

PowerPoint Presentation for Transplant Nurses and Coordinators

- This presentation was designed to be given by a health-care professional to an audience of transplant nurses and coordinators
- 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

Skin Cancer in Organ Transplant Patients: Challenges and Opportunities

Supported by an unrestricted educational grant from Connetics Corporation



After Transplantation –
Reduce Incidence of Skin Cancer

AT-RISC Alliance



After Transplantation –
Reduce Incidence of Skin Cancer



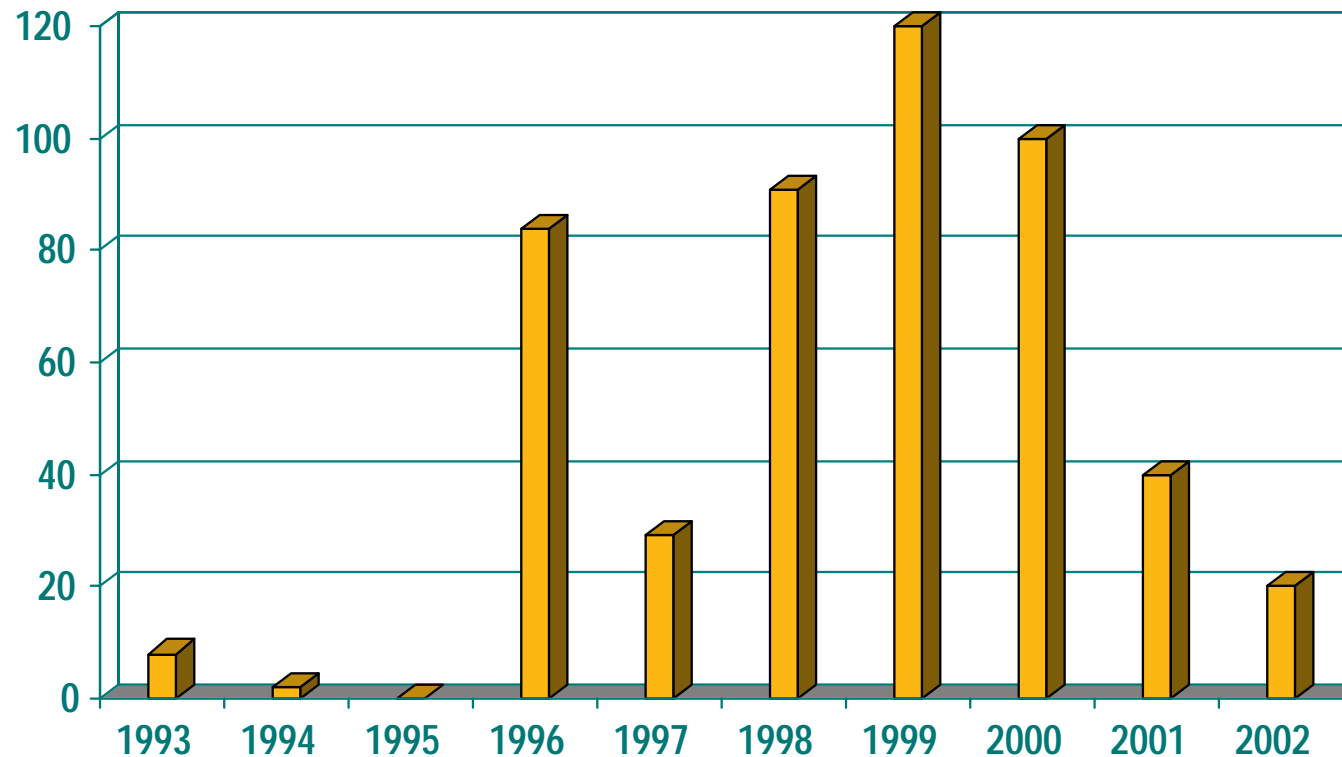
Skin Cancer Facts: the AT-RISC Fact Sheet

- 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

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

73 Year-old Outdoorsman s/p Cardiac Transplant 1993







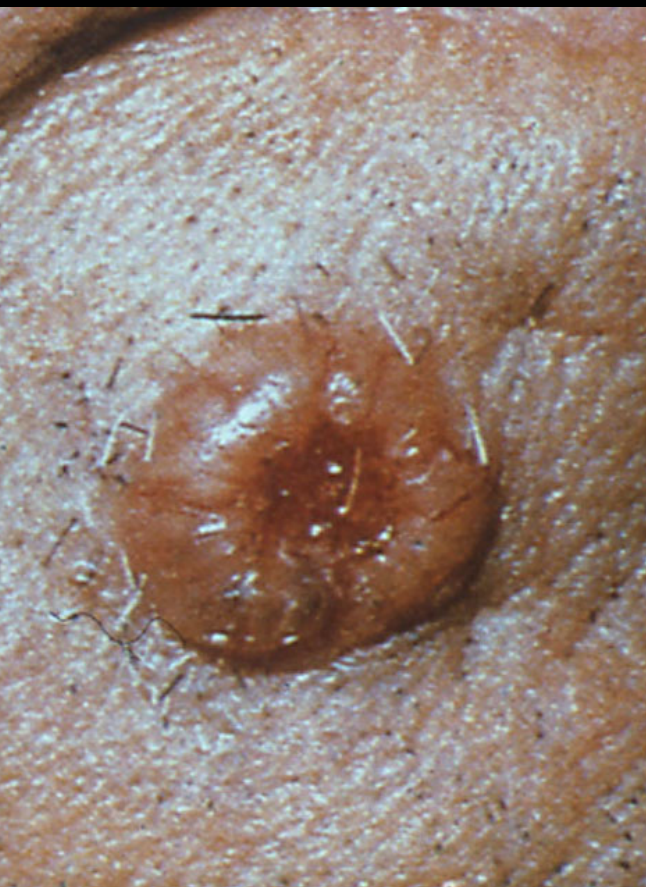


The State of Skin Cancer

- Basal Cell Carcinoma 1,000,000
 - Incidence doubles every 25 years
- Squamous Cell Carcinoma 300,000
 - Incidence doubles every 20 years
- Melanoma 51,400
 - Incidence doubles every 15 years

Skin Cancer Essentials

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



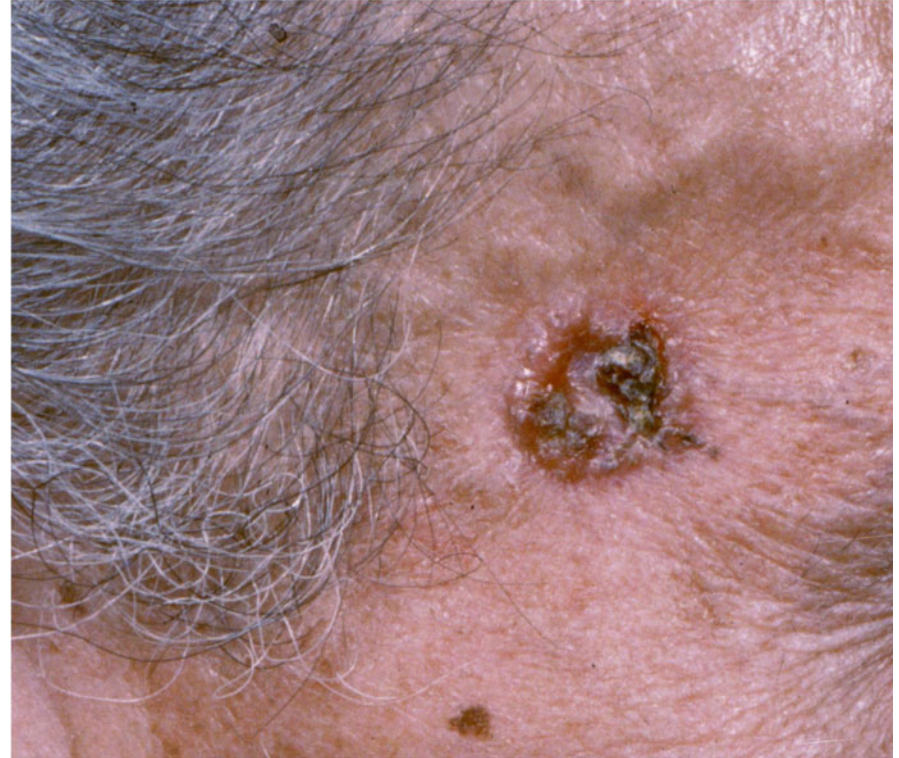


Basal Cell Carcinoma

- Over 1,000,000/year in U.S. in photodamaged adults
- Incidence doubles every 25 years
- Local destruction, rare metastasis
- ED+C, excise, XRT
- Mohs Micrographic Surgery
- Different 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



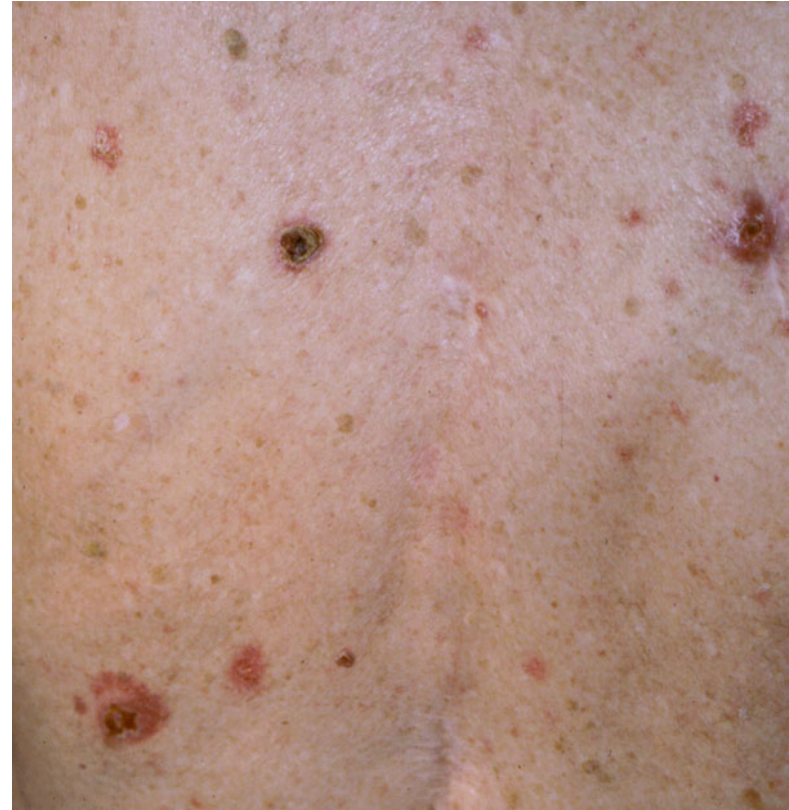


- Basal Cell Carcinoma-nodular



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



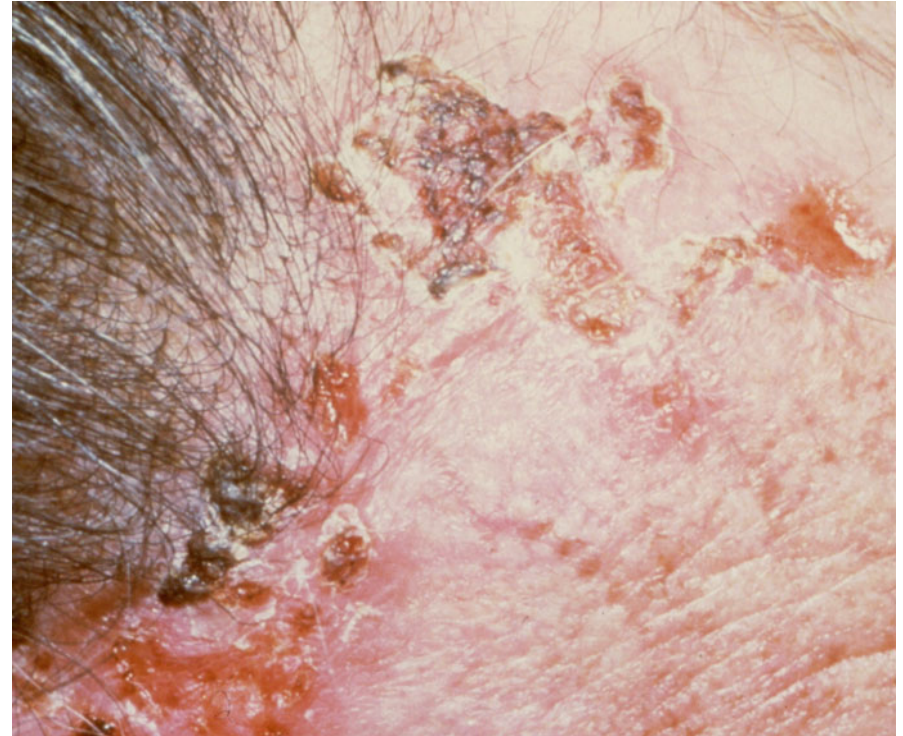


- Basal Cell Carcinoma-superficial



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

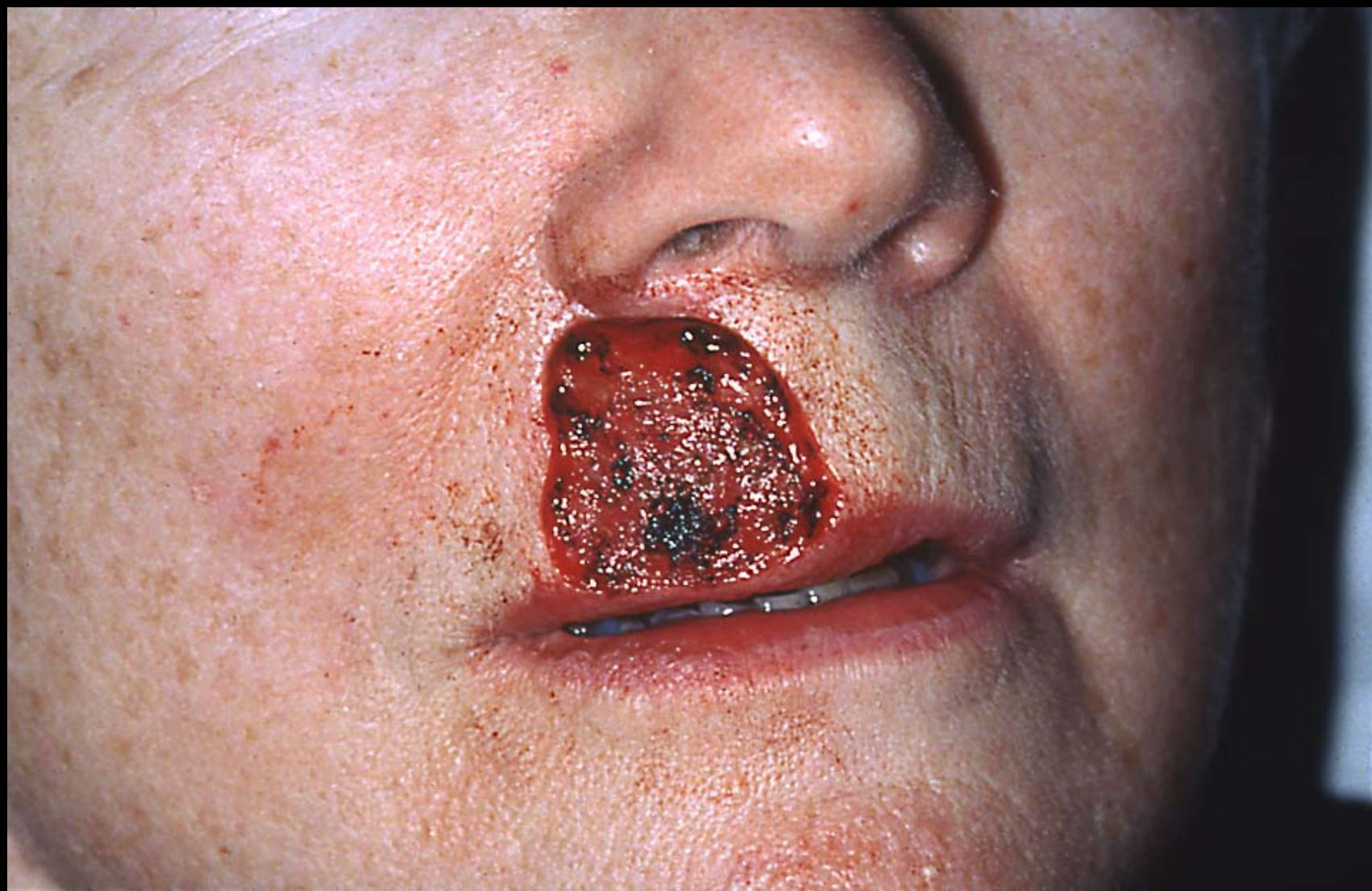




- Basal cell carcinoma-morpheaform type

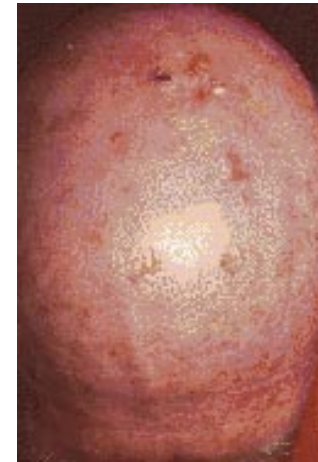






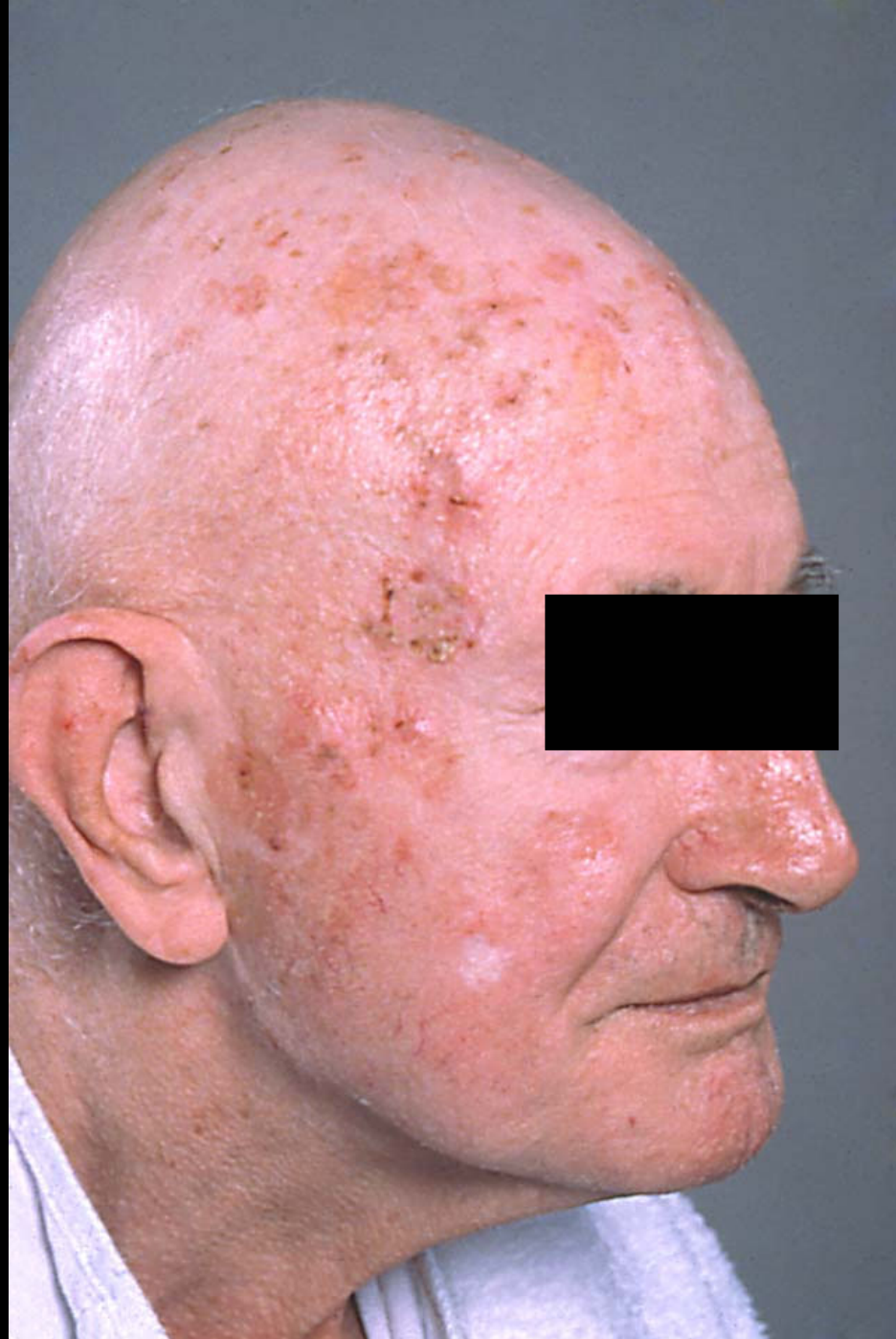
Actinic Keratosis (a.k.a. the First Stage of SCC)

- 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









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

SCC

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

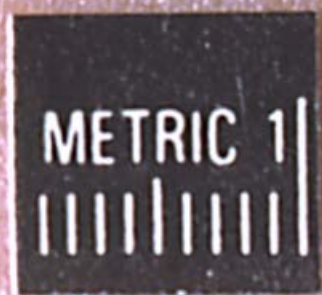




SCC

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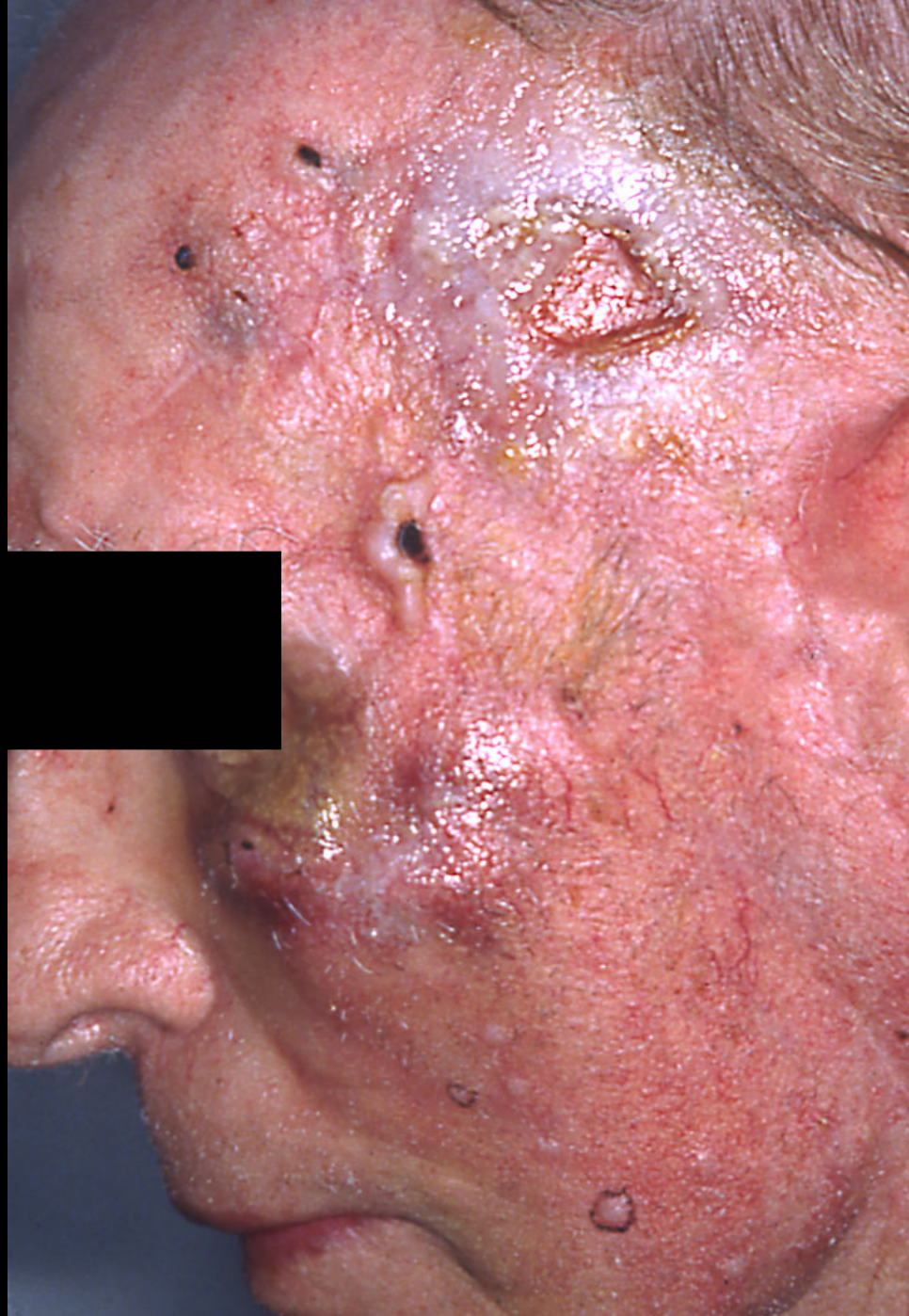


Recognizing the High-risk SCC

- 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

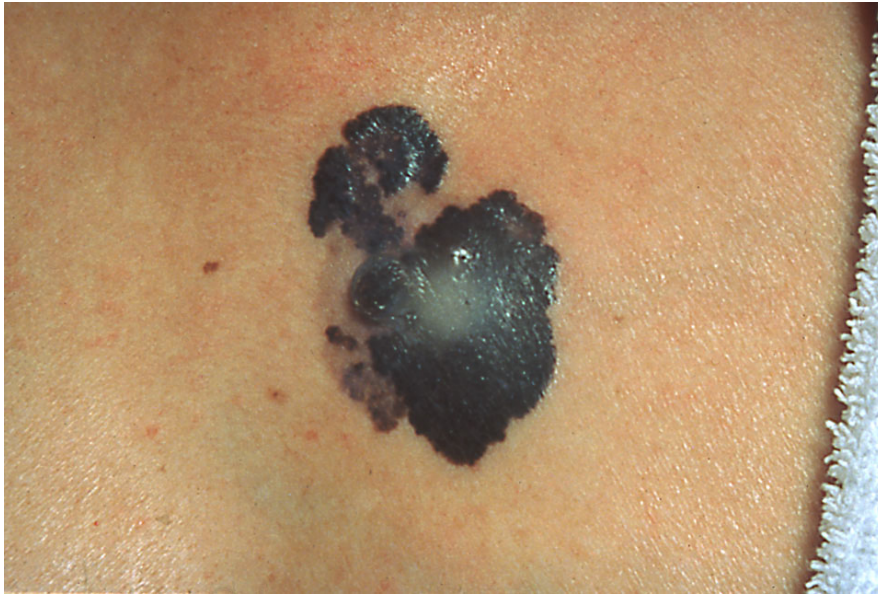






Malignant Melanoma

- 59,000 cases of invasive melanoma last year in US
- 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



Melanoma

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











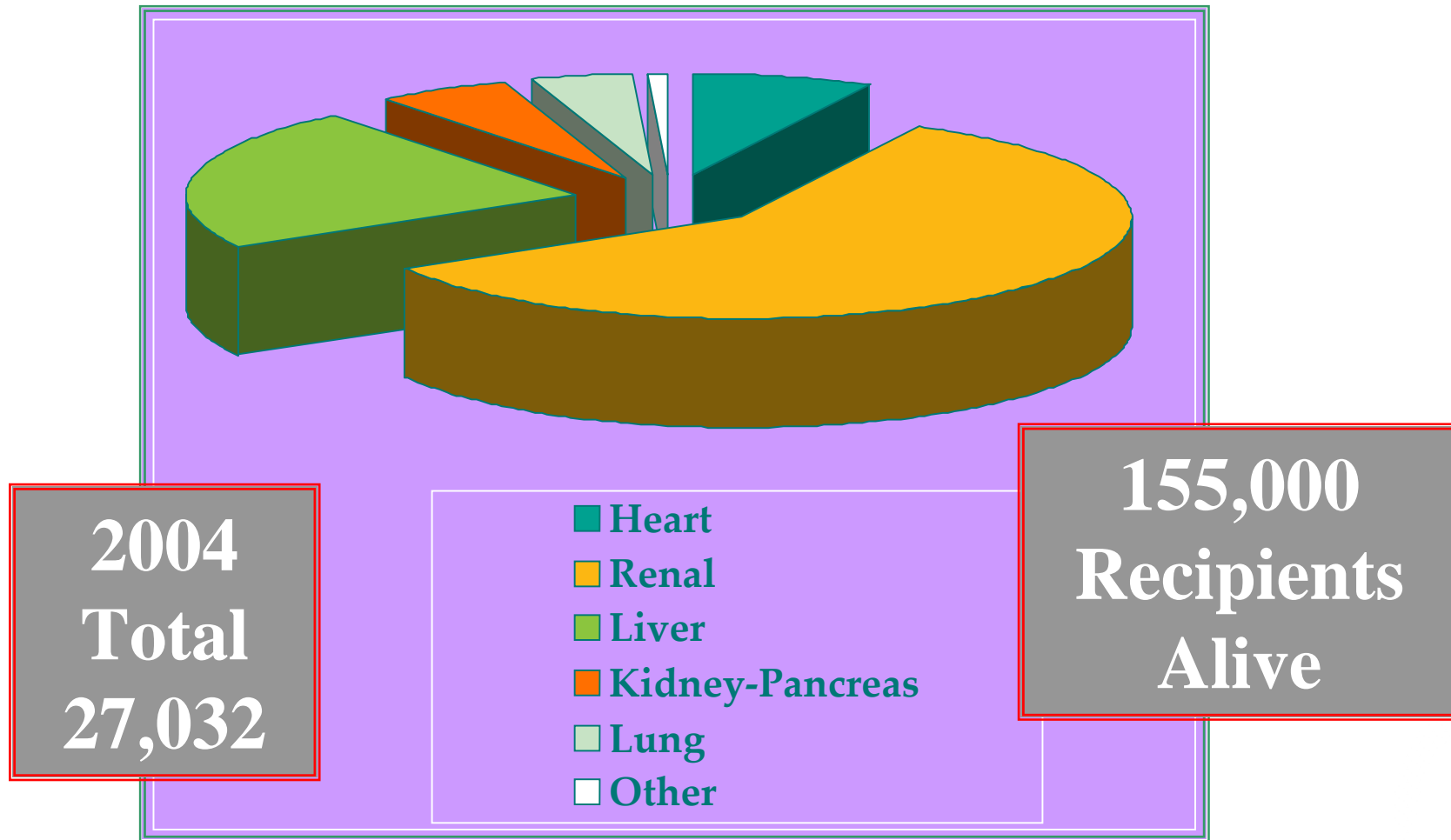




The State of Transplantation in the U.S. - UNOS Data

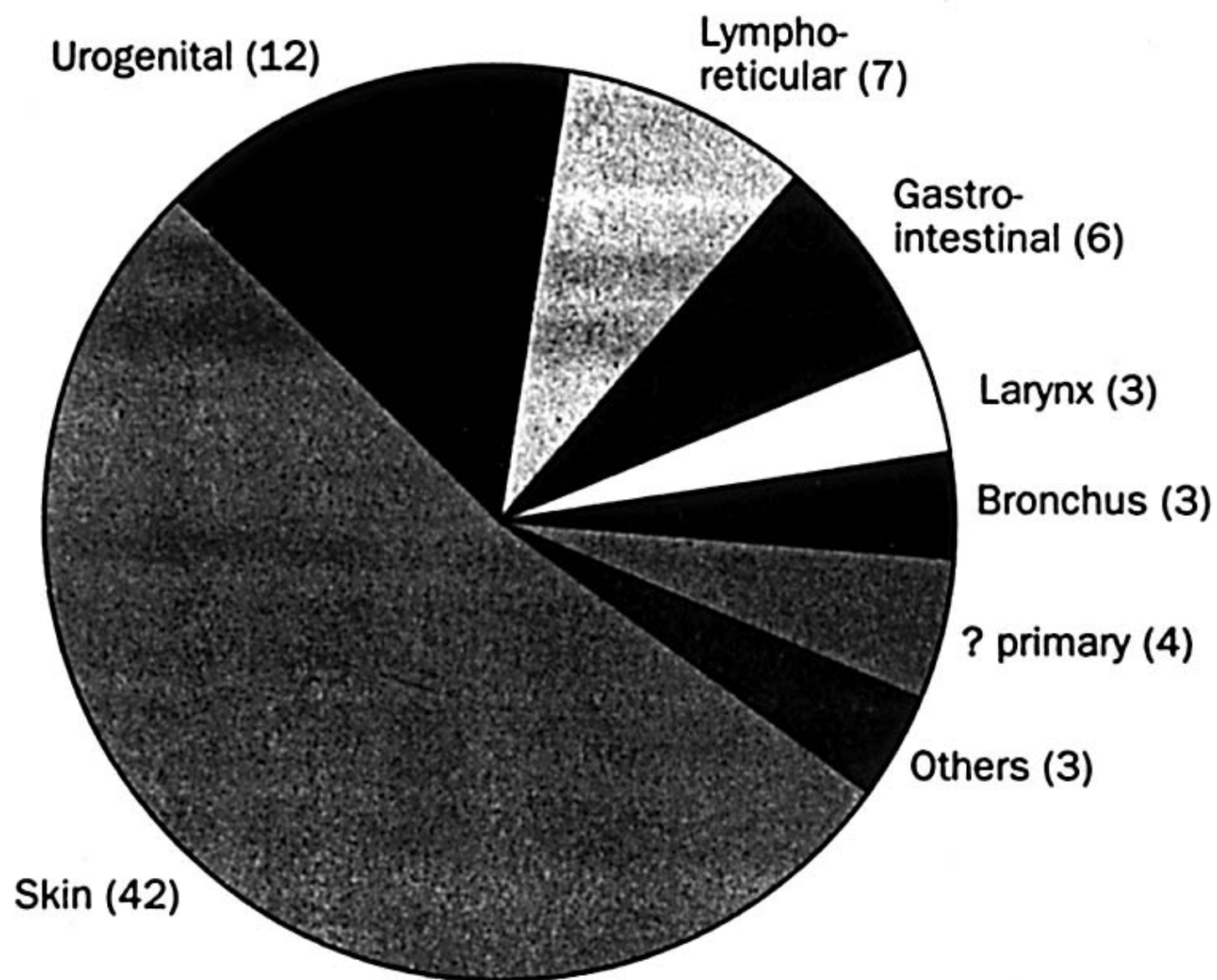
- Over 28,000 organ transplants per year (74,000 worldwide)
- Approximately 155,000 organ recipients currently alive in U.S.
- Over 90,000 people awaiting transplants
- More than 7,000 die waiting each year
- Organ donation numbers increasing only slightly
- Organ scarcity is major problem

U.S. Organ Transplants in 2004

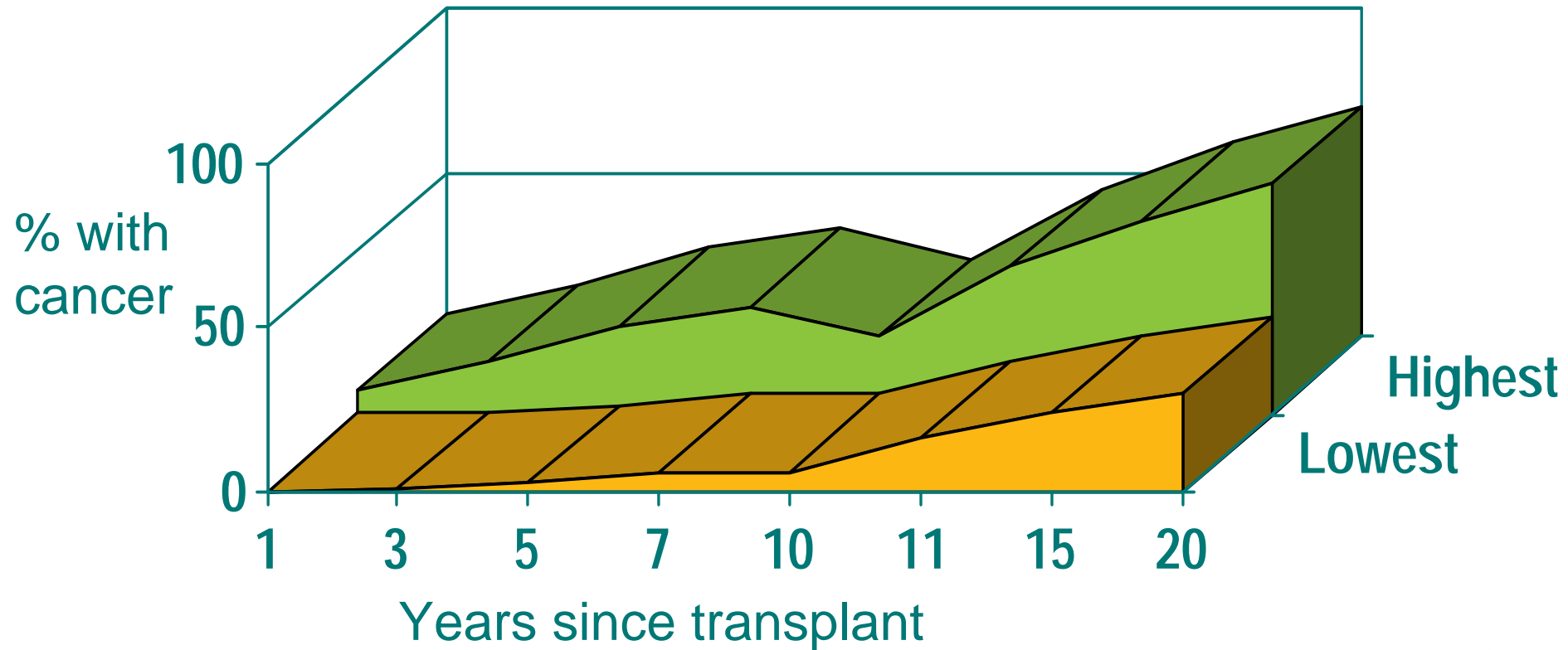


Skin Cancer in Transplant Patients - Clinical Characteristics

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



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



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

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

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

Other Cutaneous Neoplasms in Organ Transplant Patients

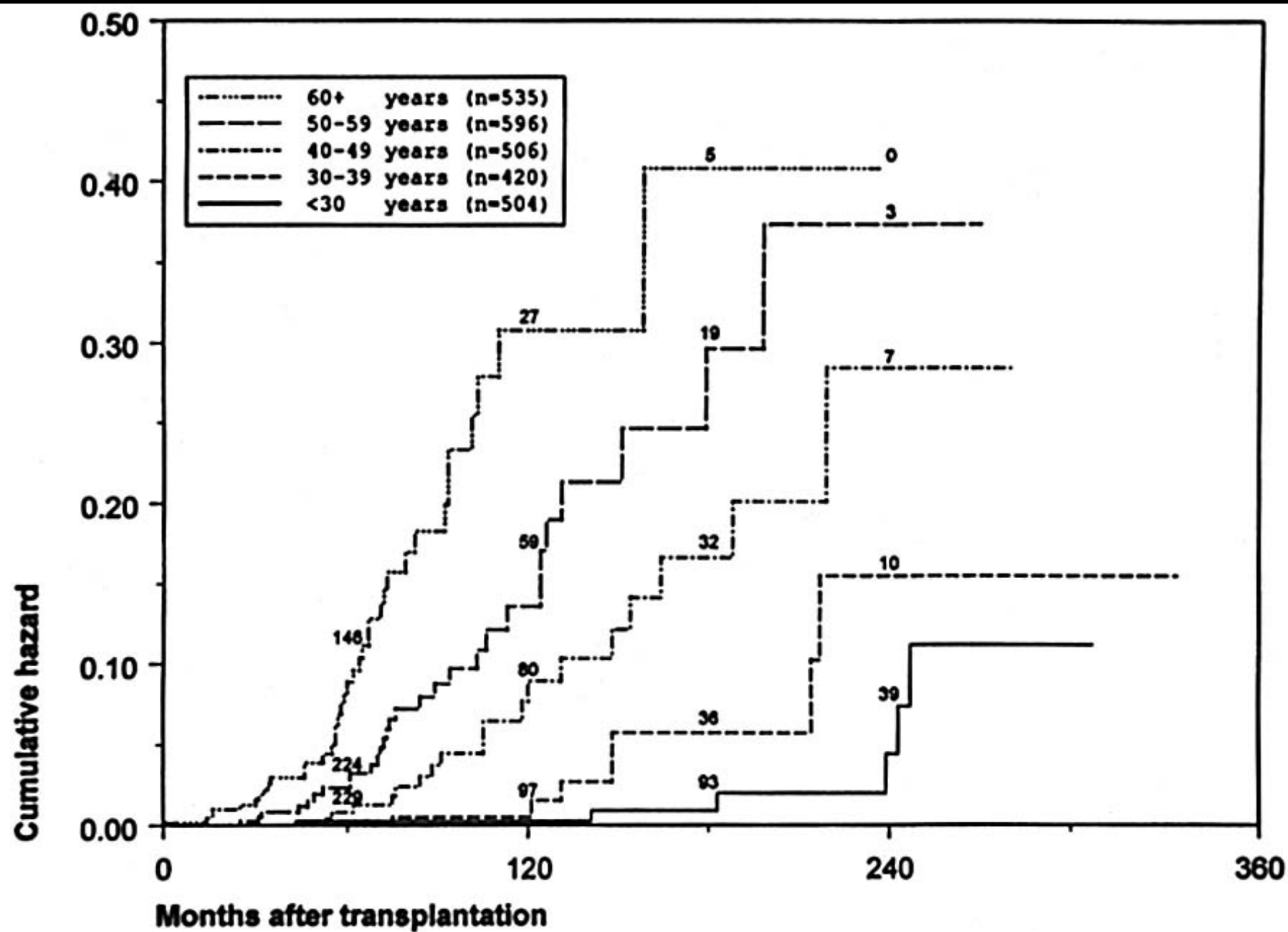
- Melanoma
- Kaposi's Sarcoma
- Angiosarcoma
- Merkel Cell Carcinoma
- Verrucous Carcinoma
- Atypical Fibroxanthoma
- Leiomyosarcoma
- Cutaneous T-cell Lymphoma
- Cutaneous B-cell Lymphoma

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

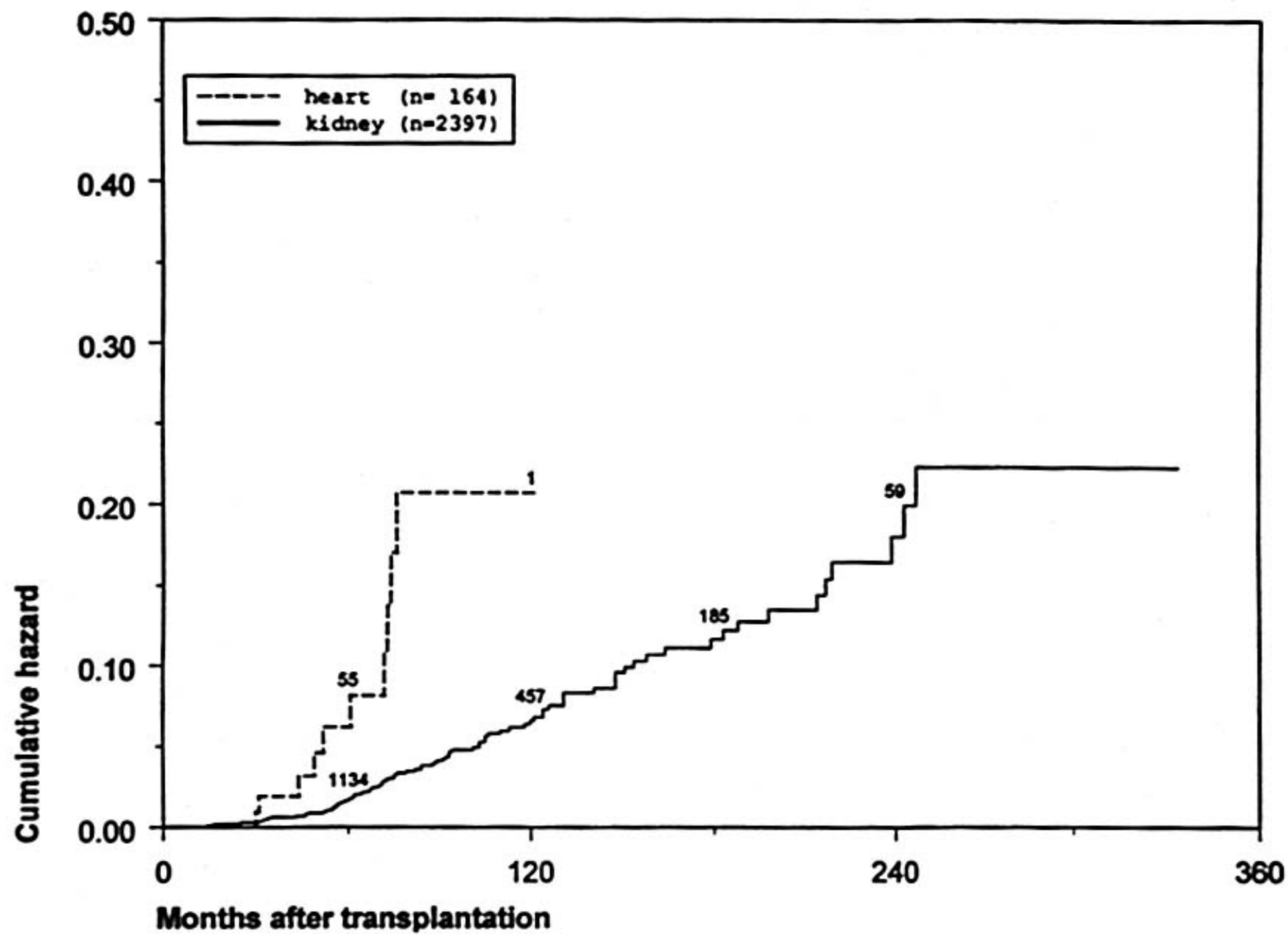
Additional Risk Factors for Skin Cancer in Organ Transplant Patients

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



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



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?

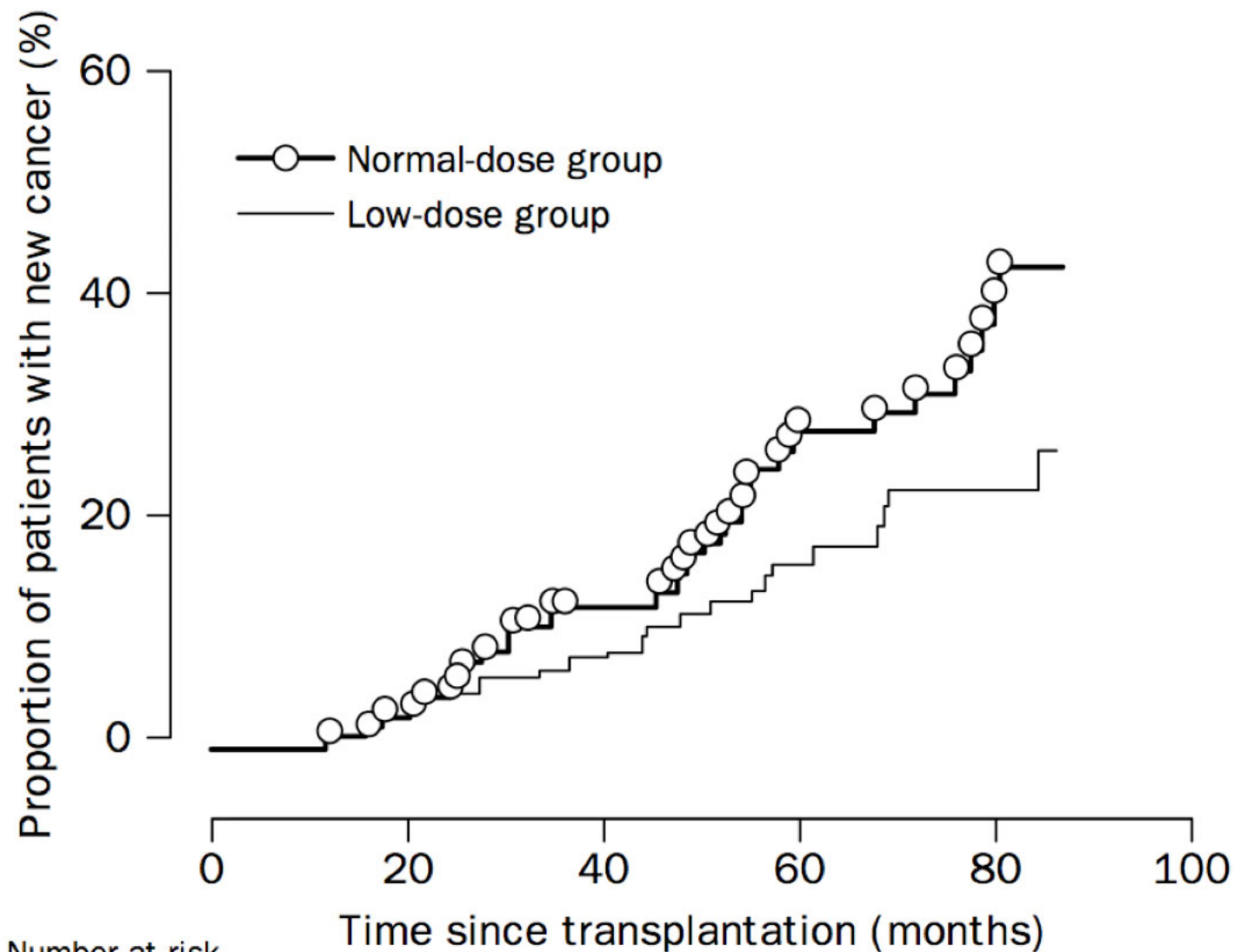
- Animal data
 - Azathioprine > Cyclosporine > steroids
- Human data
 - Minor differences between agents
 - 3 agents > 2 agents > one agent
 - Overall intensity of immunosuppression most important

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.



Number at risk

Normal-dose	115	115	111	69	35
Low- dose	116	116	104	73	37

Figure 4: **Frequency of cancer**

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%

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

Newer Immunosuppressants and Skin Cancer

- Steroids seem to play little, if any, 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

Transplant Oncology: Rapamycin

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

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

Rejection Versus Cancer

PREVENT REJECTION

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

PREVENT CANCER

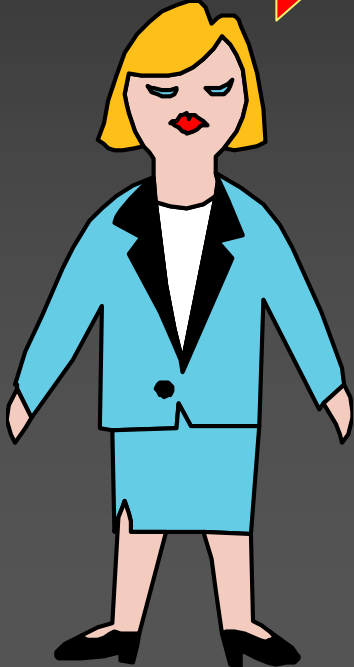
- Fewer drugs
- Less skin cancer
- Higher survival from skin cancer
- Increased QOL
- ? Increased rejection



Cells with mutations removed
by cellular immunity



Skin immunity
decreased by
UV



Cellular DNA



Mutations, p53 and others



Corrected by DNA repair
mechanisms



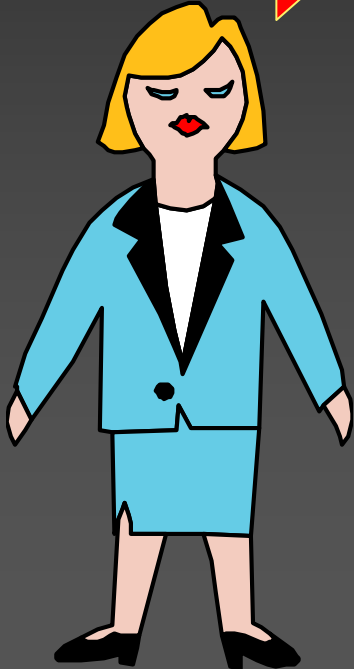
Most mutations
destroyed but a
few cancers
develop



Cells with mutations removed
by cellular immunity



Skin immunity
decreased by
UV



Cellular DNA



Mutations, p53 and others

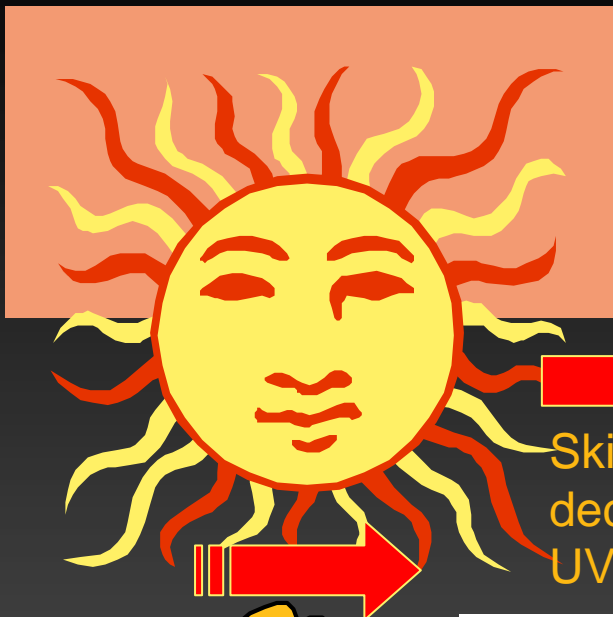
+ HPV to perpetuate
the mutation



+ HPV effect on
p53 products

Corrected by DNA repair
mechanisms

Most mutations
destroyed but a
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Cells with mutations removed
by cellular immunity

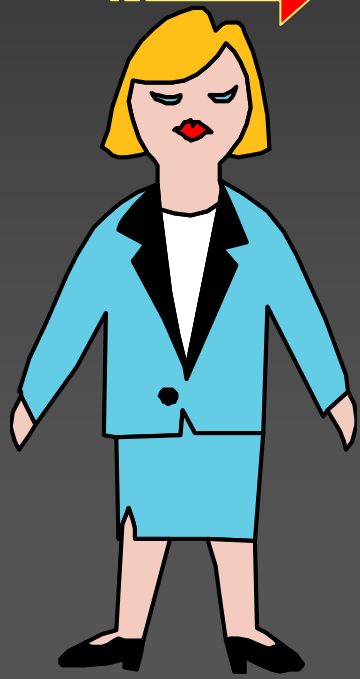


Skin immunity
decreased by
UV

Immunosuppression



+ Proliferative
effects of
medications



Cellular DNA 

Mutations, p53 and others

+ HPV to perpetuate
the mutation



Many cancers
develop

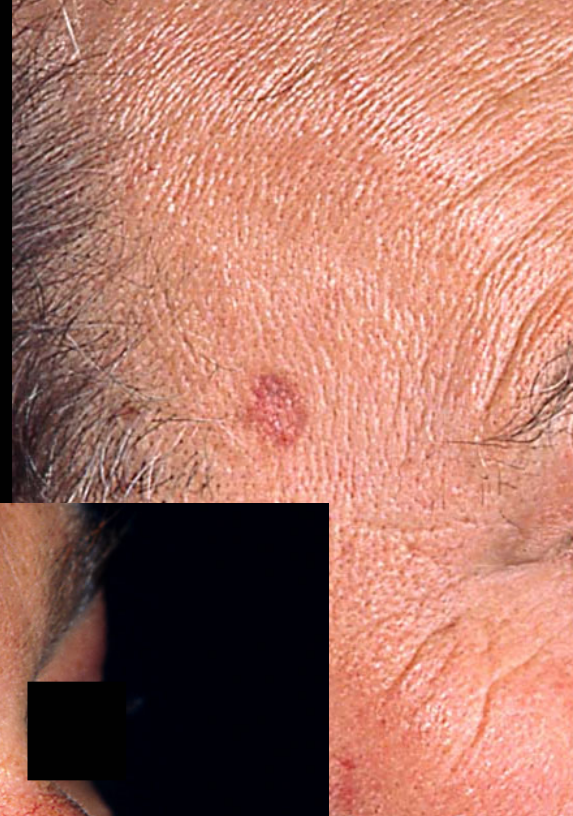
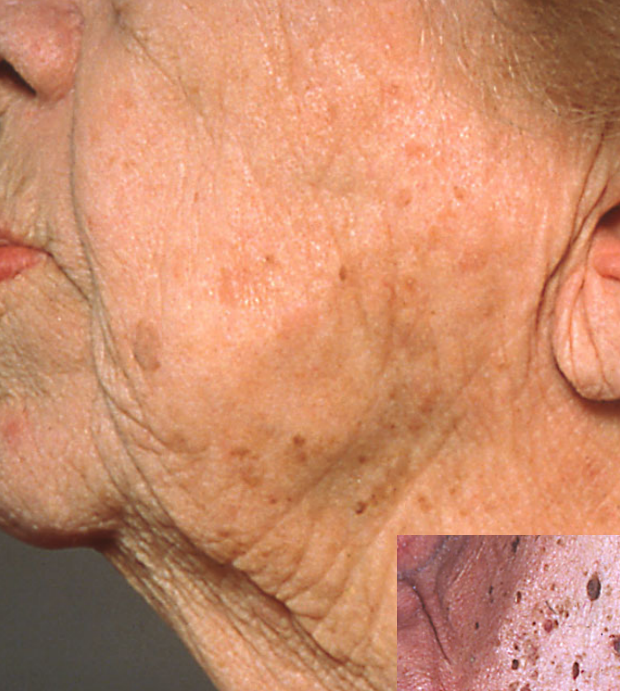
+ HPV effect on
p53 products



Corrected by DNA repair
mechanisms

Accelerated Carcinogenesis: the Life Cycle of Dysplasia

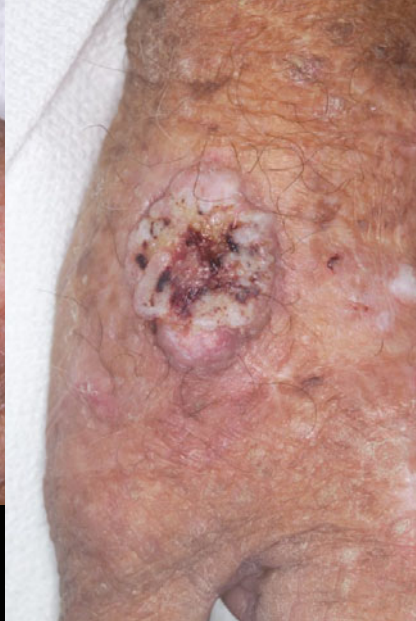
- Actinic damage
- Actinic Keratosis
- Squamous Cell Carcinoma in-situ
- Invasive Squamous Cell Carcinoma
- Metastatic Squamous Cell Carcinoma



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)



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

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

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 |

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

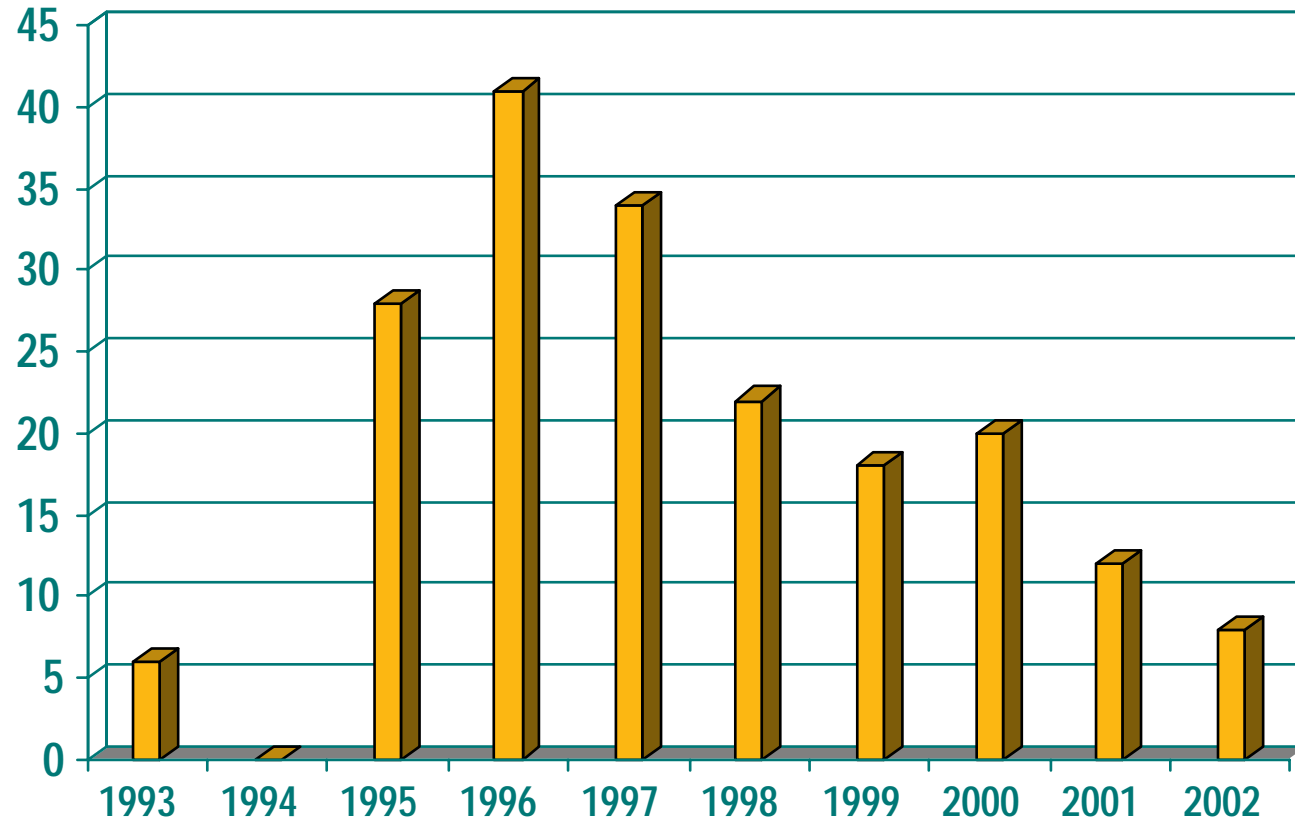
The Management of Skin Cancer in Transplant Patients

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

The Management of Skin Cancer in Transplant Patients - Basic Principles

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

73 Year-old Man s/p Renal Transplant 1992



Chemoprophylaxis in Transplant Patients

Acitretin and Isotretinoin



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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 be 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

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

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

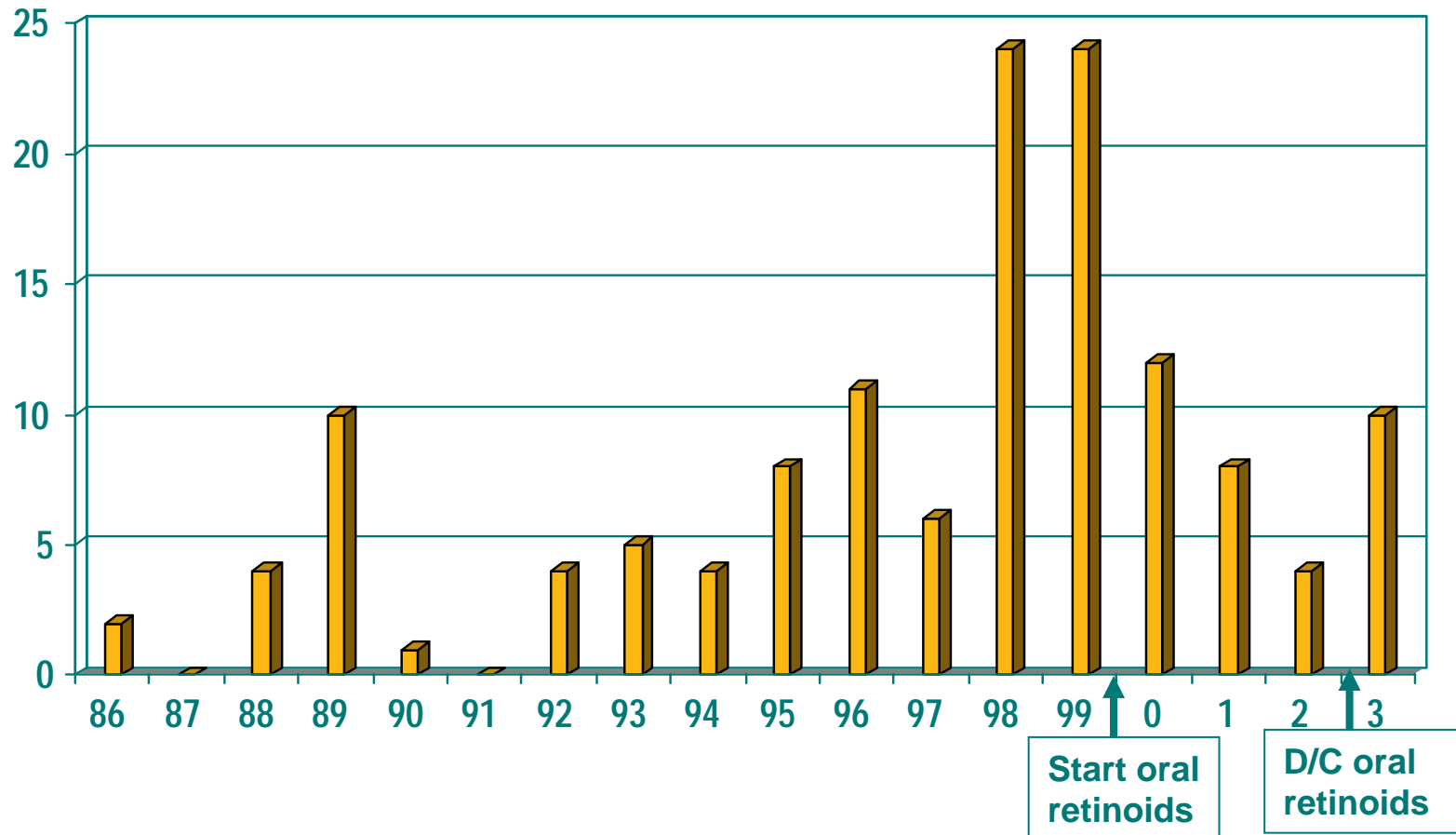
The Pros and Cons of Systemic Retinoid Therapy

- Decreased SCC
- Decreased BCC
- ? Delayed recurrence/metastasis
- Not curative
- Must continue
- Hyperlipidemia
- Liver function abnormalities
- Mucocutaneous dryness

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

64 Year-old Cowboy s/p Renal Transplant 1980



Reduction of Immunosuppression For Severe Skin Cancer in Organ Transplant Recipients



AT-RISC
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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

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

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

The Importance of a Multidisciplinary Approach

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

The Importance of a Multidisciplinary Approach

- Clinical paradigm of preventive education, early intervention and administration of prophylactic regimens against skin cancer
- Initial evaluation by Dermatology
- Direct and rapid appointment access to Dermatology and Dermatologic surgery

Otley C. Organization of a specialty clinic to optimize the care of organ transplant recipients at risk for skin cancer. *Dermatol Surg* 26;7: July 2000

What Transplant Nurses 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 and the transplant team
- Expert help is available through AT-RISC
(www.AT-RISC.org) and ITSCC (www.ITSCC.org)

What Can a Transplant Nurse Do?

- Everything!
- Education
 - Sun protection
 - Skin examination
 - Importance of follow up
- Clinical care
 - Expertise AND TLC
- Research
 - Optimal wound care, education, pain control

Transplant Nurses

- Know the patients the best
- Lead in sun protection/skin cancer education
- Early recognition of skin cancer and pre-cancer
- Referral as needed for skin care
- Coordinate communication between different specialists
- Coordinate urgent surgery for eruptive skin cancer

Transplant Nurses

- Assist with management of infections/medication changes
- Educate patients regarding treatment options
- Assist with communication of lab results
- Lead wound care
- Assess for infections
- Guidance and administration of pain medication
- Assure follow up

Transplant Nurses

- NURSES ARE THE KEY TO COMPLICATED CLINICAL CARE

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)
- International Transplant Nurses Society (www.itns.org)