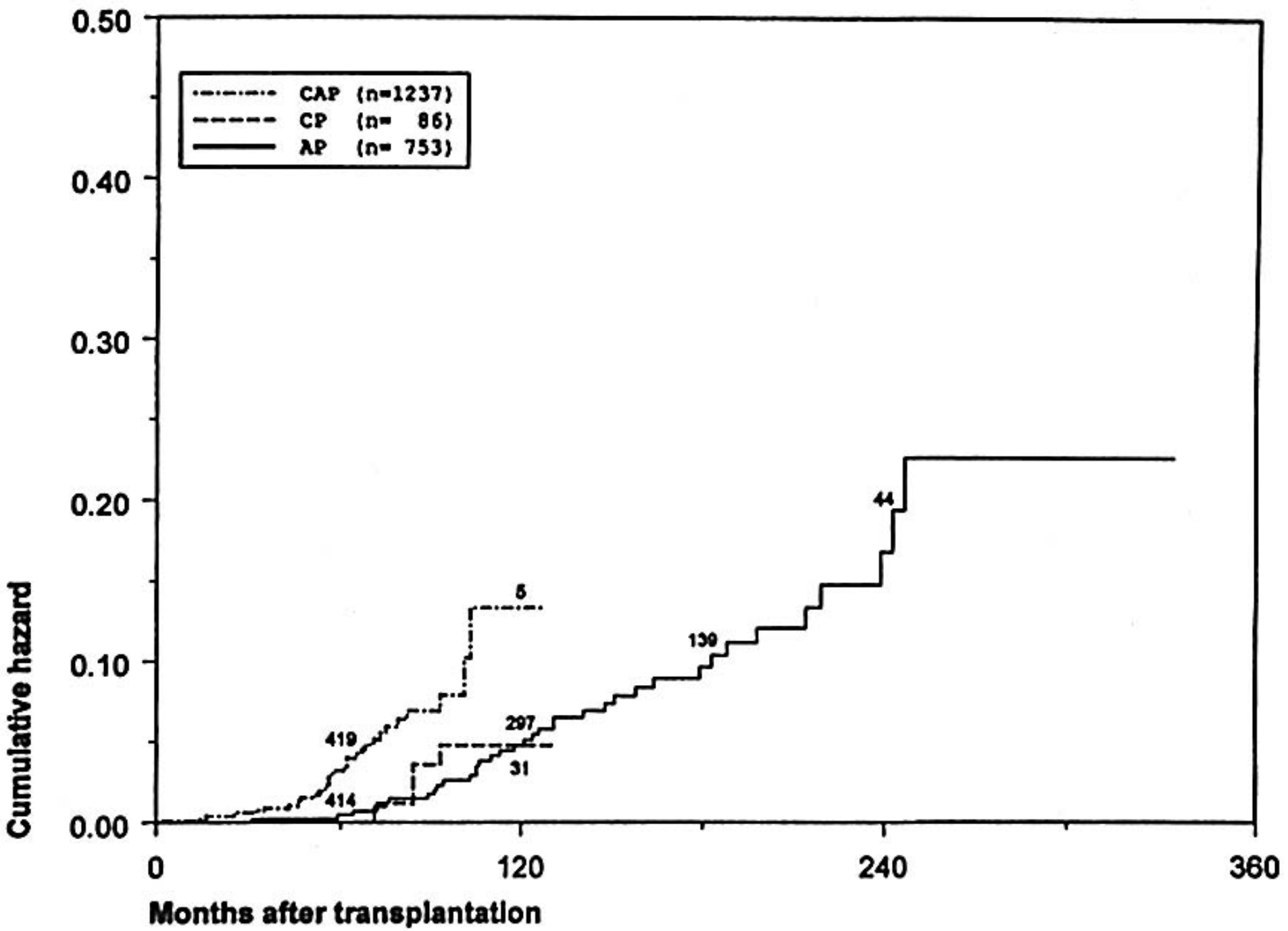


Figure 4: **Frequency of cancer**


CAP (n=1237)
CP (n= 86)
AP (n= 753)
0.50
0.40
0.30
0.20
0.10
0.00
Cumulative hazard
0
120
240
360
Months after transplantation
6
44
139
297
419
31
414

Evidence Supporting Reduction of Immunosuppression

- Moloney et al. Prolonged disease free survival from met NMSC with RI
- Kaposi's Sarcoma regresses with RI
- PTLD regresses with RI
- Merkel Cell Carcinoma can regress with RI

Ref: Otley, Maragh. Dermatol Surg 2005; 31:163-8.

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Skin Cancer Scenarios – Transplant MD Opinion

	Level of reduction of immunosuppression to consider		
	RENAL ALLOGRAFT	CARDIAC ALLOGRAFT	LIVER ALLOGRAFT
1. No history of actinic keratoses or skin cancer	None	None	None
2. History of actinic keratosis	None	None	None
3. History of ≤ 1 NMSC per year	None	None	Mild
4. History of 2-5 NMSC per year	Mild	Mild	Mild
5. History of 6-10 NMSC per year	Moderate	Moderate	Moderate
6. History of 11-25 NMSC per year	Moderate	Moderate	Moderate
7. History of > 25 NMSC per year	Moderate	Moderate	Moderate
8. Individual high risk skin cancer – 1% mortality over 3 years (average risk SCC; cutaneous and oral KS; stage IA melanoma)	Moderate	Moderate	Mild
9. Individual high risk skin cancer – 5% mortality over 3 years (moderate risk SCC; stage IB melanoma)	Moderate	Moderate	Moderate
10. Individual high risk skin cancer – 10% mortality over 3 years (high risk SCC; early Merkel cell carcinoma; stage IIA melanoma)	Severe	Moderate	Moderate
11. Individual high risk skin cancer – 25% mortality over 3 years (very high risk SCC; stage IIB melanoma)	Severe	Moderate	Moderate
12. Individual high risk skin cancer – 50% mortality over 3 years (metastatic SCC; stage IIC/III melanoma; aggressive Merkel cell carcinoma; visceral KS)	Severe	Severe	Severe
13. Individual high risk skin cancer – 90% mortality over 3 years (untreatable metastatic SCC; stage IV melanoma; metastatic Merkel cell carcinoma)	Severe	Severe	Severe

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Chemoprophylaxis in Transplant Patients

Acitretin and Isotretinoin

AT-RISC ALLIANCE

After Transplantation – Reduce Incidence of Skin Cancer

The Data on Systemic Retinoids for Chemoprevention

- Organ transplant
  - Decreased SCCs with etretinate in various regimens: 50 mg qd, 1 mg/kg, 0.3 mg/kg
  - Decreased SCCs with acitretin: 0.5 mg/kg
  - Etretinate 10 mg qd not better than 0.025% tretinoin cream plus etretinate

Ref: Gibson. J Eur Acad Dermatol Venereol 1998;10:42/Rook Transplantation 1995;59:714

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Systemic Retinoid Chemoprophylaxis

- Oral retinoid therapy may reduce the number of SCC developing in the post-transplant period
- Oral retinoid therapy may also helpful in reducing AKs and non-specific keratotic lesions
- Studies have reported minimal severe side effects
  - Most adverse events involve mucocutaneous effects (dryness, alopecia), elevation of blood lipid levels or increase in liver function tests. (LFT, TG, Chol)
- No evidence of problems with graft function

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Systemic Retinoid Chemoprophylaxis

Rebound effect off therapy

- If a patient has a good response, he will usually rapidly develop more tumors if therapy is discontinued
- Continuous treatment is required to maintain a protective effect

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Systemic Retinoid Chemoprophylaxis

- Female patients MUST NOT become pregnant while on retinoid therapy
- Causes severe birth defects
- Skin cancer chemoprophylaxis is not an FDA approved indication

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

The Pros and Cons of Systemic Retinoid Therapy

- Decreased SCC
- Decreased BCC
- ? Delayed recurrence/ metastasis

- Not curative
- Must continue or rebound
- Hyperlipidemia
- Liver function abnormalities
- Mucocutaneous dryness

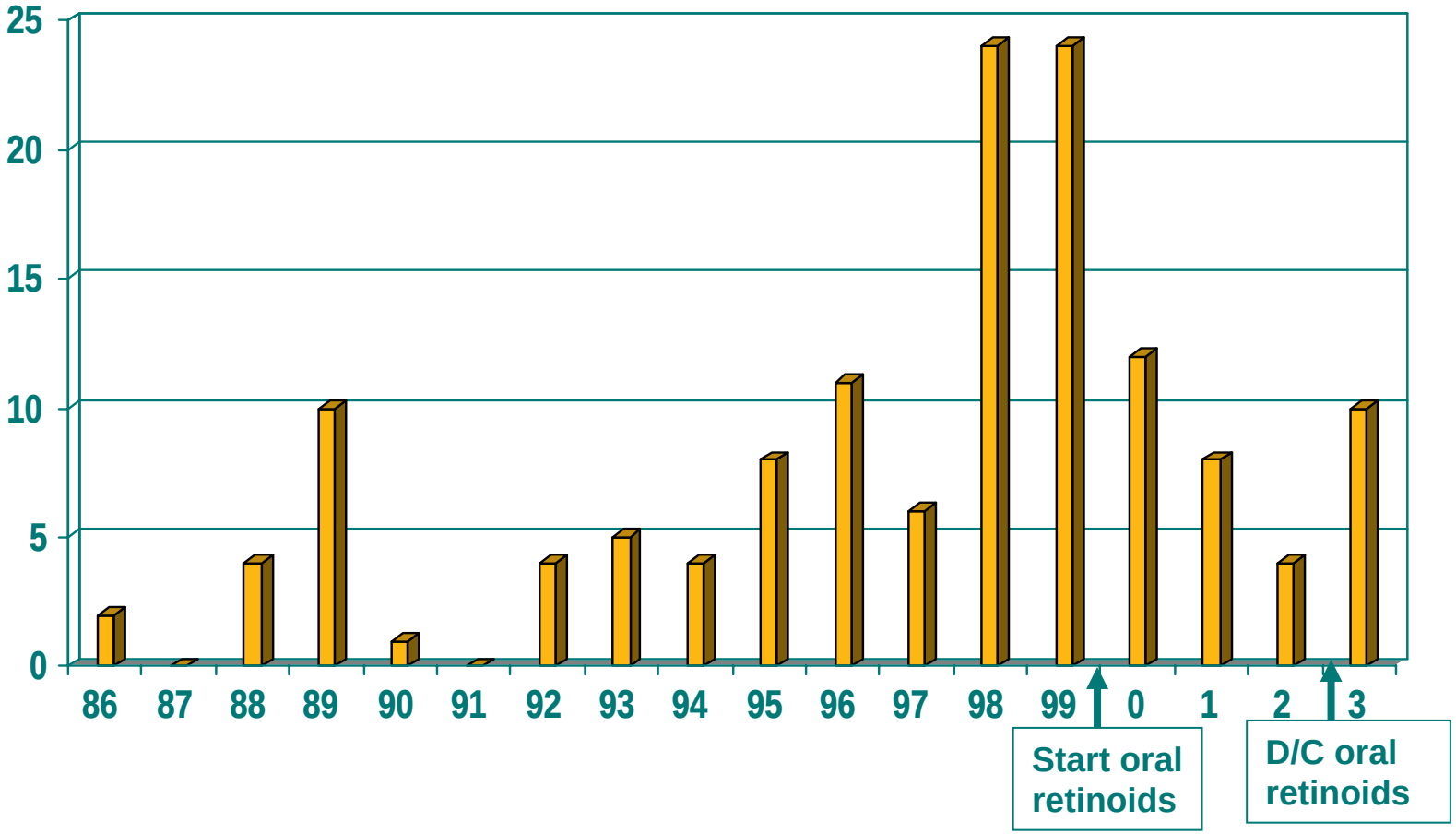
AT-RISC ALLIANCE
After Transplantation– Reduce Incidence of Skin Cancer

When To Consider Systemic Retinoids

- Numerous skin cancers per year (5-10/year)
- Metastatic skin cancer
- In conjunction with decreased immunosuppression
- After clearing significant tumors

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

64 Year-old Cowboy
s/p Renal Transplant 1980



AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer

Should Patients With Prior Skin Cancer Be Transplant Donors Or Recipients?

- Depends on specifics of cancer
- Validated prognostic factors
- Accentuation of risk by immunosuppression poorly quantified
- Consult with transplant dermatologist

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Table 2: Pre-transplantation skin cancer suggested assessment

Skin cancer	May receive transplant	Consult with transplant dermatologist	Should not receive transplant	Re-evaluation interval after primary tumor diagnosis if denied transplant, y
Basal cell carcinoma				
Primary	X			
Metastatic, in remission			X	5
Metastatic, not in remission			X	NA
Squamous cell carcinoma				
Primary, low risk	X			
Primary, high risk		X		3
Metastatic, in remission			X	3–5
Metastatic, not in remission			X	NA
Melanoma				
In situ	X			
Stage I		X		3–10
Stage II			X	5–10
Stage III			X	10
Stage IV			X	10
Merkel cell carcinoma				
Primary		X		2–3
Metastatic, in remission			X	3–5
Metastatic, not in remission			X	NA
Kaposi sarcoma		X		NA
Atypical fibroxanthoma		X		3
Dermatofibrosarcoma protuberans	X			
Sebaceous carcinoma		X		3
Eccrine carcinoma		X		3
Microcystic adnexal carcinoma		X		3
Extramammary Paget disease		X		3

NA: not applicable.

The Importance of a Multidisciplinary Approach

- Dermatology/Dermatologic surgery
- Transplant medicine
- Pathology/ Dermatopathology
- Otorhinolaryngology
- Plastic surgery
- Ophthalmology
- Radiation Oncology
- Medical Oncology
- Radiology

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

What Transplant Physicians Need to Know About Skin Cancer in OTRs

- Skin cancer can ruin a life
- Skin cancer can take a life
- Prevention must come early; EARLY = CURE
- Less immunosuppression means less cancer
- Dermatologic surgeons and dermatologists want to work with you
- Expert help is available through AT-RISC

(www.AT-RISC.org) and ITSCC (www.itscc.org)

AT-RISC ALLIANCE
After Transplantation–Reduce Incidence of Skin Cancer

Challenges and Opportunities

AT-RISC ALLIANCE

After Transplantation–
Reduce Incidence of Skin Cancer

What The Future Holds

- Skin cancer is a serious problem for transplant recipients
- There is great opportunity for innovation and intervention
- AT-RISC Alliance (www.AT-RISC.org)
- International Transplant-Skin Cancer Collaborative (www.ITSCC.org)
- Skin Care for Organ Transplant Patients, Europe (SCOPE) (www.scopnetwork.org)

AT-RISC ALLIANCE
After Transplantation – Reduce Incidence of Skin Cancer