PowerPoint Presentation for Dermatologists

- This presentation was designed to be given by a health-care professional to an audience of dermatologists.
- The presentation is long (approximately 90 minutes). 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.

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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

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Take home messages

1. Some transplant patients will die of NMSC
2. Some transplant patients will have significant morbidity from MNSC Treatment
3. Try to limit risk factors
4. Early evaluation, treatment and close follow-up are vital

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Table 49.2 Progress in transplantation*

Year	Event	Result
1902	Kidney transplant in a dog (Ullman)	Successful
1933	Human kidney allograft transplantation (Voronoy)	Unsuccessful
1946	Human kidney allograft for acute renal failure	Brief period of function
WWII	Dialysis	Aided in the progress of kidney transplantation
1951	Six human allograft transplants (Hume)	Functioned for up to 6 months without immunosuppression
1953	First living related kidney transplant (Michon)	Unsuccessful
1954	First identical twins kidney transplant	Successful
1958	Use of total body irradiation for immunosuppression	No long term success
1959	6-mercaptopurine (Dameshek & Schwartz)	Successful systemic immunosuppression
1961	Azathioprine available	Less toxic systemic immunosuppression
1962	Use of tissue matching	Increased understanding of rejection
1963	Azathioprine + prednisone	Start of modern era of transplantation
1963	First human liver transplant (Starzl)	
1966	First pancreas transplant (Lillehei)	
1967	First heart transplant (Bernard)	Brought transplants to public awareness
1968	Polyclonal antilymphocyte globulin	Use in induction/acute rejection
1975	Murine monoclonal antibodies	Use in induction/acute rejection
1981	Monoclonal anti CD-3	Use in acute rejection
1983	Cyclosporine A released	Greatly improved graft survival
1989	Tacrolimus	Improved side effect profile over ciclosporine
1991	Mycophenolate mofitil	Improved side effect profile and dosing over azathioprine
1998	Sirolimus	Improved renal function and possible antiproliferative effects

**Adapted from:*
Halloran PF, Gourishankar S. Principles and overview of immunosuppression. In: Norman DJ, Turka LA, eds. Primer on transplantation. 2nd ed. Mt Laurel, NJ: American Society of Transplantation 2001; 87–98.
Hamilton D. A history of transplantation. In Morris P, ed. Tissue transplantation. 2nd ed. Edinburgh: Churchill Livingston; 1982.
Crumbly AJ, Bromberg JS, Cofer JB, Rajagopalan PR, Fitts CT. Medical aspects of transplantation. J S Carolina Med Assn 1991; June:313–328.

Organ Recipient Survival: The Early Events

Year	Description	Survival
1962	1st Cadaver Kidney	1 year
1967	1st Heart: Barnard	18 Days
1982	1st Heart-Lung	< 1 year

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Organ Recipient Survival: Now

- Overall improved since 1995
- 5 year survival:
  - Kidney – 80 to 90%*
  - Cardiac – 70%
  - Liver – 72 to 86%*
  - Lung – 42%

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Transplants in the United States

	To Date
All Organs	340,770
Kidney	203,083
Liver	69,567
Pancreas	4,326
Kidney / Pancreas	12,456
Heart	36,911
Lung	12,561
Heart / Lung	874
Intestine	992

60%

20%

11%

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The State of Transplantation in U.S. UNOS Data

- Over 28,000 organ transplants per year (74,000 worldwide)
- 155,000 organ recipients currently alive in US
- 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

www.unos.org

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Solid Organ Transplants

- Every 16 minutes a new name is added to the transplant list
- Over 90,000 patients on the waiting list
- 7030 died while on the wait list in 2004
- Lack of organ donors is the limiting factor
- Transplants in the US

2005	28,110
2004	27,035
2003	25,464
2002	24,905
2001	24,212
2000	23,239
1998	21,416
1988	12,626

Renal Transplants

Type of Donor	Number		
	1990	2000	2004
Deceased	4306	5489	6326
Living	2094	5493	6648
Total	**6400**	**10,982**	**12,974**

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MNSC and OTRs

- Increased risk of NMSC
- Onset at a younger age
- More aggressive tumors with increased morbidity and mortality
- Some patients develop tremendous numbers of tumors

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Increased risk of NMSC

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

Skin Cancer	Increased Incidence in Transplant Patients
SCC	65 fold
SCC of lip	20 fold
BCC	10 fold
Melanoma	1.6 to 3.4 fold
Kaposi's Sarcoma	84 fold

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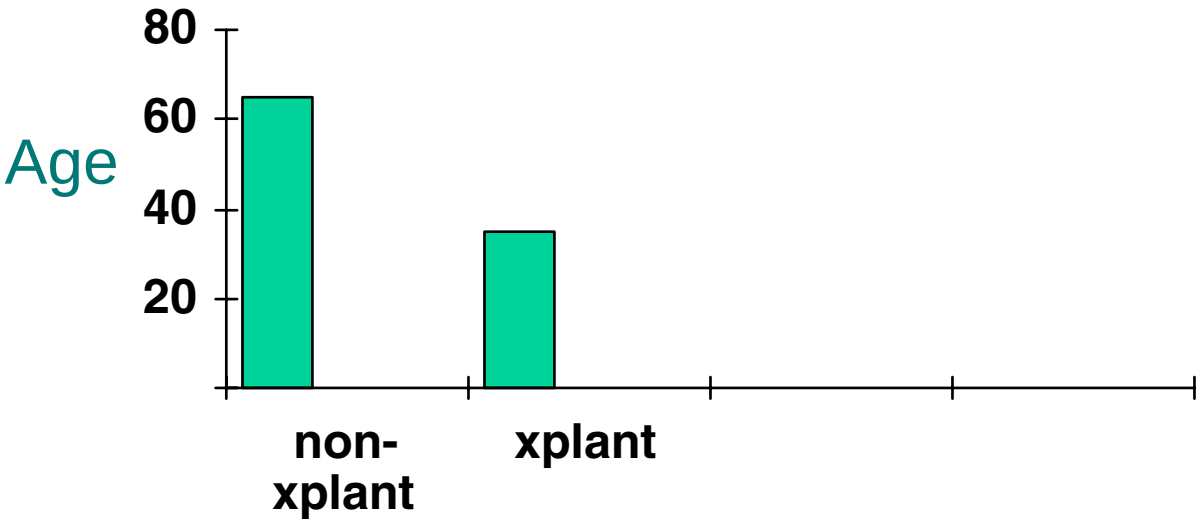
Onset at a younger age

- Essentially every study shows an increase in incidence with increasing age
- However, the average age of onset is decreased by ~ 30 years



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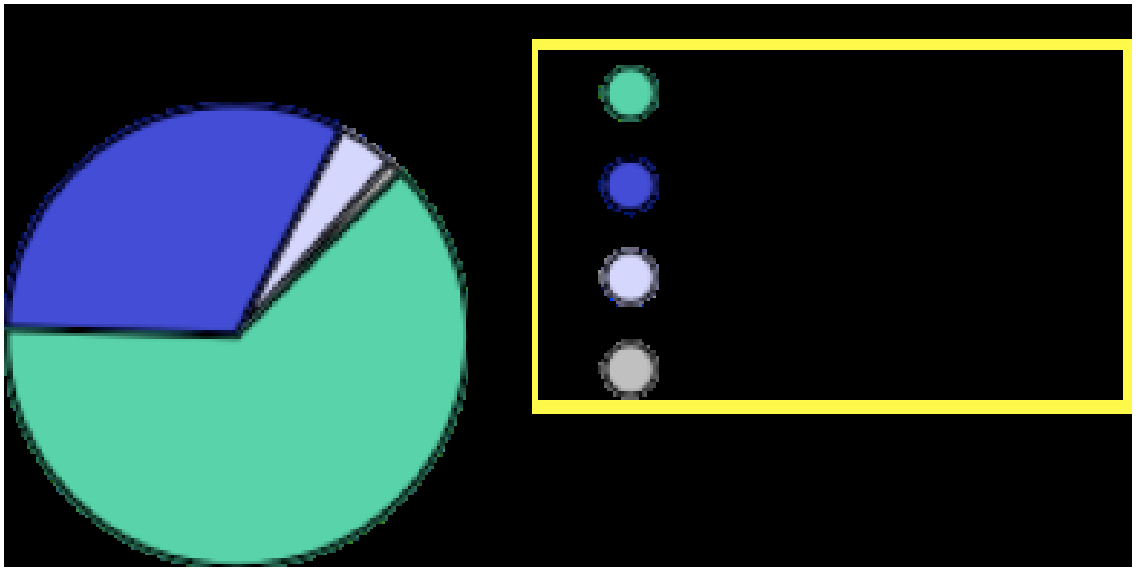
More aggressive tumors with increased morbidity and mortality

- Tumors are more aggressive than in non-transplant patients
- Cincinnati Transplant Tumor Registry
- 5.2% of individuals with skin cancer died of their tumors



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More aggressive tumors with increased morbidity and mortality

- Heart transplant patients in Sidney, Australia(JAAD, Jan99)
  - 43% with skin cancer at 10 years
  - 4 patients had more than 50 skin cancers
  - Metastases in 9/113 patients with SCC
  - Metastases in 4/7 patients with melanoma
  - 11 deaths--27% of deaths 4 years+

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Increased Aggressiveness: Metastasis

Metastatic rate for SCC in transplant recipients: 7%

Martinez et al. Arch Derm 2003;139:301

- 3 yr disease-specific survival: 56%
- 1 yr disease-specific survival for distant metastases: 39%
- Mean interval from primary to metastasis: 1.4 years

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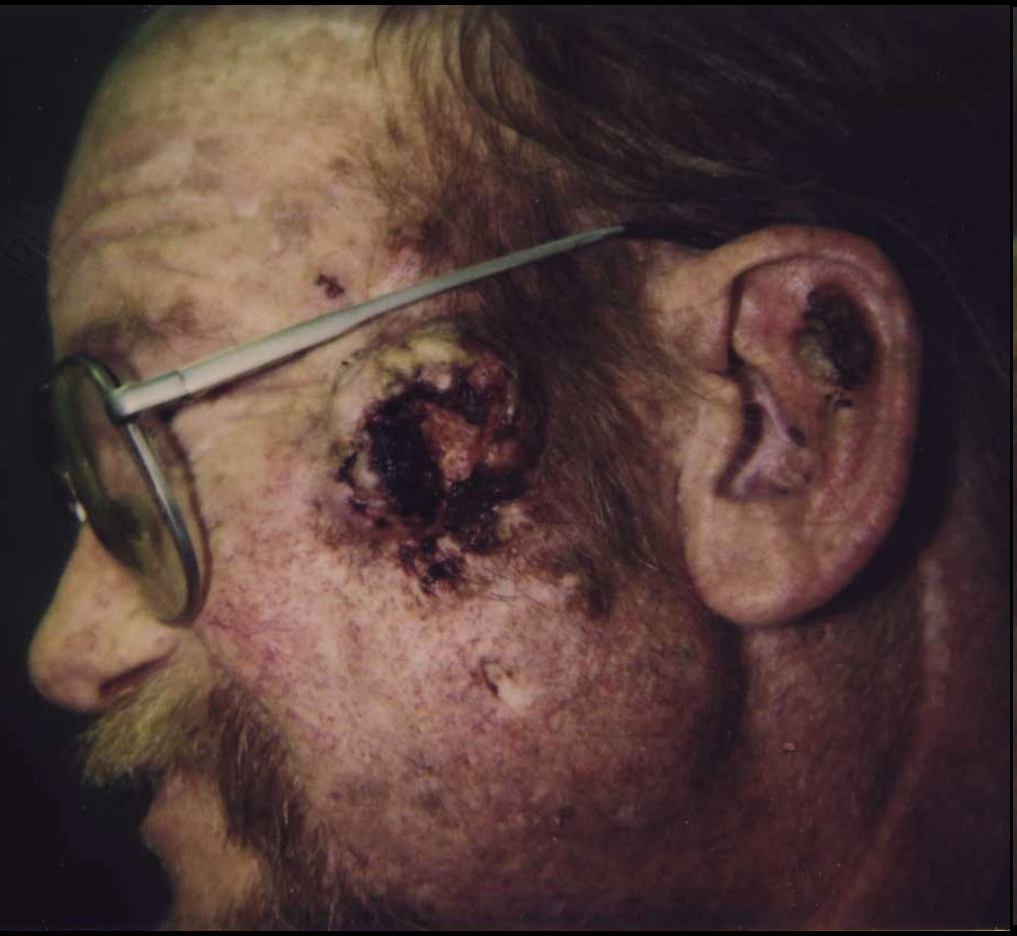
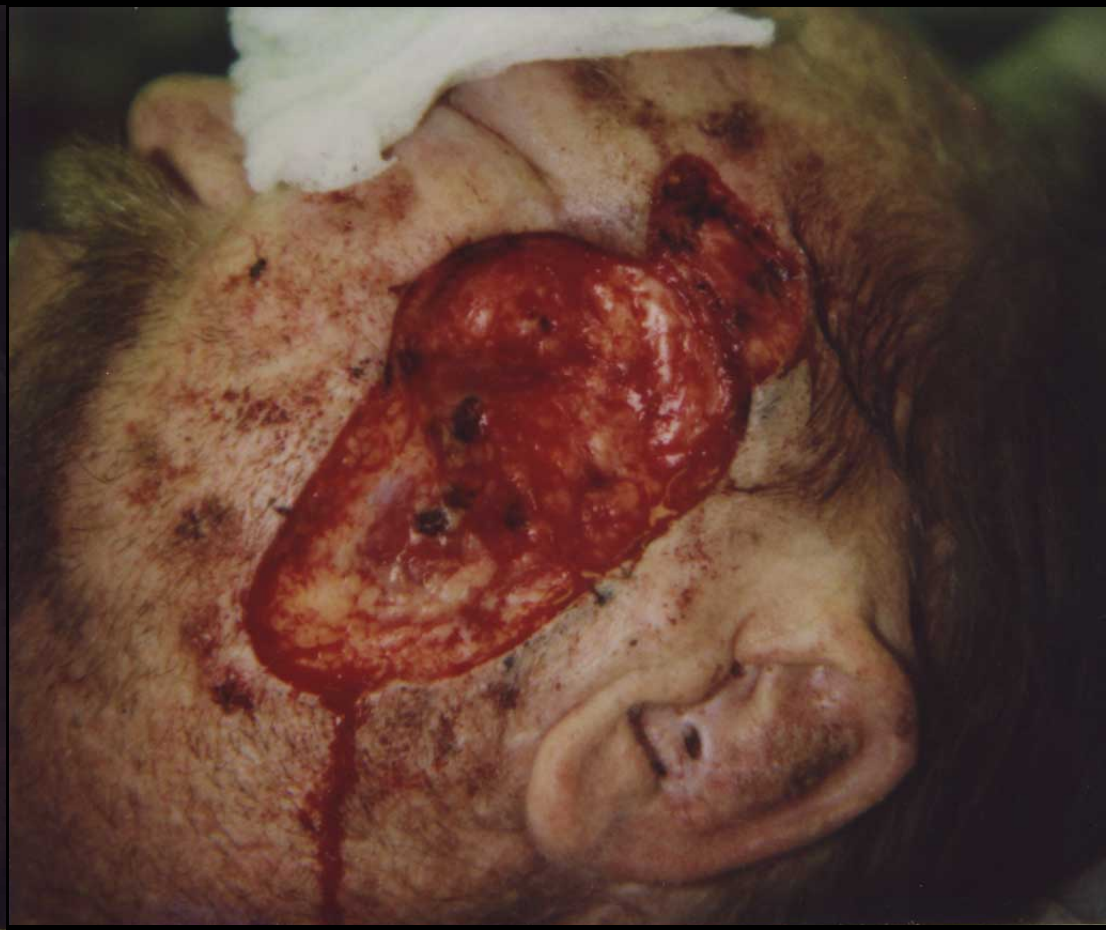
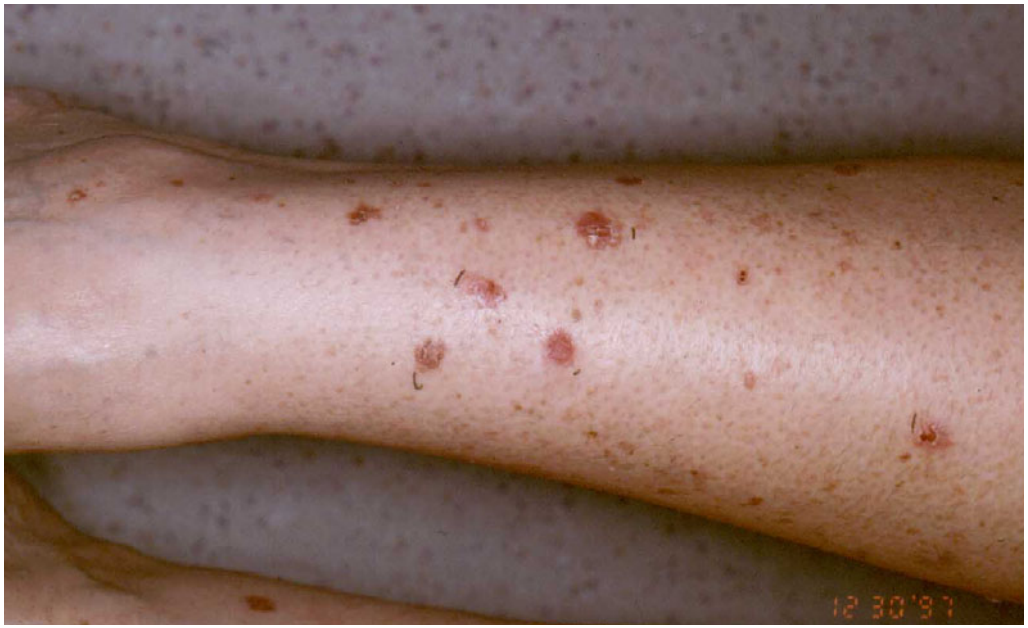




Some patients develop tremendous numbers of tumors

	Number of SCC
All Cancers	7.5 +/-SD 17.5
SCC Only	3.9 +/-SD 5.6
Both BCC & SCC	12.6+/-SD 23.1



Bouwes Bavinck, J.N., et al., The risk of skin cancer in renal transplant recipients in Queensland, Australia. A follow-up study. Transplantation, 1996. 61(5): p. 715-21.

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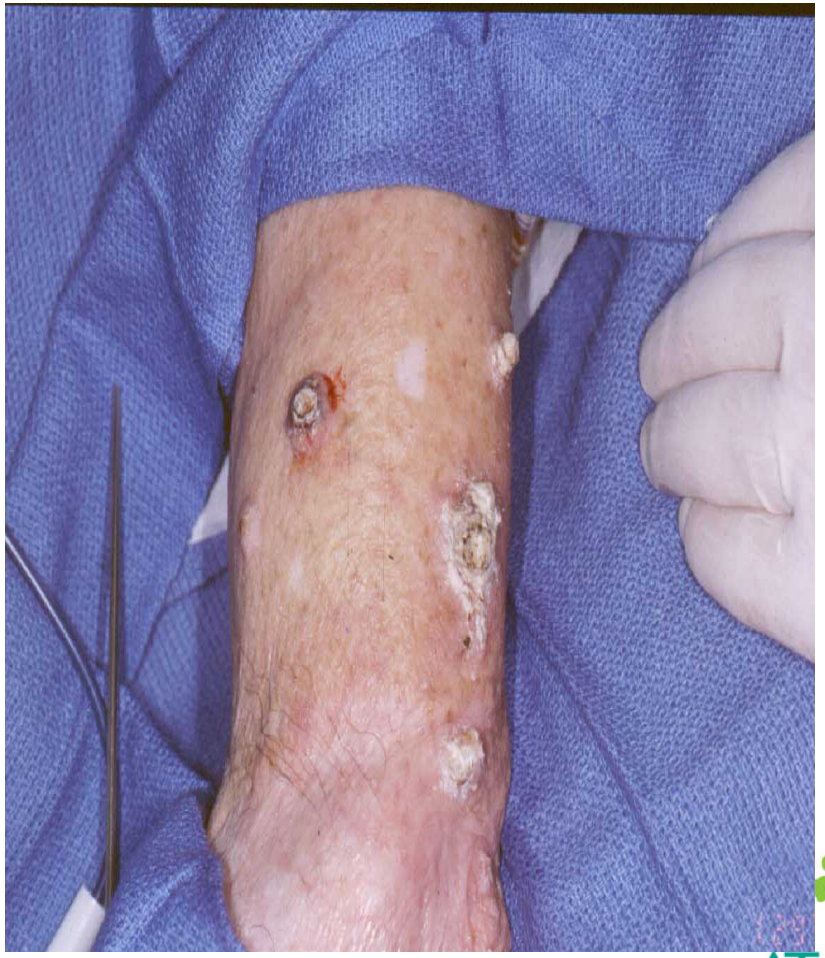
Some patients develop tremendous numbers of tumors

- Retrospective record review
- Cardiac transplant year groups
  - 1990: 36 Cardiac Transplants
- 110 Total NMSC in 7 recipients in 1990 Cohort
  - 104 NMSC in three recipients
  - 23, 37, and 44 NMSC



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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

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Risk Factors for NMSC

- Advancing age
- Hereditary
- Fair Skin, blond or red hair
- Blue, green or gray eyes
- Celtic background

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Sun Exposure as a Risk Factor

Mean time from transplant to detection of skin cancer

Center	Latitude	Time (months)
Oxford	52	84.6
Wisconsin	45	78
Denver	40	58
Brisbane	34	32.6

From Liddington, et al. Skin cancer in renal transplant recipients. Br J Surg 1989; 76: 1002-5.

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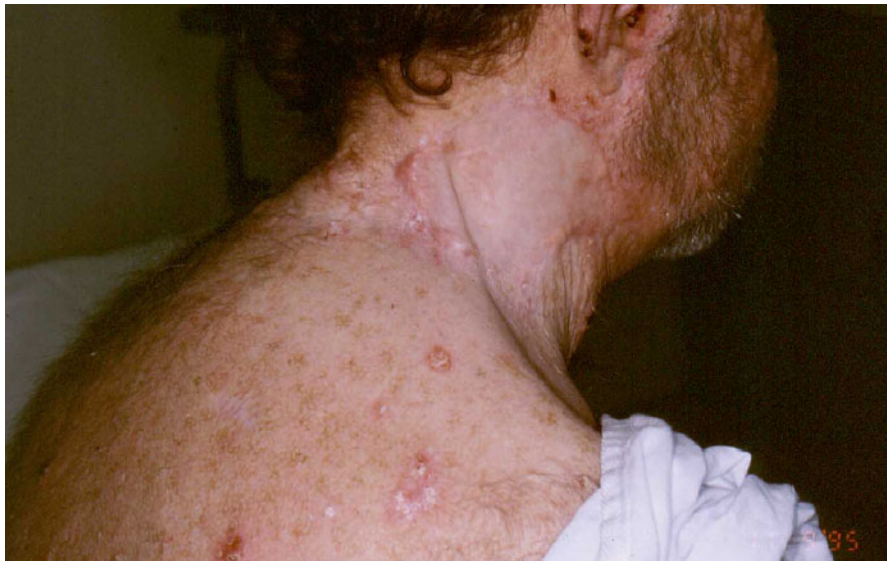
Sunlight and RTR

- Skin Cancers positively associated with
  - Sun-exposed body areas
  - Life-time exposure to sunlight
  - High exposure before the age of 30 may be more significant
  - Two or more episodes of painful sunburn
- Moderate exposure vs Low -- 2.4X
- High exposure vs Low -- 47.6X



Bavinck, et al. Sunlight, keratotic skin lesions and skin cancer in renal transplant recipients. Br J Dermatol 1993;129:242-249

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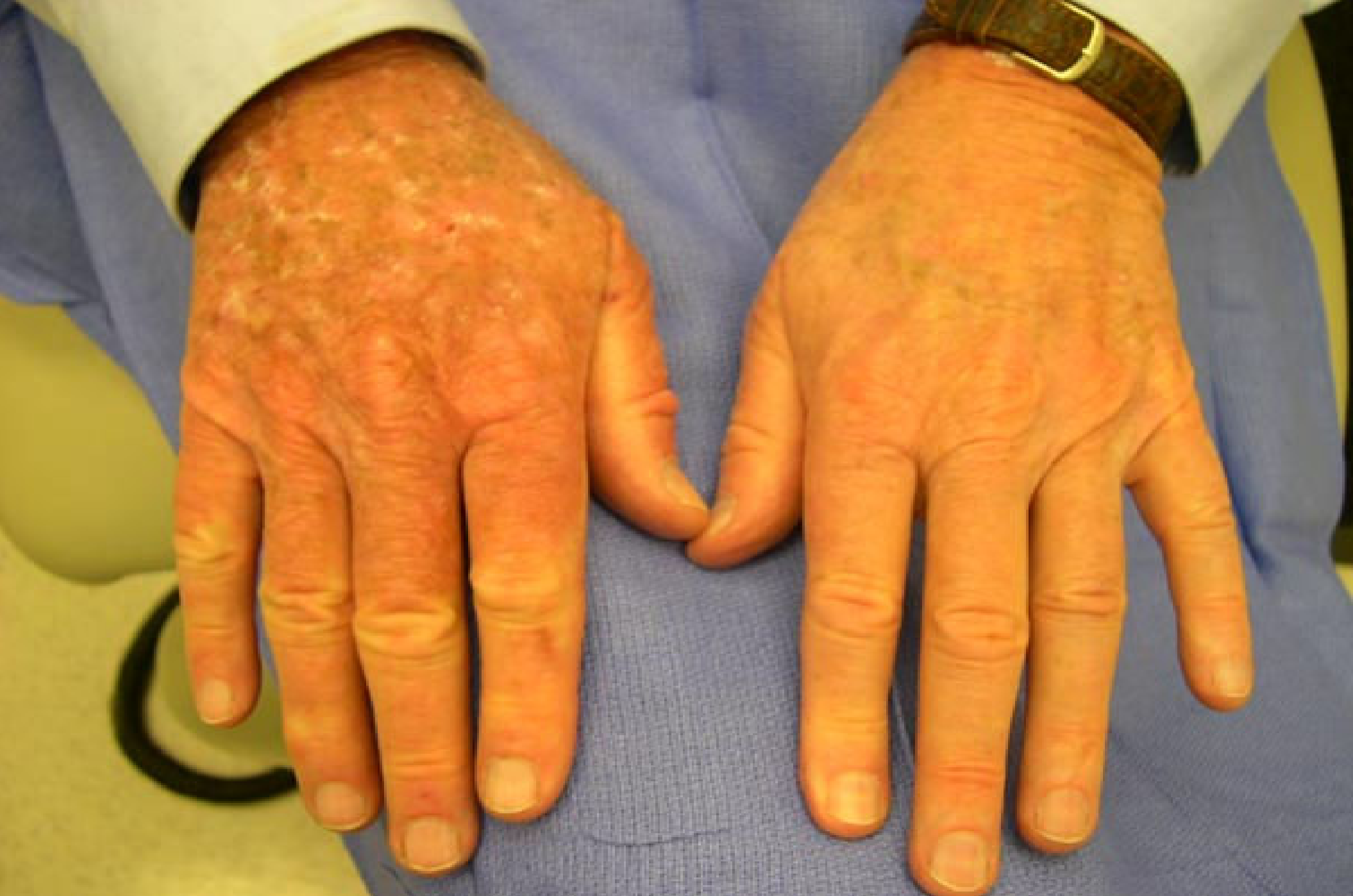
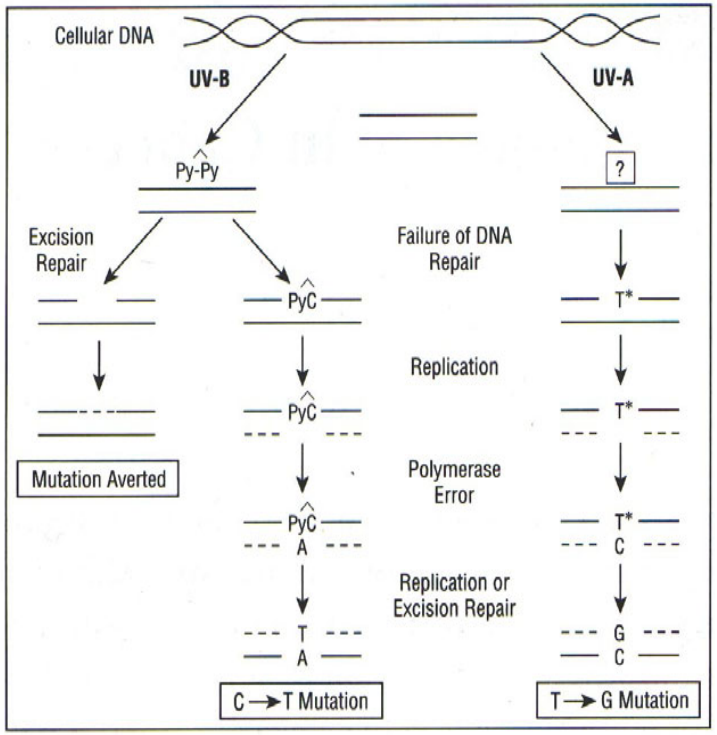


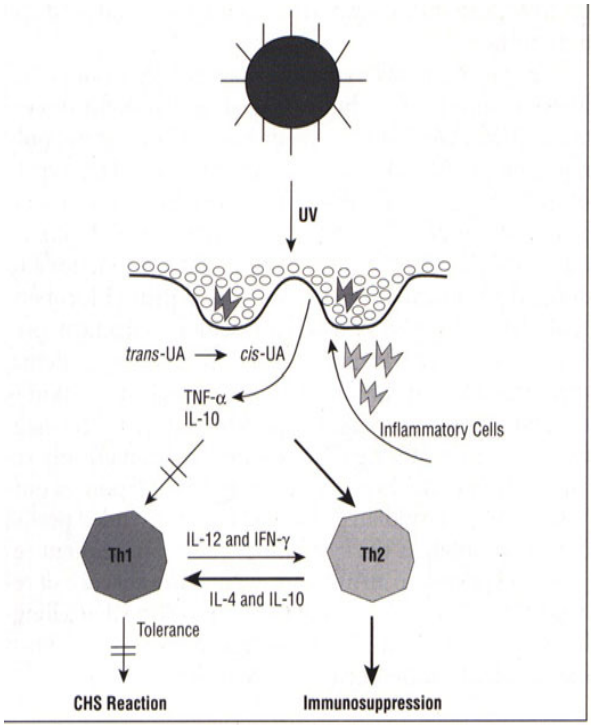
UV Carcinogenesis may have more than one mechanism of action

UV induced mutations



UVB(290-320 nm) is 10,000 time more mutagenic than UVA(320-400 nm)

UV induced immunosuppression



Favors generation of suppressor over helper immune pathways

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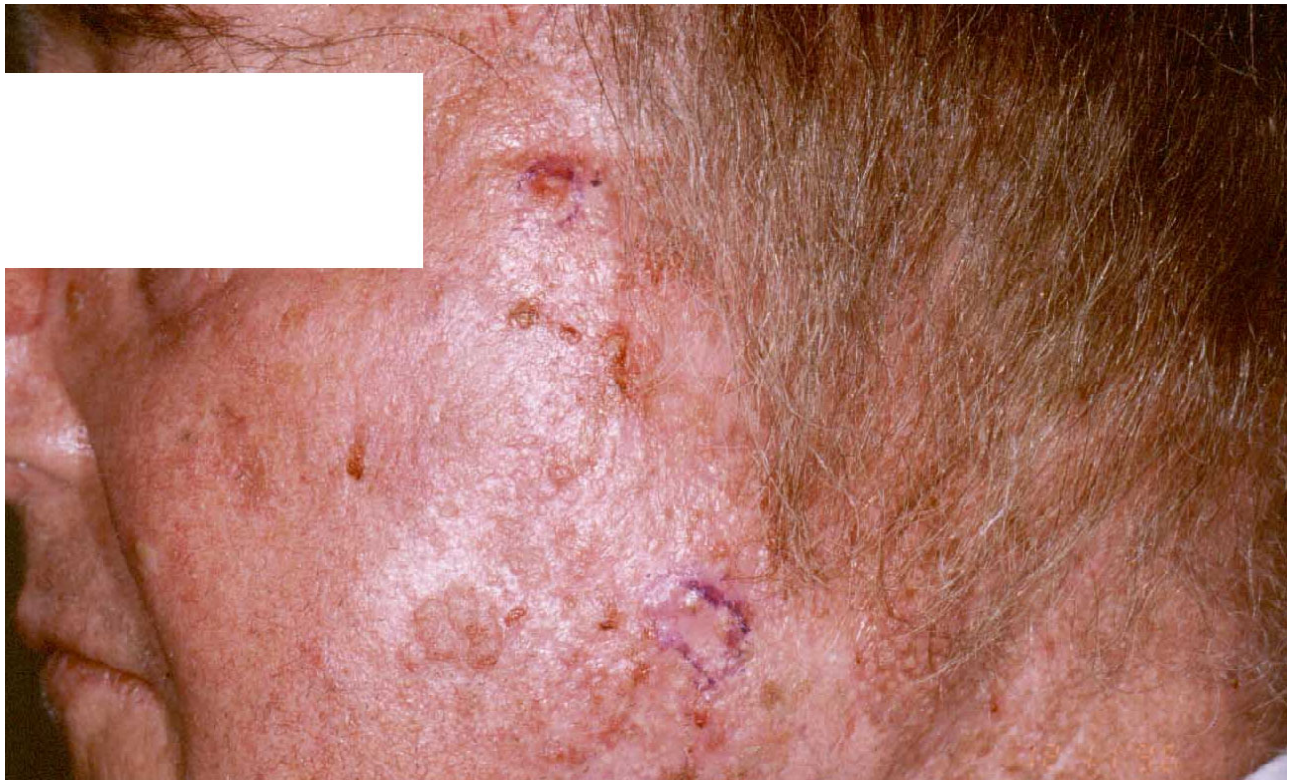
RTR’s with skin cancer prior to transplant

- 76% developed additional skin cancers after transplant
- Average of 16.5 lesions per patient



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Risk Factors for NMSC

- Some are related to the immunosuppressed transplant environment
  - Age at transplantation
  - Duration of immunosuppression
  - Type of immunosuppression
  - Viral infections---HPV

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Onset at a younger age

- Relative risk is higher in those transplanted at age <40 compared to >60

	All cancers			Nonmelanoma skin cancer		
	Obs	RR	95% CI	Obs	RR	95% CI
Follow-up (years)						
<1	93	1	ref	10	1	ref
1–4	248	0.9	0.7–1.1	86	2.3	1.2–4.5
5–9	200	1.0	0.8–1.3	92	2.8	1.4–5.3
10+	151	0.9	0.7–1.2	90	2.4	1.2–4.7
Age at transplantation (years)						
<39	155	2.5	2.0–3.1	71	3.8	2.7–5.4
40–49	158	1.4	1.1–1.8	51	1.5	1.0–2.2
50–59	229	1.2	0.9–1.4	90	1.4	1.0–1.9
60+	150	1	ref	66	1	ref

Br J Cancer 2003, 89:1221-1227

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Onset at a younger age

Age corrected study of Irish renal transplants

- Transplant at 50+ years--increase in relative risk of skin cancer beginning in the first year, increased in years 2-6, then level
- Transplant at <50 years--delay in increase in relative risk of skin cancer (no skin cancers in initial 3 years) but by 8 years SIR reached 200

A population-based study of skin cancer incidence and prevalence in renal transplant recipients. Moloney FJ, et al. Br J Dermatol 2006 154,498-504.

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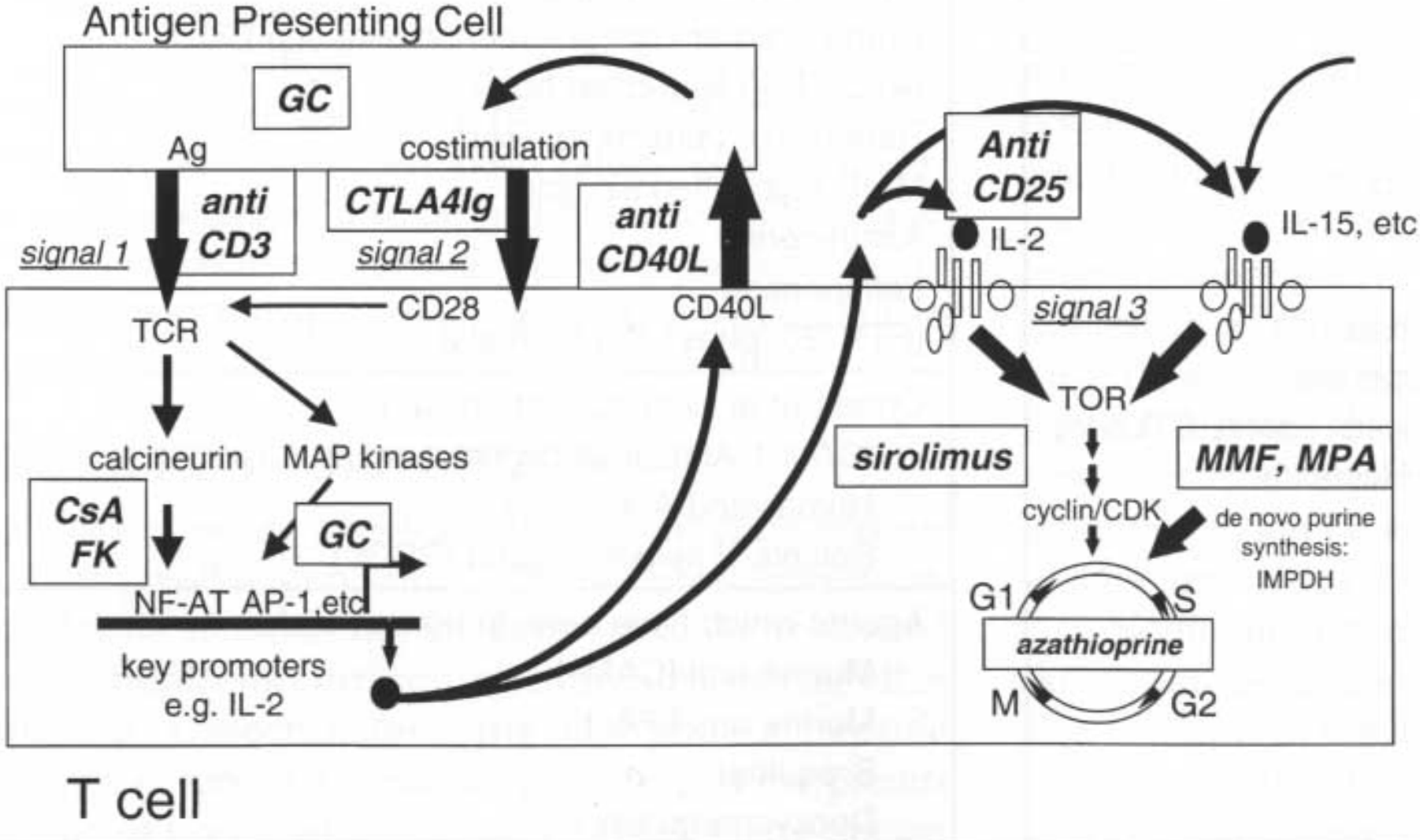
Immunosuppression

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

Immunosuppression

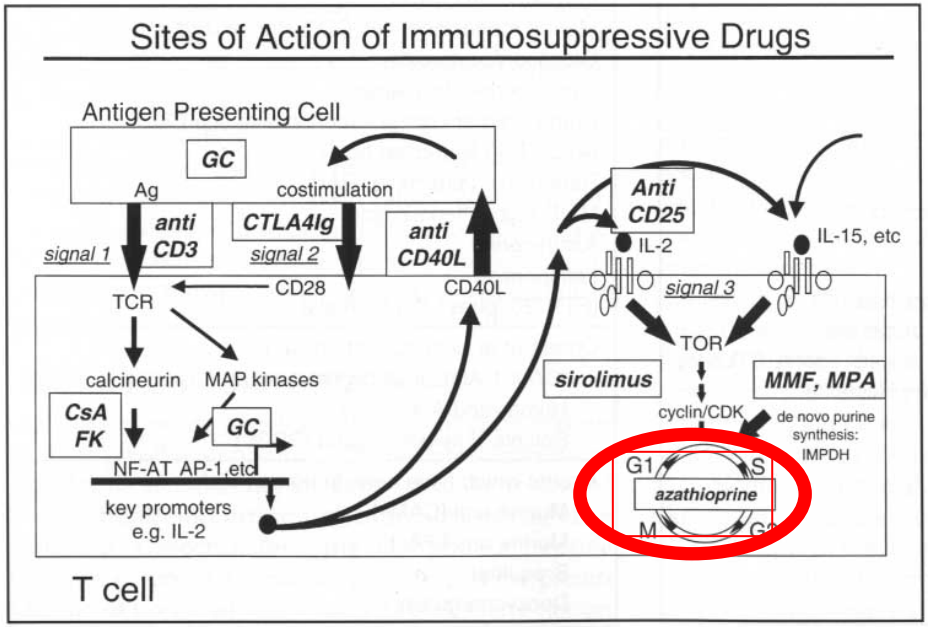
- Multi-agent, intense immunosuppression
- Highly variable regimens
  - Rapamycin
  - Deoxyspergualin
  - Leflunomide
  - Mizoribine
  - Brequinar
  - Immunomodulating antibodies
    - Anti-CD40 and CTLA4-Ig
    - Anti- LFA-1
    - Anti-IL-2 receptor antibody
    - Anti-ICAM-1 antibody

Sites of Action of Immunosuppressive Drugs



Azathioprine

- Early mainstay of transplant immunosuppression
- Slow release form of 6-mercaptopurine
  - Converted to 6-mercaptopurine in vivo
- Inhibits purine synthesis
- Inhibits effector T & B lymphocyte clones in the proliferative cycle
- Prevents onset of acute rejection, little value in therapy of ongoing rejection



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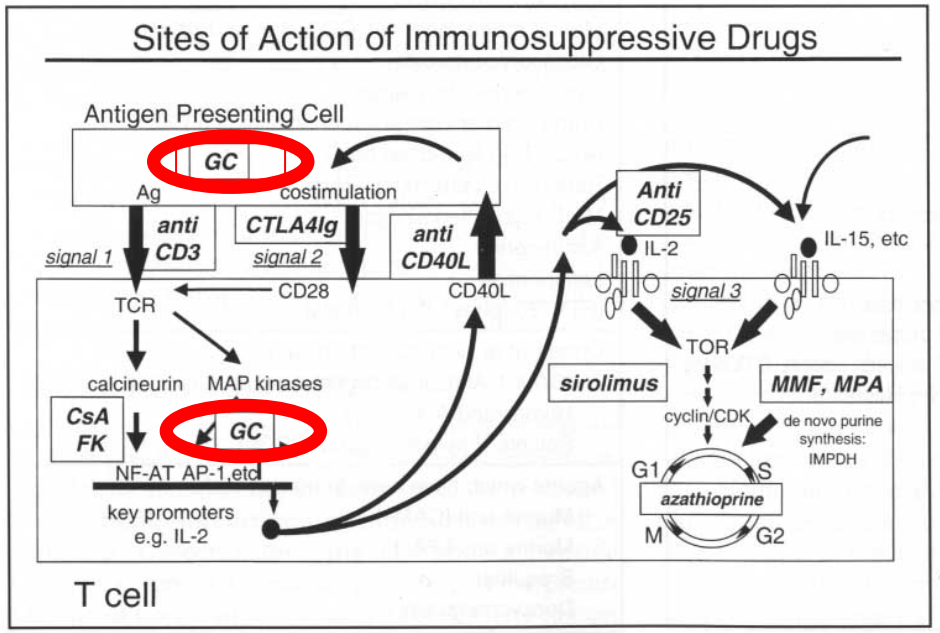
Azathioprine

- Must be given on a continuous basis
  - Temporary stoppage soon after transplant causes marked increase in graft failure
- 2-3 mg/kg/day
- Side effects
  - myleosuppression
  - hepatotoxicity
  - pancreatitis

Corticosteroids

- Inhibit antigen driven T-cell proliferation
- Modest doses in maintenaince immunosuppression protocols with azathioprine or cyclosporine
- Higher doses to treat acute cellular rejection
- Side Effects



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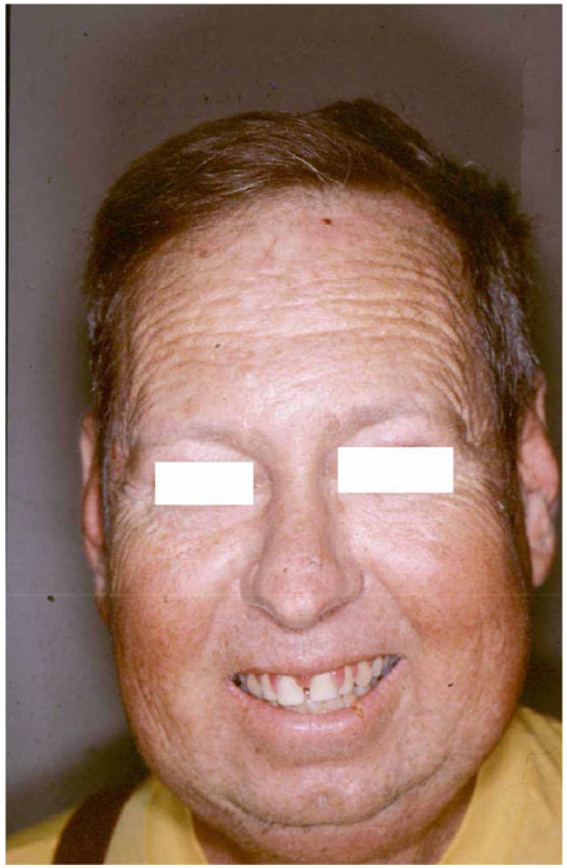
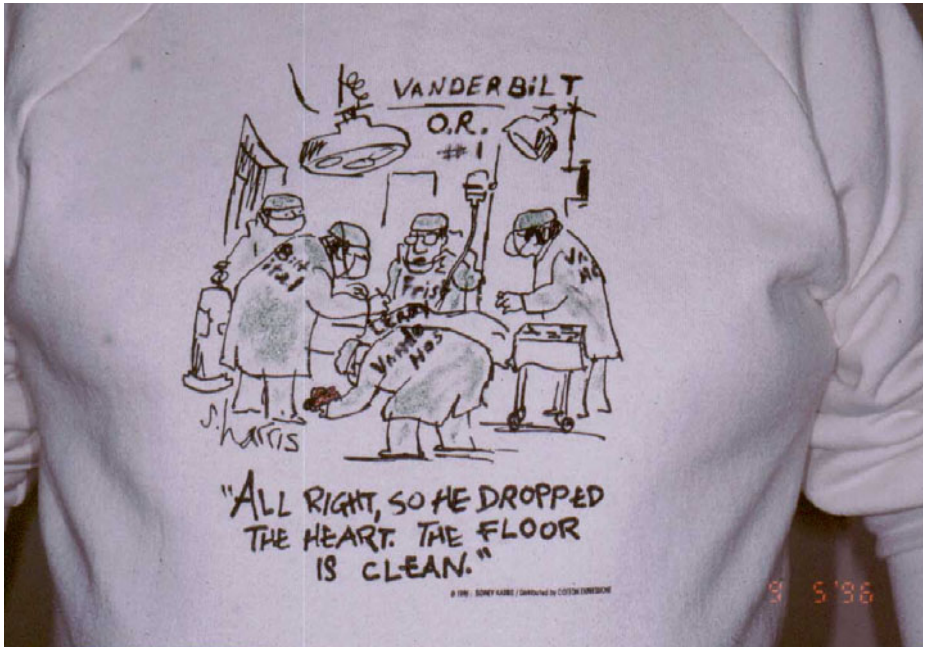
Side effects of steroids

Moon Facies



Euphoria



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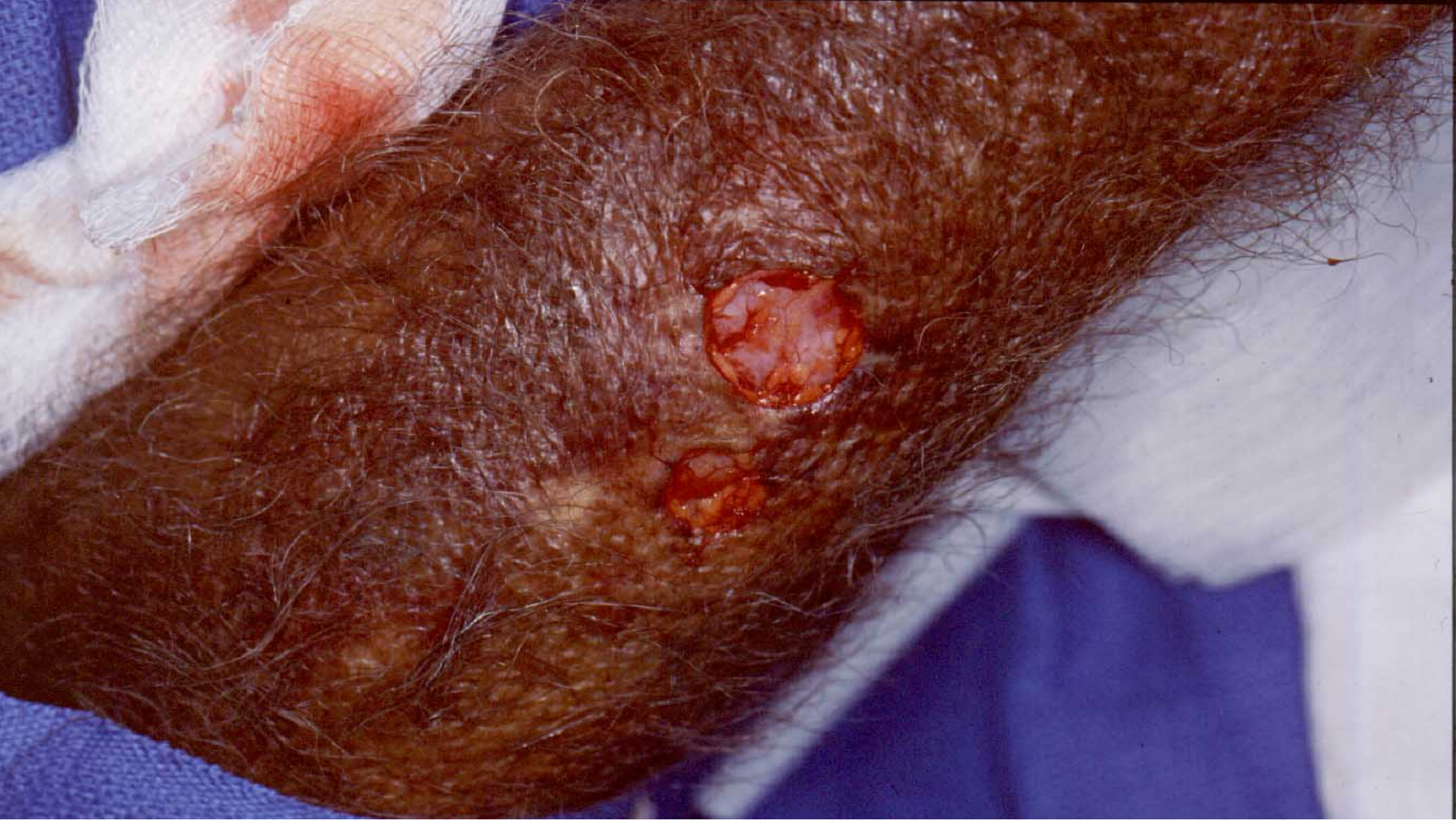
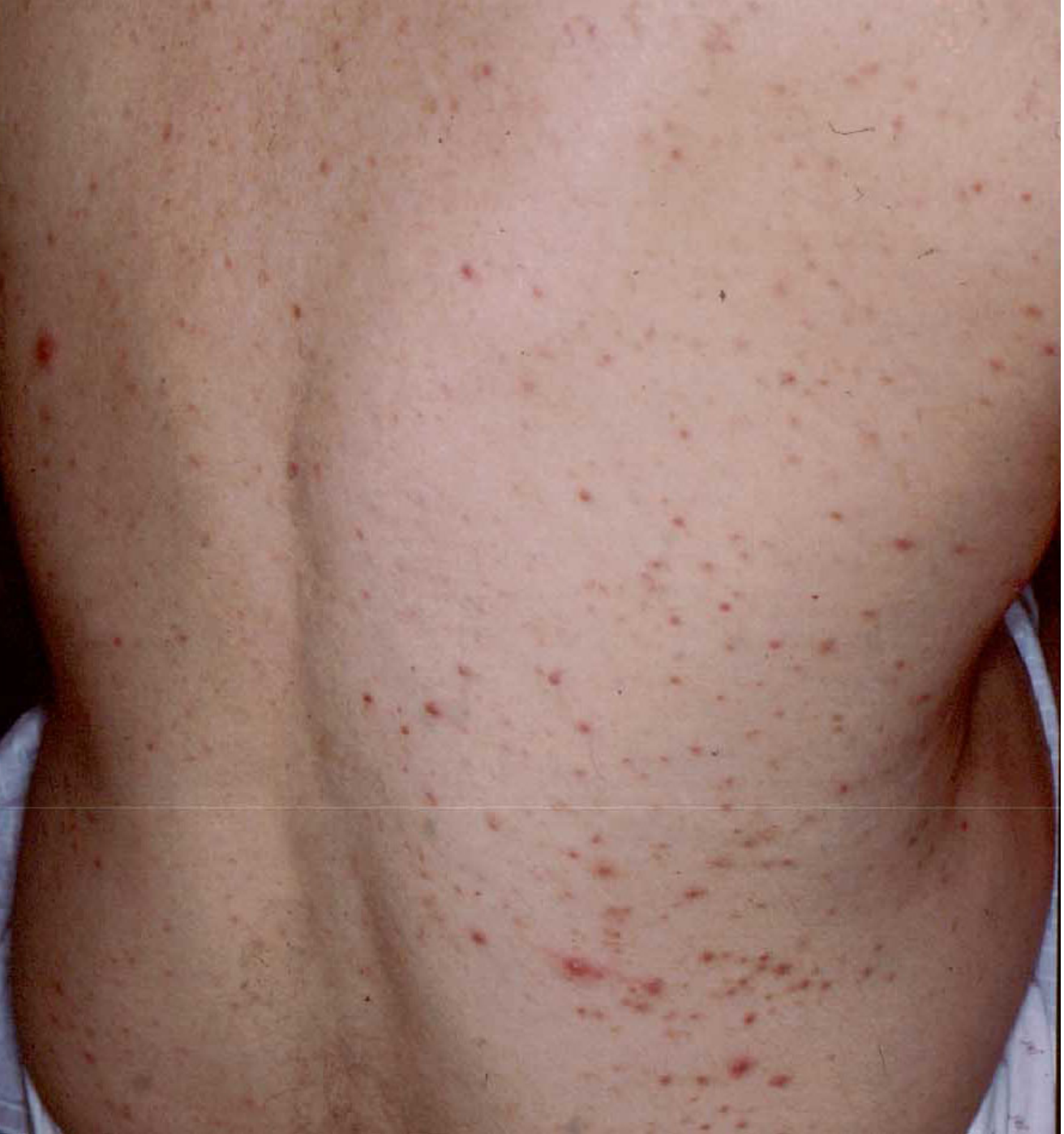


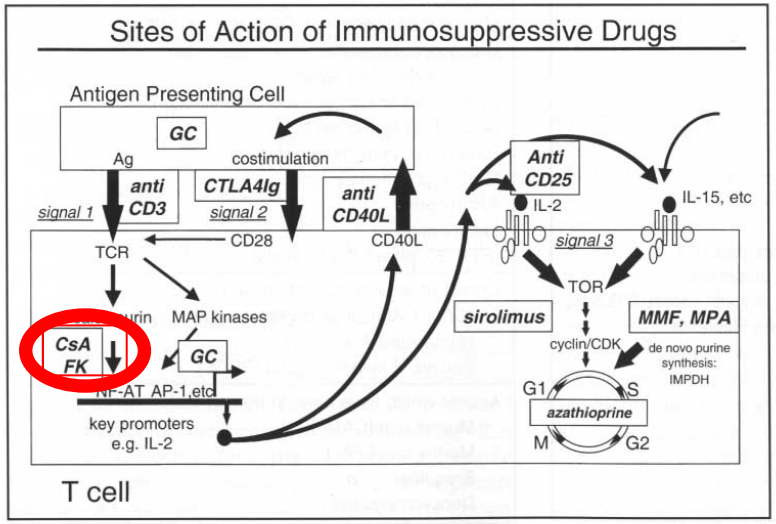
Skin Fragility

Easy Bruising and Ecchymosis



Folliculitis and Acne

Cyclosporine



Combined with prednisone: 15-20% renal graft survival improvement over azathioprine/prednisone, doubled graft survival rates in liver transplants, greatly improved heart and lung transplants

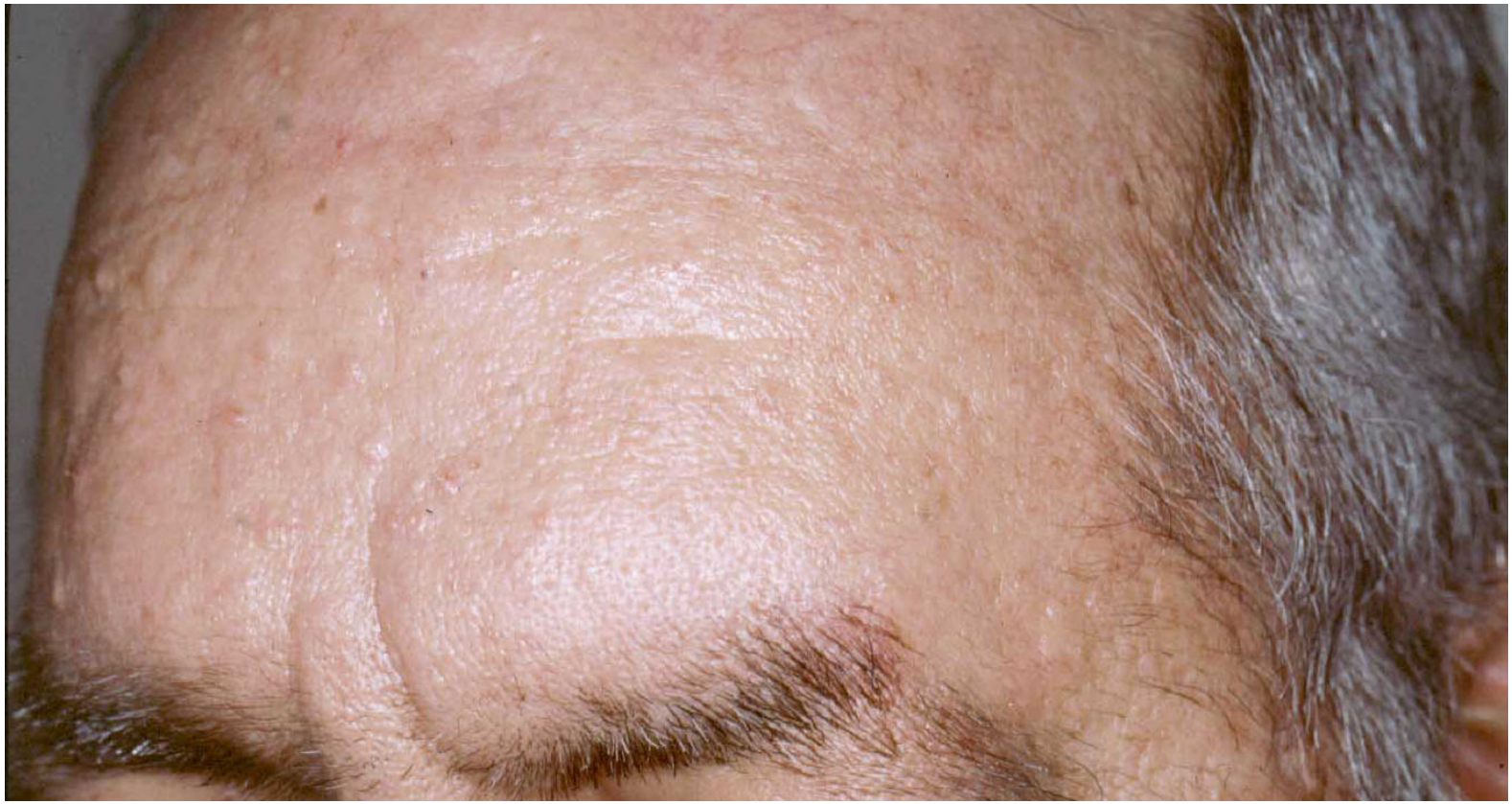
- Inhibits transcription of mRNA for lymphokines (including interleukin 2) and the enzymes required for cytotoxicity
- Lymphocyte specific at early stage of activation
- Blocks entry of T lymphocytes into the S phase
- T suppressor cells are largely unaffected

Cyclosporine

- Toxicity
  - Renal
    - Due to renal arteriolar vasoconstriction
    - Dose limiting
    - Gradually rising creatinine
    - Hypertension
  - Hepatotoxicity
  - Neurotoxicity

Cyclosporine

- Sebaceous Hyperplasia



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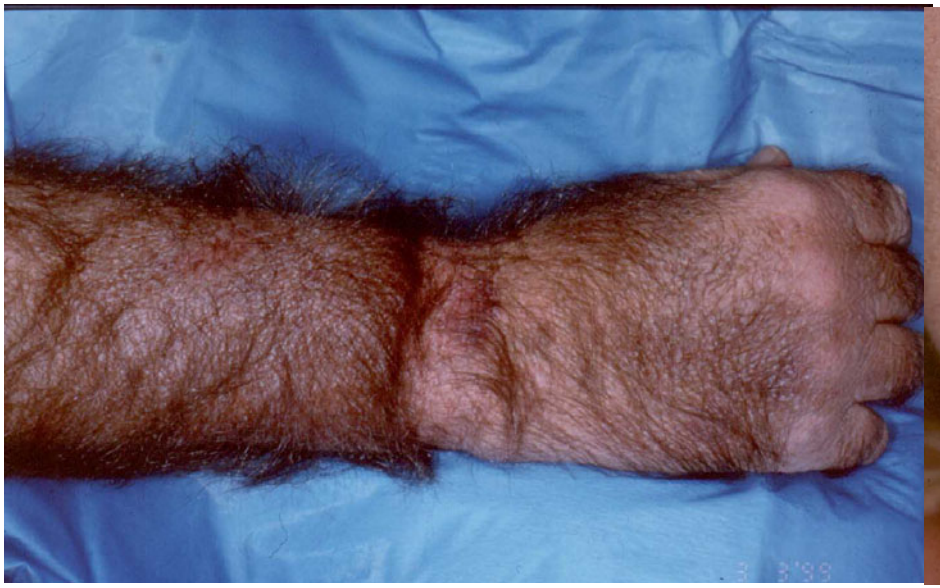
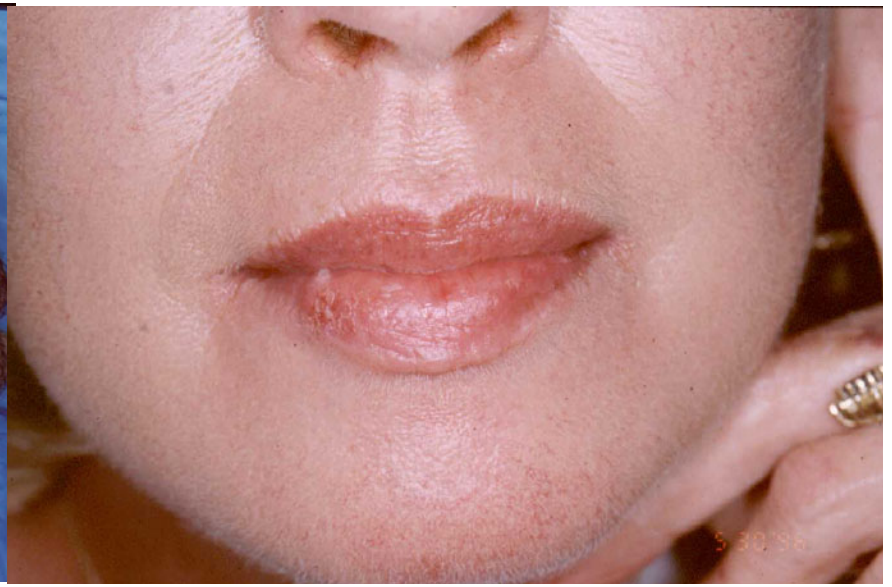
Cyclosporine

- Hirsutism





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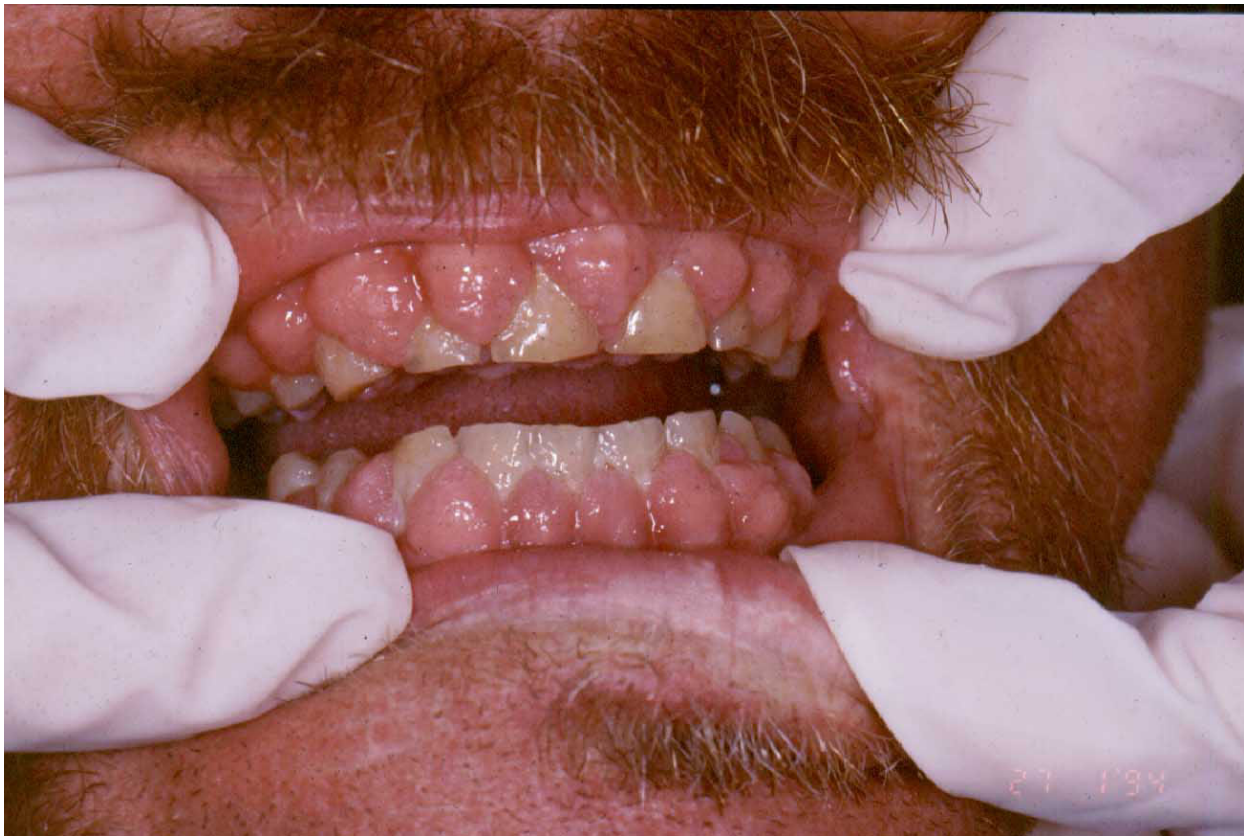
Cyclosporine

- Gingival hyperplasia



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Cyclosporine

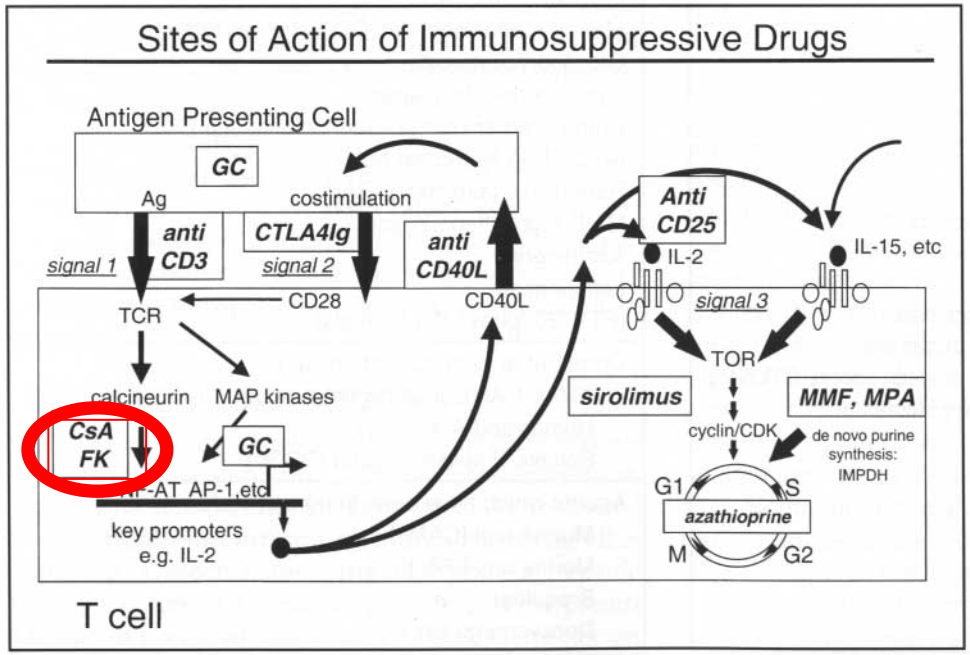
- Difficult dosing
  - Bioavailability and metabolism vary
  - Narrow therapeutic range
  - Regulate according to blood levels
- Expensive

Cyclosporine

- Metabolized in the liver via P-450 pathway
- Increased levels:
  - ketoconazole
  - erythromycin
  - corticosteroids
  - diltiazem, verapamil
- Decreased levels
  - Nafcillin, rifampin, valproic acid, phenobarbital, phenytoin

FK-506--Tacrolimus--Prograf

- 100X more potent than cyclosporine
- Similar mechanism-used in place of cyclosporine
- Does not spare suppressor T cell function



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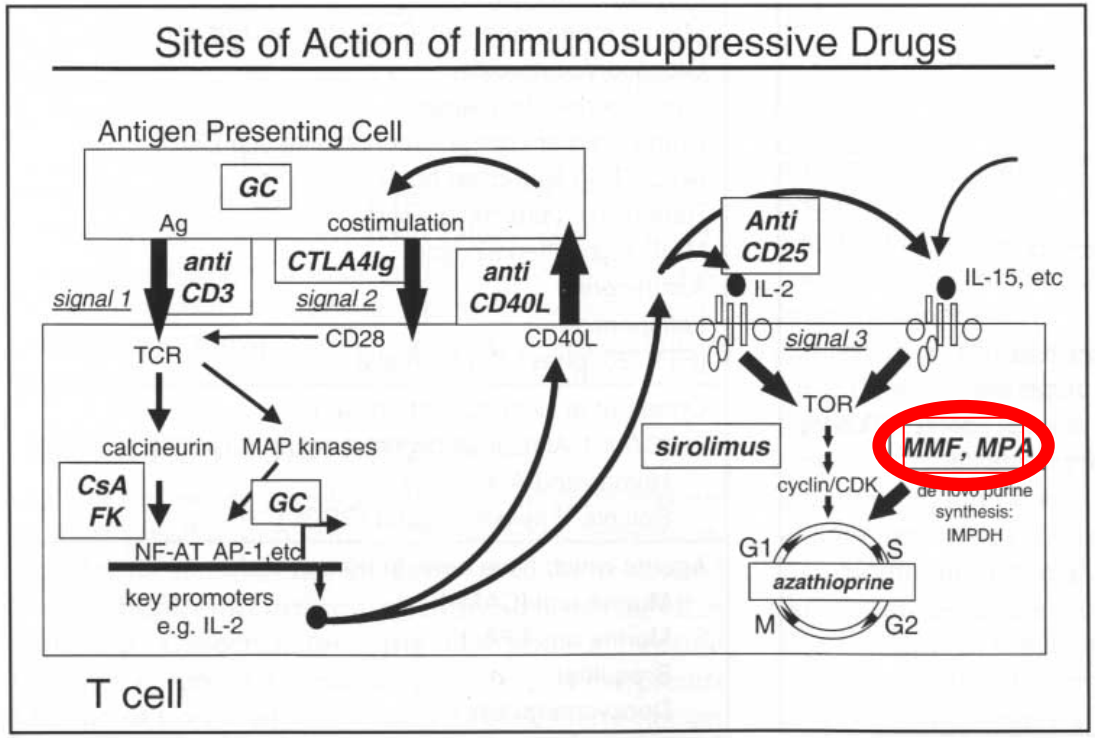
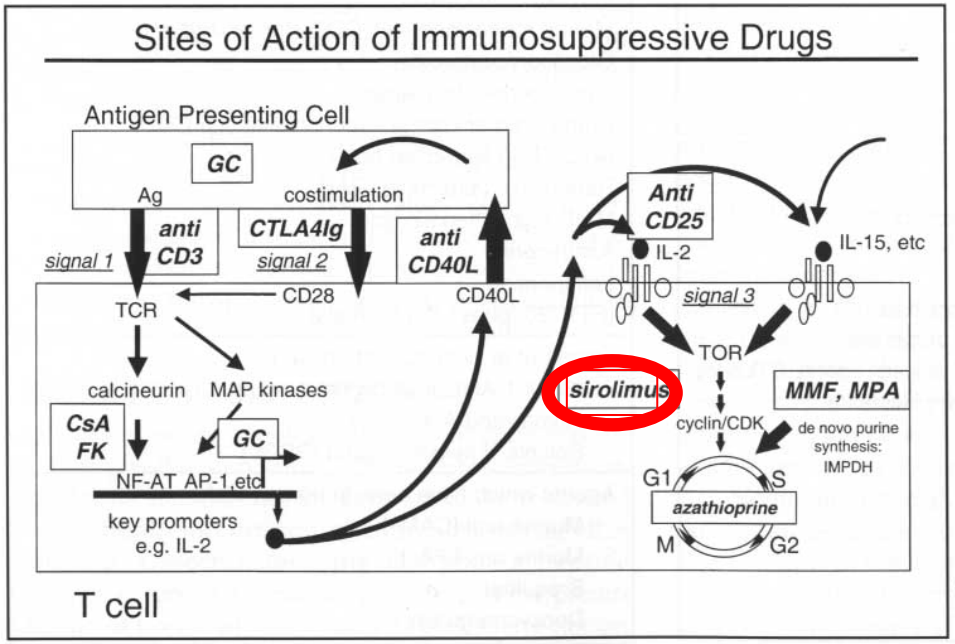
Mycophenolate Mofetil--CellCept

- Actions similar to azathioprine
- Is said to increase risk of malignancy



Sirolimus--Rapamycin--Rapamune

- Synergistic with cyclosporine (not a calcineurin inhibitior)
  - Used with cyclosporine in early trials
  - May be better in CsA sparing regimens
- Antiproliferative effects--has been used in cardiac stents to prevent restenosis
- Induces permanent tolerance in some lab animals



Sirolimus--Rapamycin--Rapamune

- Reports of abnormal healing following transplant surgery
  - Sirolimus linked with fatal bronchial anastomotic dehiscence--not recommended for lung transplantation
- Liver transplantation--not recommended
  - Excess mortality, graft loss and hepatic artery thrombosis

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

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.

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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.

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After Transplantation–Reduce Incidence of Skin Cancer

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.

Skin Cancer and Immunosuppression

In the hairless mouse exposed to UV irridation

- Prednisolone has no effect
- Cyclosporine caused a moderate reduction in the tumor induction latent period
- Azathioprine
  - Latent period decreased
  - Tumor yield per mouse increased
  - Induction of a larger proportion of carcinomas
- Cyclophosphamide
  - Same as azathioprine except no increased tumor induction

Kelly GE, et al. Effects of Immunosuppressive Therapy on the Induction of Skin Tumors by Ultraviolet Irradiation in Hairless Mice. Transplantation1987; 44:429-34.

Drugs As Direct Carcinogens

- Azathioprine implicated as direct carcinogen

Taylor, et al. Skin cancer after renal transplantation: the causal role of azathioprine. Acta Derm Venereol 1992;72:115-119

- Cyclosporine induced TGF-beta production by tumour cells promotes cell invasiveness by a cell-autonomous mechanism that is independent and/or complementary to cyclosporine's immunosuppressive effect on the host's immune system

Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. [see comments]. Nature. 1999;397:530-4.

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Skin Cancer and Immunosuppression

- Renal Transplant Recipients
  - AP 29 NMSC/1000 person-years
  - CAP 48 NMSC/1000 person-years
- CAP group
  - Increased risk of SCC, not BCC
  - Malignancies occurred earlier

Glover, M. T., et al. "Immunosuppression and risk of non-melanoma skin cancer in renal transplant recipients [letter]." Lancet 349.9049 (1997): 398.

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Skin Cancer and Immunosuppression

- Single-center Norwegian cohort of kidney and heart transplant patients (JAAD, Feb99)
- CAP vs. AP 2.8 times higher risk of SCC
- CP intermediate risk

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After Transplantation – Reduce Incidence of Skin Cancer

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.

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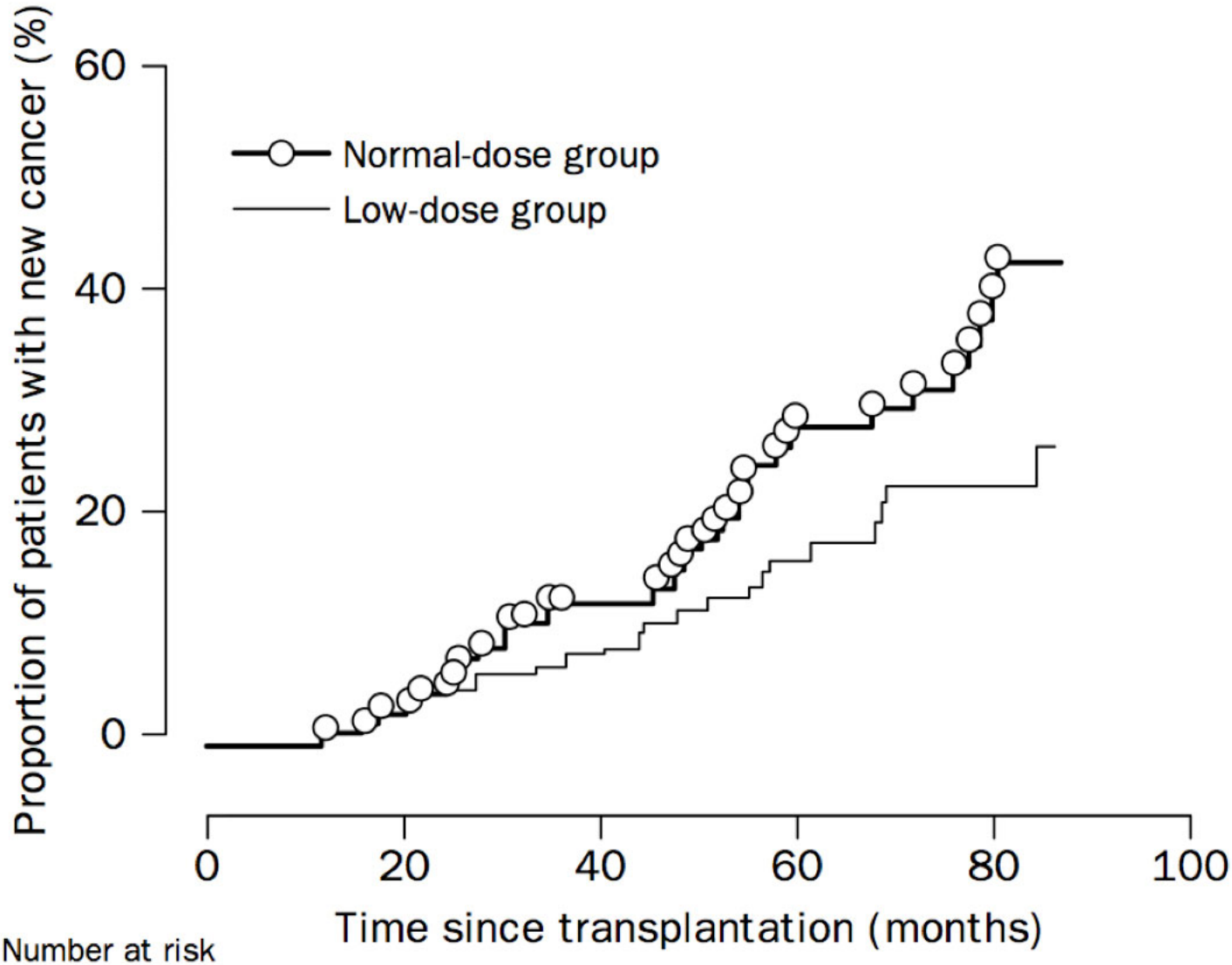
After Transplantation – Reduce Incidence of Skin Cancer



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

Figure 4: **Frequency of cancer**

Common current regimens

- Azathioprine/Prednisone --predominately patients transplanted prior to about 1985
- Cyclosporine/Prednisone
- Cyclosporine/Azathioprine/Prednisone
- Tacrolimus may be substituted for Cyclosporine
- Mycophenolate mofetil may be substituted for Azathioprine and/or cyclosporine
- Sirolimus may be added to spare or replace cyclosporine

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%

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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

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Newer Immunosuppressants and Skin Cancer

Substitution of immunosuppressive agents.

- Mycophenolate mofetil for azathioprine
- Tacrolimus for cyclosporine

→ For both-- an improvement is probably due to easier dosing and lower levels of immunosuppression

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.

Rejection Versus Cancer

- **Prevent Rejection**
  - More drugs
  - Less rejection
  - Higher graft survival
  - More cancer
- **Prevent Cancer**
  - Fewer drugs
  - Less skin cancer
  - Higher survival from cancer
  - Increased QOL
  - ? More rejection

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The Hope

- Donor specific tolerance

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Is Risk Organ Dependent?

- SCC 2-3 X more likely in cardiac than renal transplant patients
  - Age-adjusted population studies
- Lower risk for Liver transplant patients

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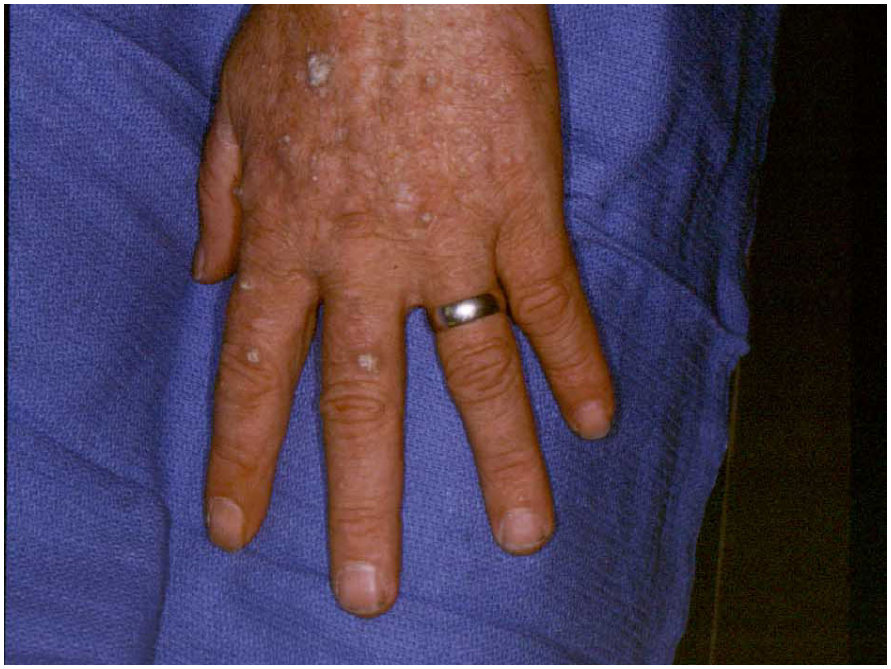
After Transplantation– Reduce Incidence of Skin Cancer

The Role of Human Papilloma Virus

- RTR's
  - HPV in 65% of SCC's
  - HPV in 60% of BCC's
- Non-immunosuppressed
  - HPV in 31% of SCC's
  - HPV in 36% of BCC's
- Conclusion: HPV is a possible etiologic factor in skin neoplasm



Shamanin, V., et al., Human papillomavirus infections in nonmelanoma skin cancers from renal transplant recipients and nonimmunosuppressed patients. Journal of the National Cancer Institute, 1996. 88(12): p. 802-11.

The Role of Human Papilloma Virus

- Eyebrow hairs were plucked from RTR's and non-immunosuppressed controls
- HPV DNA detected in hair samples of 100% of RTR's
  38/49 types sequenced--EV-HPV Types
- HPV DNA detected in hair samples of 45% of controls
  17/20 types sequenced--EV-HPV Types
- Utilized nested PCR technique

Boxman, I. L., et al. "Detection of human papillomavirus DNA in plucked hairs from renal transplant recipients and healthy volunteers." J Invest Dermatol 108.5 (1997): 712-5.

Role of HPV in Skin Cancer

- HPV 16, 18 strong association with cervix CA
- E6 oncoprotein
  - Inactivates p53
  - Inhibits UV apoptosis INDEPENDENT of p53
    - Occurs in p53 null mice (Jackson et al. Oncogene 2000)
- E7 oncoprotein
  - Inhibits retinoblastoma protein (pRb)

Virus and Skin Cancer in Transplant Patients

"It is possible that HPV may have an effect, mainly through induction of keratinocyte proliferation at multiple sites, the virus persisting because of the lack of an effective immune response. Changes in epidermal DNA caused by UVR may then be perpetuated by the HPV-stimulated cellular proliferation"

I. M. Leigh and M. T. Glover. Cutaneous warts and tumours in immunosuppressed patients. Journal of the Royal Society of Medicine, 1995:88.61-2. Feb

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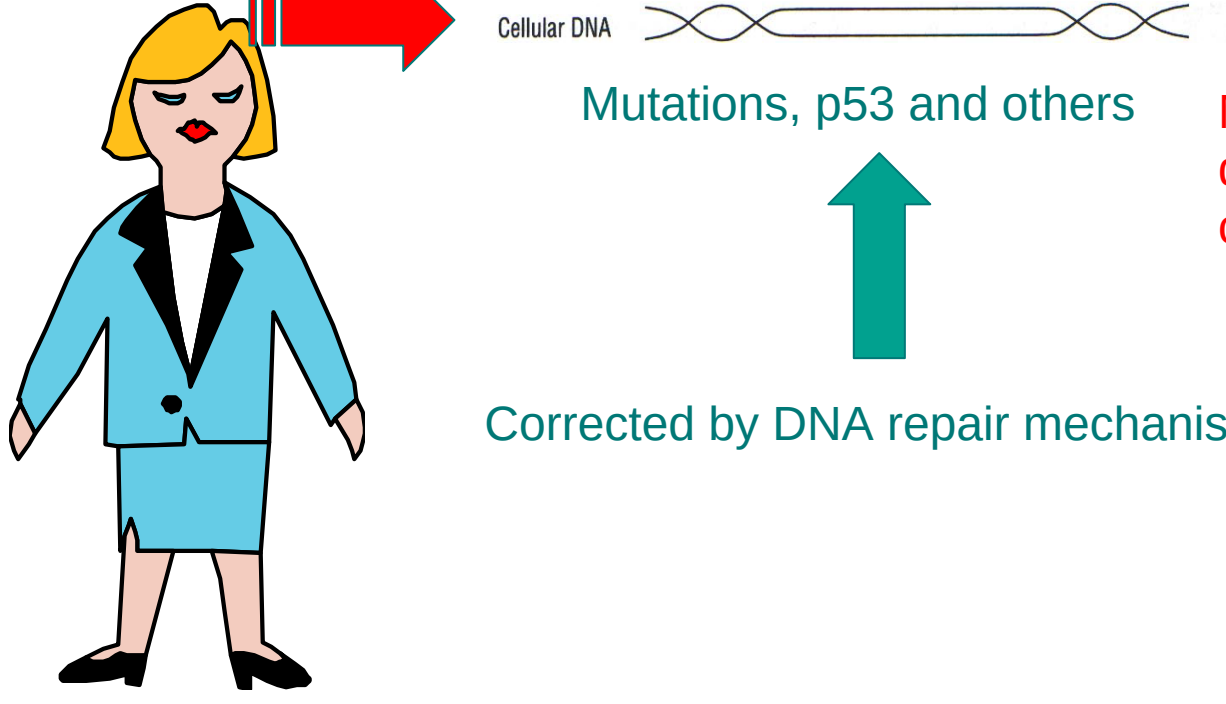
After Transplantation – Reduce Incidence of Skin Cancer

Cells with mutations removed
by cellular immunity

Skin immunity
decreased by UV



Mutations, p53 and others

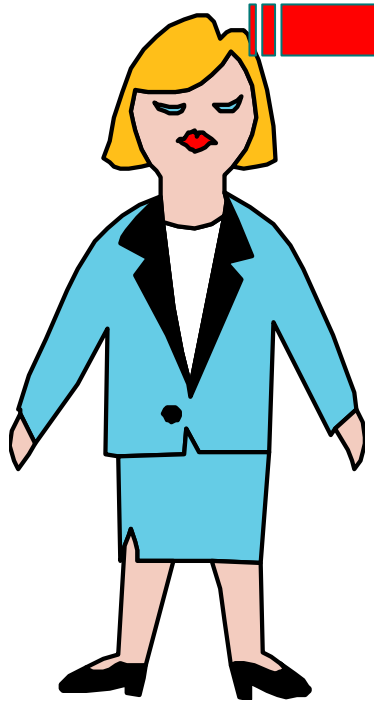
Most mutations
destroyed a few
cancers persist

Corrected by DNA repair mechanisms

Cells with mutations removed by cellular immunity

HPV controlled by cellular immunity

Skin immunity decreased by UV



+ HPV to perpetuate the mutation

Mutations, p53 and others

+ HPV effect on p53 products

Corrected by DNA repair mechanisms

Most mutations destroyed but a few cancers persist

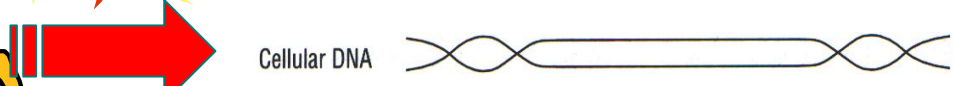
Cells with mutations removed by cellular immunity

HPV controlled by cellular immunity

Immunosuppression

Skin immunity decreased by UV

+ Proliferative effects of medications



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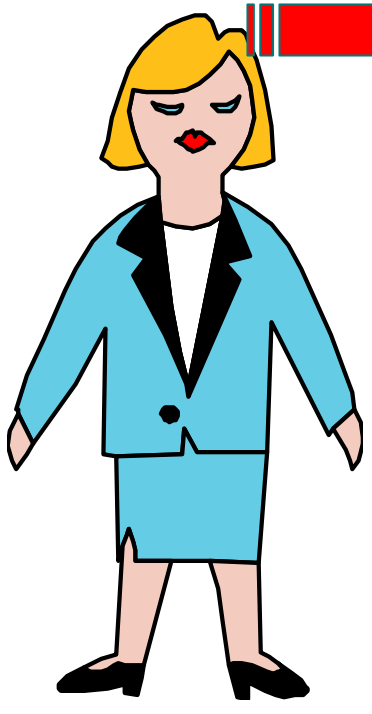

Accelerated Carcinogenesis: The Life Cycle of Dysplasia

- Actinic damage
- Actinic keratosis
- Squamous cell carcinoma in situ
- Invasive squamous cell carcinoma
- Metastatic squamous cell carcinoma

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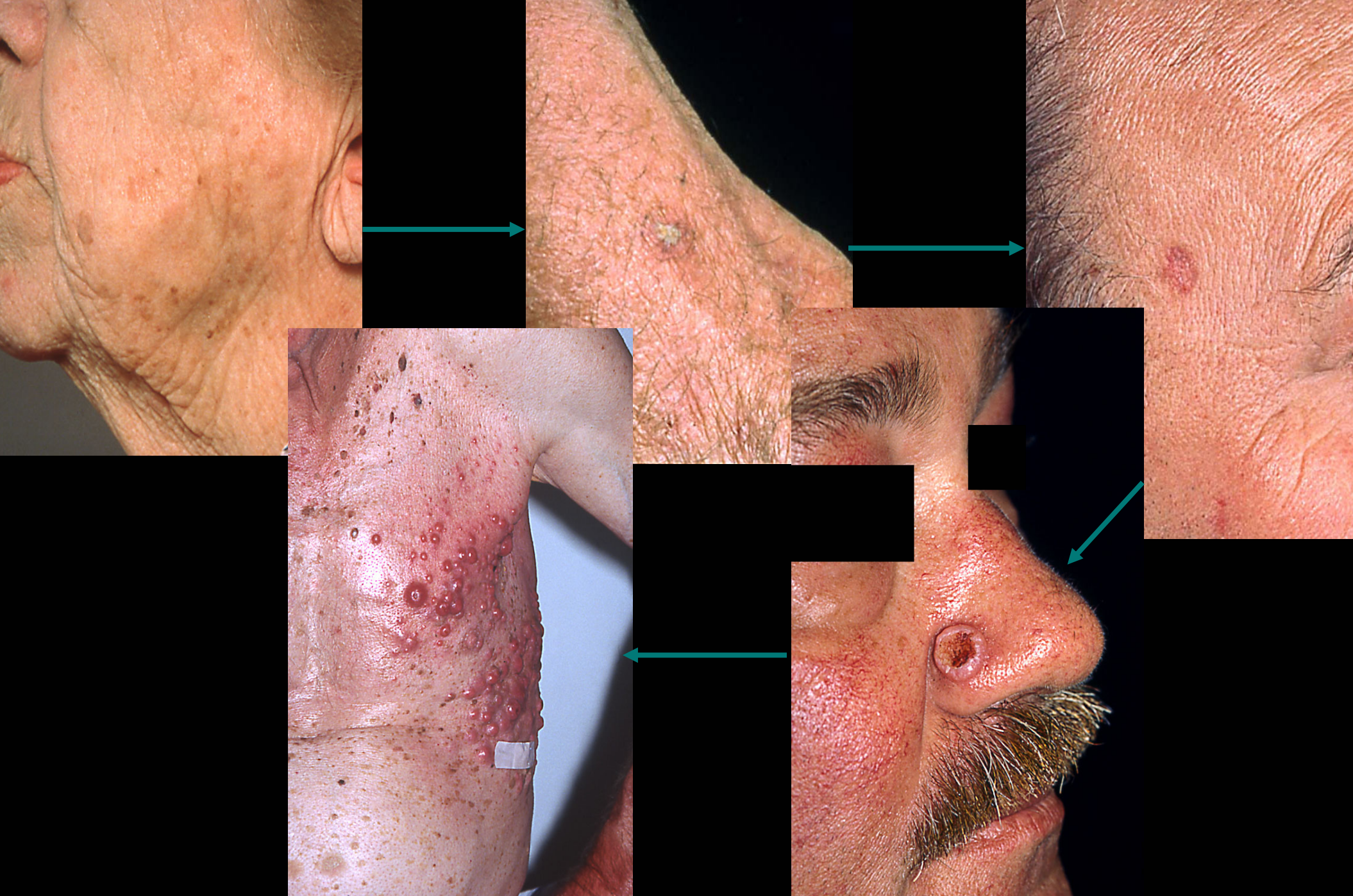
After Transplantation–Reduce Incidence of Skin Cancer



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)

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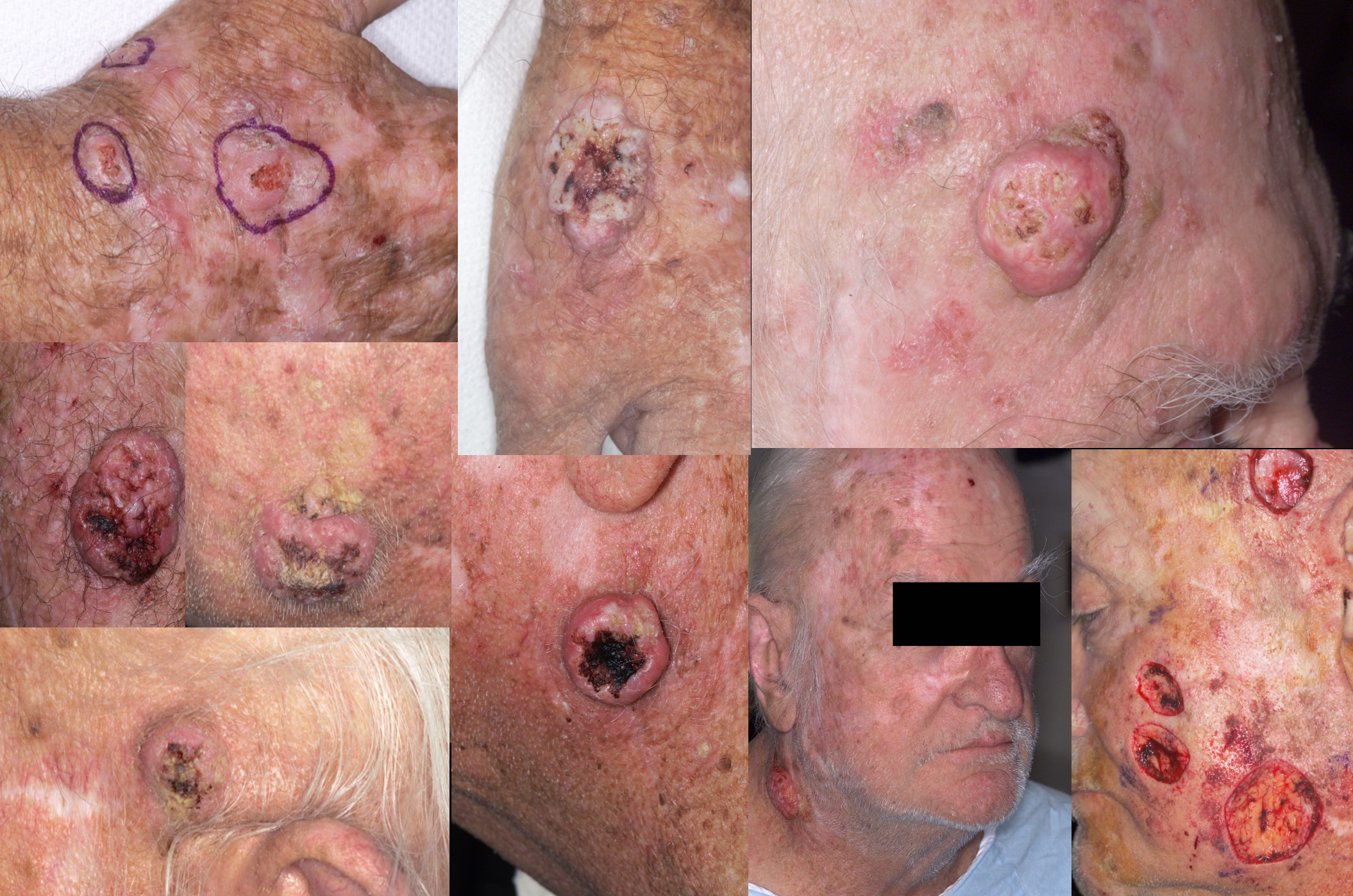
After Transplantation–Reduce Incidence of Skin Cancer



Guidelines of Care

- Whenever possible, references for proposed treatments will be provided
- Many times such references are scant or relate to very small studies
- Much is anecdotal
- Everyone may not agree on treatments and treatment priorities

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After Transplantation – Reduce Incidence of Skin Cancer

Guidelines of Care

- Care must be individualized.
- Physicians reviewing this material must use independent medical judgment in the context of each patient's circumstances to develop the patient's treatment plan.

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After Transplantation–Reduce Incidence of Skin Cancer

Guidelines of Care

- Treatment of nonmelanoma skin cancer in organ transplant recipients: Review of responses to a survey

  J Am Acad Dermatol 2003;49:413-6.

- International Transplant-Skin Cancer Collaborative / European Skin Care in Organ Transplant Patients Network:

  Guidelines for the Management of Squamous Cell Carcinoma In Organ Transplant Recipients

  Dermatol Surg 2004;30:642-650

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After Transplantation – Reduce Incidence of Skin Cancer

Screening and Education

- Although there is little hard data, it seems prudent that all transplant patients should be instructed in AGGRESSIVE SUN PROTECTION
  - Protective clothing
  - Limit outdoor activities 10 am - 4 pm
  - Daily use of sunscreens SPF 30 or higher
  - No sunbathing
  - No tanning parlors
- Such instruction should be included in the pre-transplant educational program

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After Transplantation–Reduce Incidence of Skin Cancer

Screening and Education

- 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

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After Transplantation–Reduce Incidence of Skin Cancer

Screening and Education

- Compliance with advice about sun protection--RTR's in Leeds, UK
  - 44% recalled being given advice
  - 46% did not
  - 30% knew why, as RTR's, they needed extra precautions
  - Only 18% avoided mid-day sun
  - 57% used sunscreen

Seukeran, D. et al. The compliance of renal transplant recipeints with advice about sun protection measures. British Journal of Dermatology. 1998(138): p301-303.

Screening and Education

Ideally, all patients should be seen prior to transplant

- Full exam for pre-existing lesions and treatment
  - Risk of recurrence of skin cancer after transplant is 60% vs 41% de novo
- Sun-protection education
- Patient self exam education and begin routine follow-up schedule

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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

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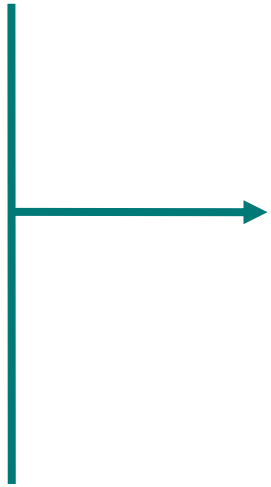
After Transplantation–Reduce Incidence of Skin Cancer

Screening and Education

Patients should receive a skin cancer oriented history and physical prior to transplantation if practical. All patients should be given education regarding sun exposure and the recognition of premalignant and malignant skin lesions, high risk patients should be identified for closer follow-up

Premalignant lesions:
Actinic keratosis/wart
Complete skin exam
Education
- Prevention
- Skin cancer appearance



Skin exam every
3-6 mo

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Reduce Incidence of Skin Cancer

Premalignant Lesions

There is a lag time for the development of dysplastic lesions and skin cancers. It is unknown whether preventive treatment during this period would help

- Cryotherapy
- Efudex
- Imiquimod
- Photodynamic therapy
- Chemical peels/Dermabrasion
- Topical retinoids
- Systemic retinoids
- Reduction of immunosuppression

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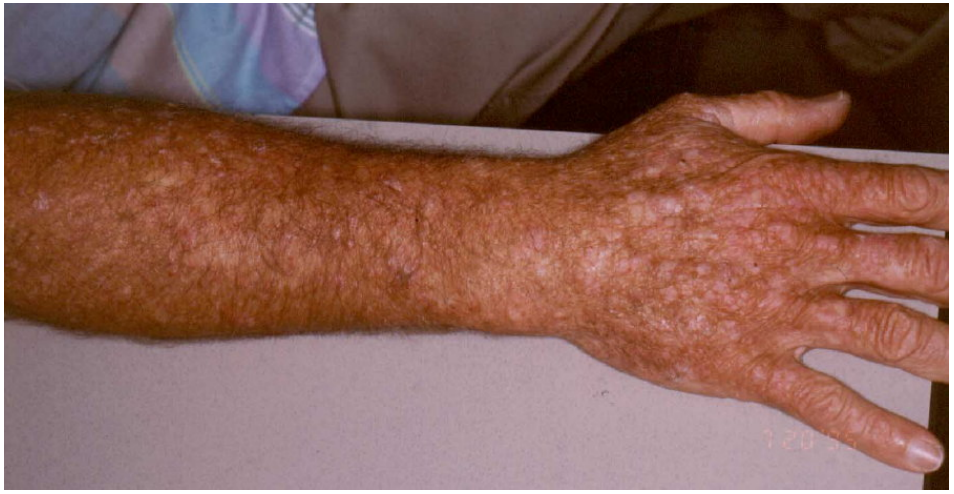
After Transplantation–Reduce Incidence of Skin Cancer

Low Risk: Premalignant and early SCC



Warts
Actinic Keratoses
Early, small SCC

Modality	Survey usage
Cryotherapy	23/24
Topical 5-FU	20/24
Topical Imiquimod	7/24
Topical PDT	4/24

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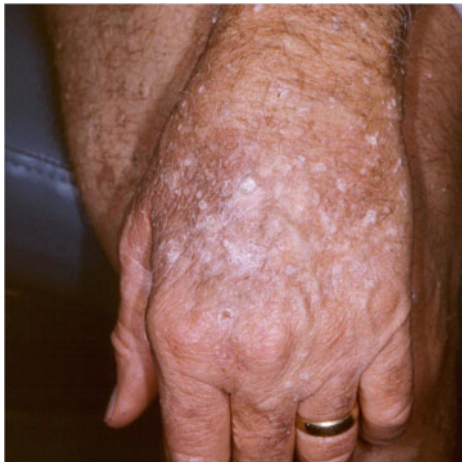
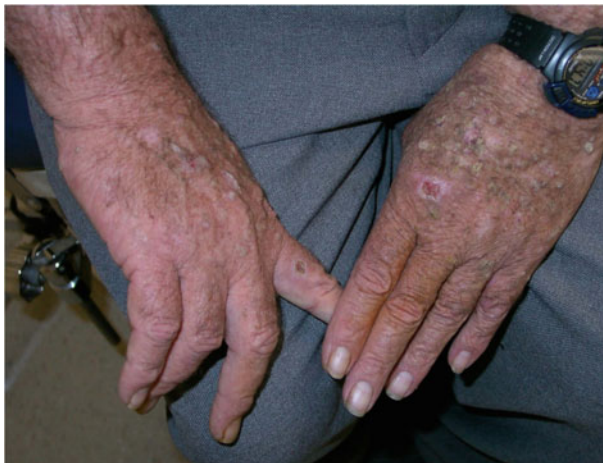
Topical 5-FU

- May be useful to decrease size and number of lesions, especially on forearms and hands
- May need to use continuously
- May see little or no erythema
- May be useful to combine with alpha/beta hydroxy acids, topical tretinoin





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After Transplantation–Reduce Incidence of Skin Cancer

Imiquimod

- Topically applied, non-specific immune modulator
- Recently approved for treatment of actinic keratoses
- 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
- Efficacy in organ transplant recipients--can OTR's respond?
  - Unpublished European reports indicate: yes

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After Transplantation–Reduce Incidence of Skin Cancer

Imiquimod

- 5 patients -- SCC in-situ of legs
- Treatment -- imiquimod + topical 5-FU
- Results
  - Clearing of areas of SCC in-situ
  - No observed effects on systemic immunity

K. J. Smith, M. Germain and H. Skelton, Squamous cell carcinoma in situ (Bowen's disease) in renal transplant patients treated with 5% imiquimod and 5% 5-fluorouracil therapy Dermatol Surg 27 6 561-4 2001.

Efficacy of imiquimod 5% cream for basal cell carcinoma in transplant patients.

D Vidal and A Alomar — Clin Exp Dermatol, May 1, 2004; 29(3): 237-9.

- Four renal transplant patients and one cardiac transplant with 10 basal cell carcinomas.
- 4 were superficial, 3 nodular and 3 infiltrative.
- 5 basal cell carcinomas received imiquimod 5% cream at night four times weekly for 6 weeks and 5 were treated on 5 nights per week for 5 weeks.
- Biopsies taken 6 weeks after the end of treatment
- No tumor in 7 of 10 of the cases.
  - 4/4 superficial
  - 2/3 nodular
  - 1/3 infiltrative

Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial.

Brown VL, Atkins CL, Ghali L, Cerio R, Harwood CA, Proby CM. — Arch Dermatol. Aug 2005;141(8):985-993.

- 14 imiquimod 6 placebo
- applied 3 times a week for 16 weeks to 1 dorsal hand or forearm, up to 60 cm2, 8 months of follow-up
- Imiquimod:
- 7/14 reduced skin atypia (1/6 controls)
- 7/14 reduced viral warts (0/6 controls)
- 5/14 less dysplasia histologically (1/6 controls)
- In 1 year, fewer squamous skin tumors arose in imiquimod-treated skin than in control areas
- Renal function was not adversely affected.

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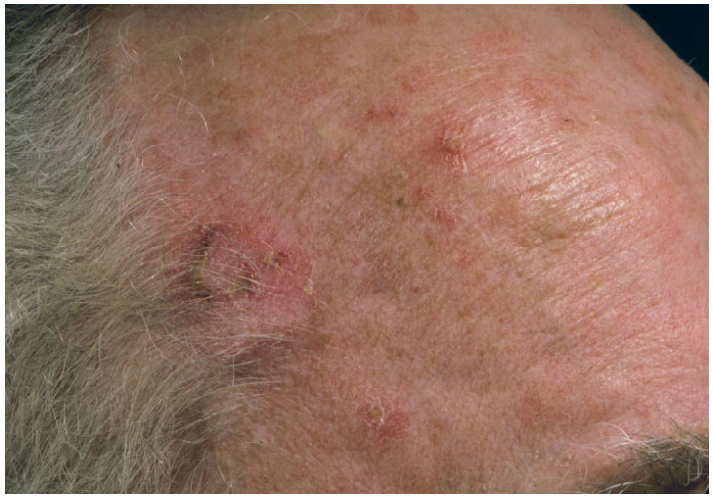
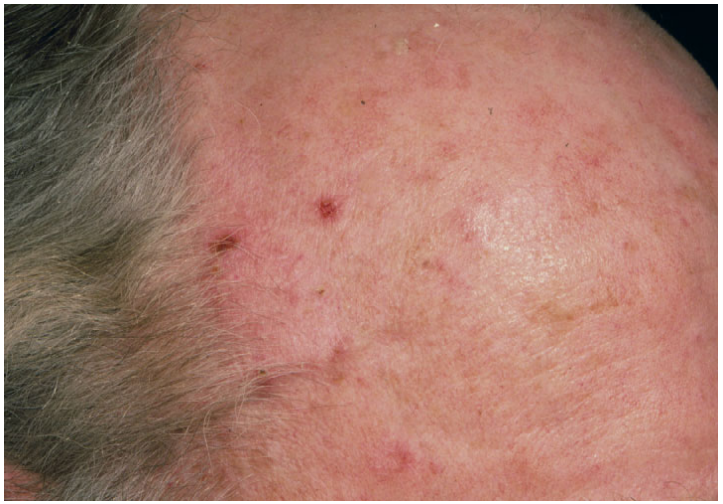
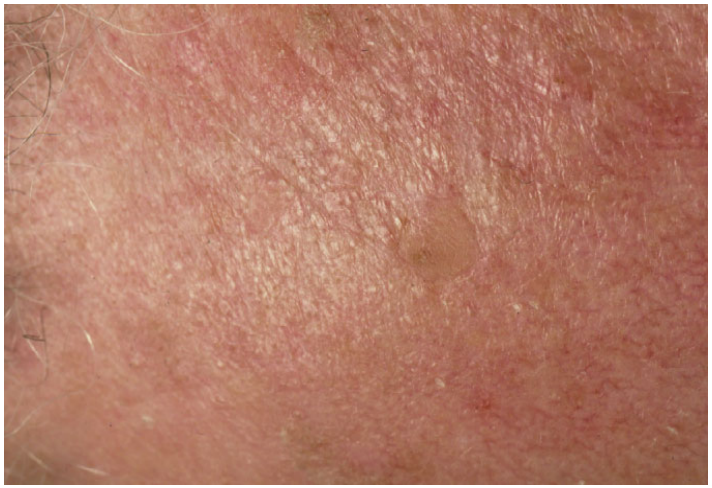
Daily Application for 6-12 weeks



4 weeks



8 weeks



After completion

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After Transplantation – Reduce Incidence of Skin Cancer

Photodynamic Therapy

Several small studies indicate usefulness in OTRs

- Dragieva G, Prinz BM, Hafner J, et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol.* Jul 2004;151(1):196-200.
- Dragieva G, Hafner J, Dummer R, et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation*. Jan 15 2004;77(1):115-121.
- Hyckel P, Schleier P, Meerbach A, Berndt A, Kosmehl H, Wutzler P. The therapy of virus-associated epithelial tumors of the face and the lips in organ transplant recipients. *Med Microbiol Immunol (Berl).* Aug 2003;192(3):171-176.

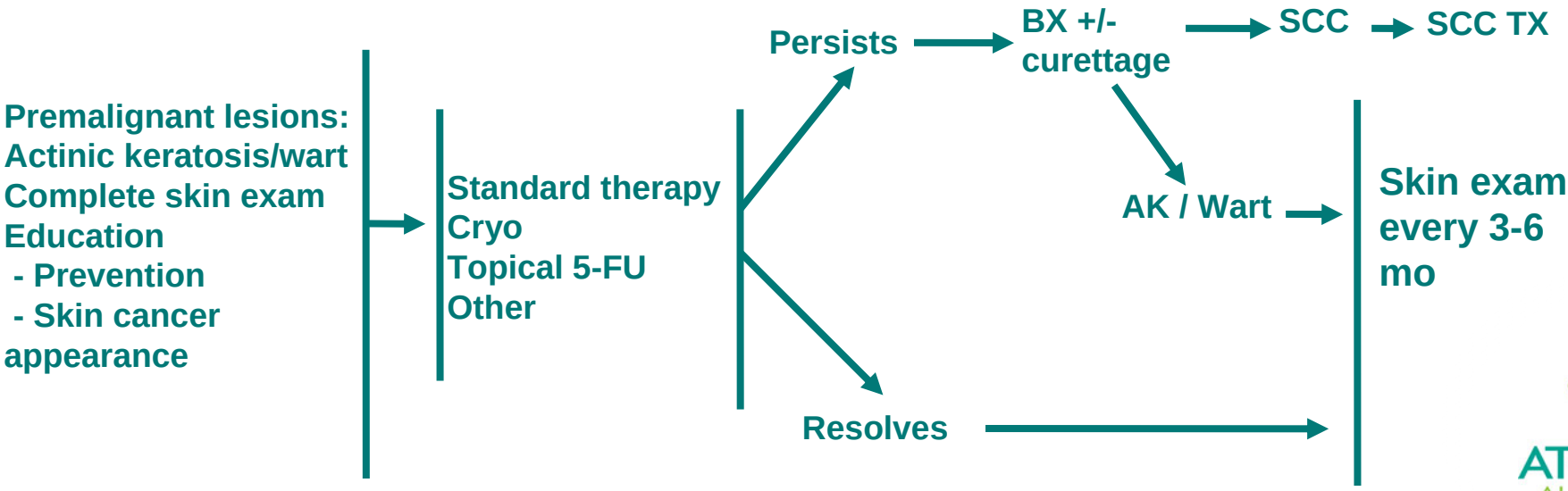
Photodynamic Therapy

- Did not prevent the occurrence of new SCC
- Reduced the incidence of keratotic lesions

de Graff YGL, Kennedy C,Wolterbeek R, et al. Photodynamic therapy does not prevent cutaneous squamous-cell carcinoma in organ-transplant recipients: results of a randomized-controlled trial. J Invest Dermatol. 2006 126, 569-574.

Evaluation And Management Of Warts And Premalignant Lesions

- Warts, actinic keratoses, porokeratoses should be treated aggressively at first development.
- Warts, actinic keratoses, porokeratoses which have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.



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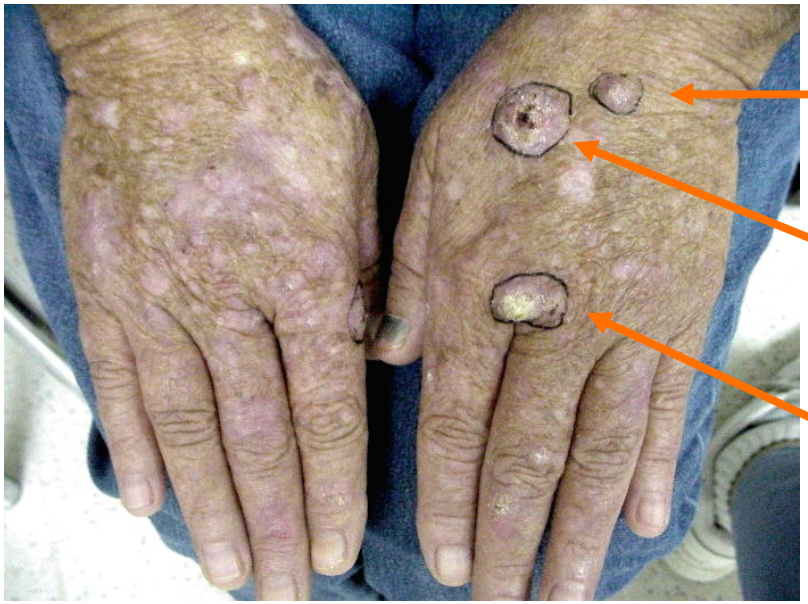
After Transplantation – Reduce Incidence of Skin Cancer

AK and SCC may be difficult to distinguish in OTRs

- Hard to clinically differentiate actinic keratosis from squamous cell carcinoma in OTR
- Actinic keratosis in OTR can look clinically benign, BUT be histologically malignant.



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After Transplantation – Reduce Incidence of Skin Cancer

Treatment of Skin Cancers in Renal Transplant Patients

- Individual tumors managed according to traditional principles, with increased diligence
  - Mohs micrographic surgery
  - Electrodesiccation and curettage
  - Cryotherapy
  - Excision
  - Radiation
- If multiple lesions may need to temper treatment with limitations of time, resources and patient tolerances
- Must pay attention to risk of metastasis

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

Treatment of Multiple Skin Cancers in Transplant Patients

- If multiple lower-risk lesions, may need to temper treatment with limitations of time, resources and patient tolerance
  - Aggressive ED&C or Cryosurgery
  - Mohs Micrographic Surgery for larger lesions, rapidly growing lesions, recurrent lesions
- Lower-risk lesions
  - < 0.6 cm, “mask” areas of the face(central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular areas, temple and ear), genitalia, hands and feet
  - <1.0 cm, cheeks, forehead, neck and scalp
  - <2.0 cm, trunk and extremities
  - Location NOT on scalp, ear, lip, mid-face, genitalia, nail unit or within an anatomic fusion plane
- Still must pay attention to risk of metastasis

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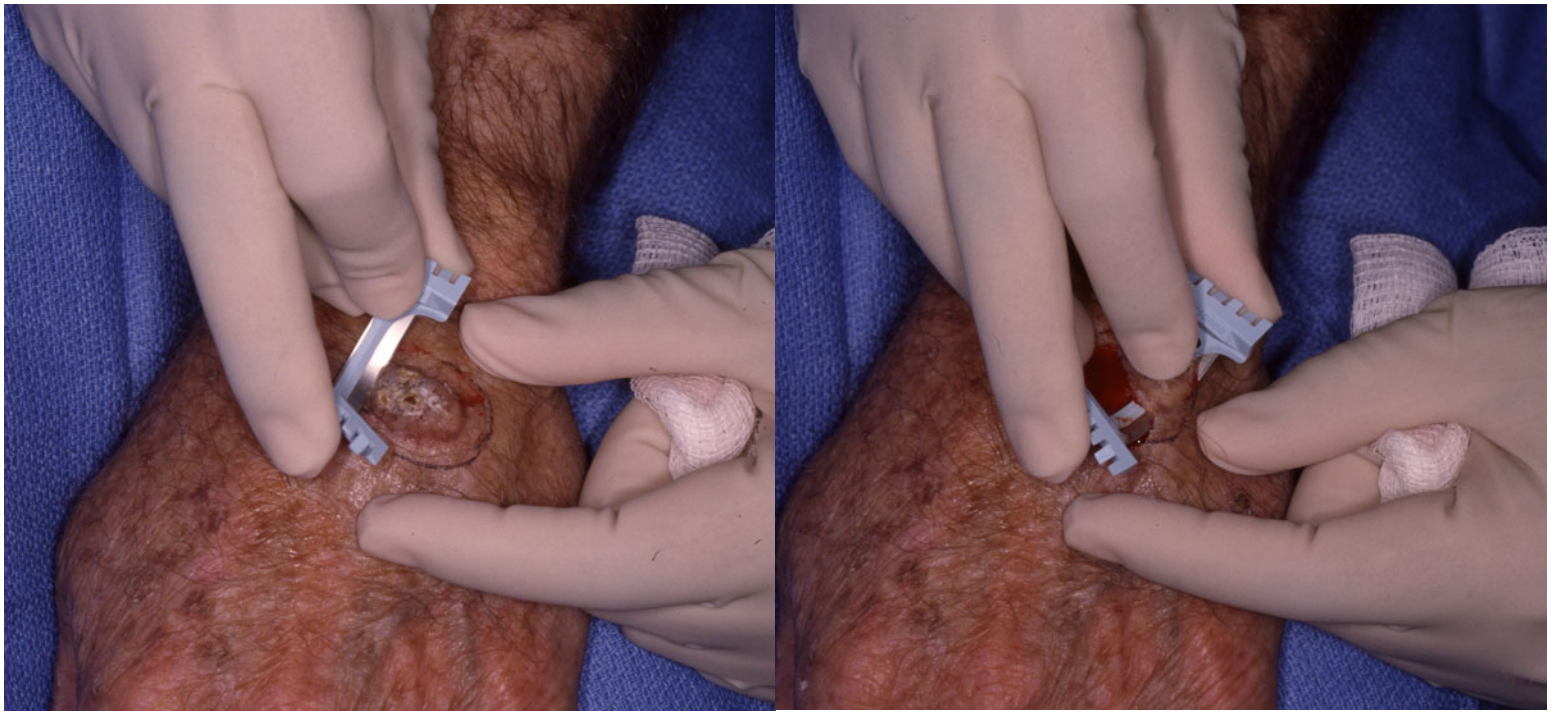
After Transplantation–Reduce Incidence of Skin Cancer

Aggressive C & D

- Start with deep shave biopsy--some prefer the term shave excision



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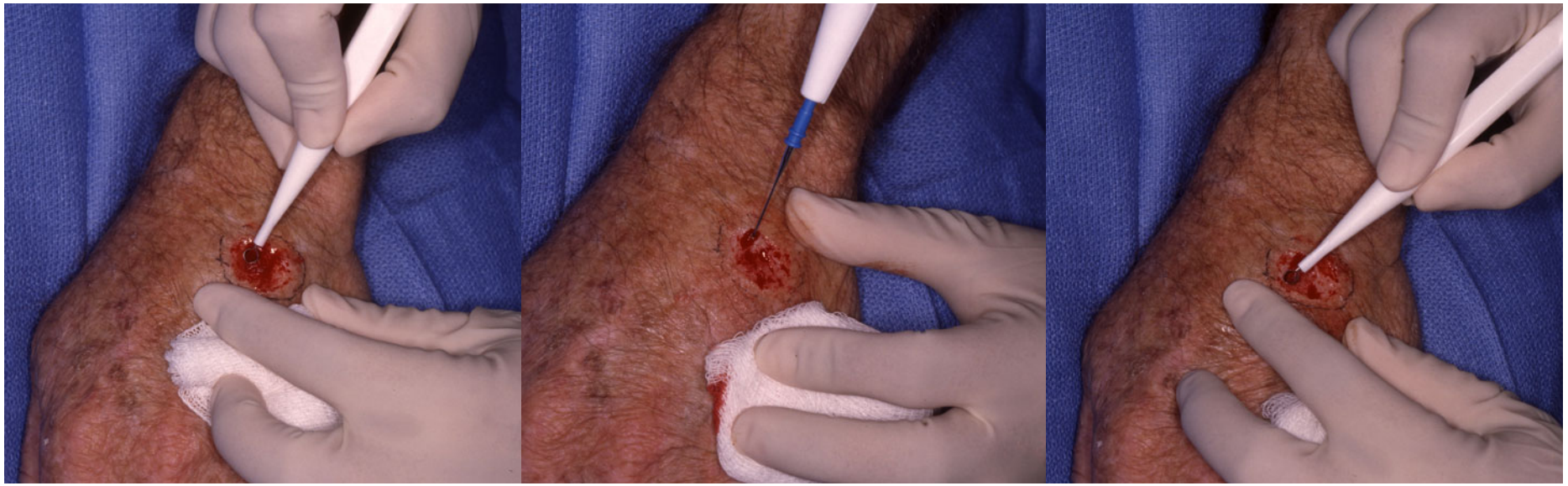
After Transplantation–Reduce Incidence of Skin Cancer

Aggressive C & D

- Follow by curettage and electrodessication X 3



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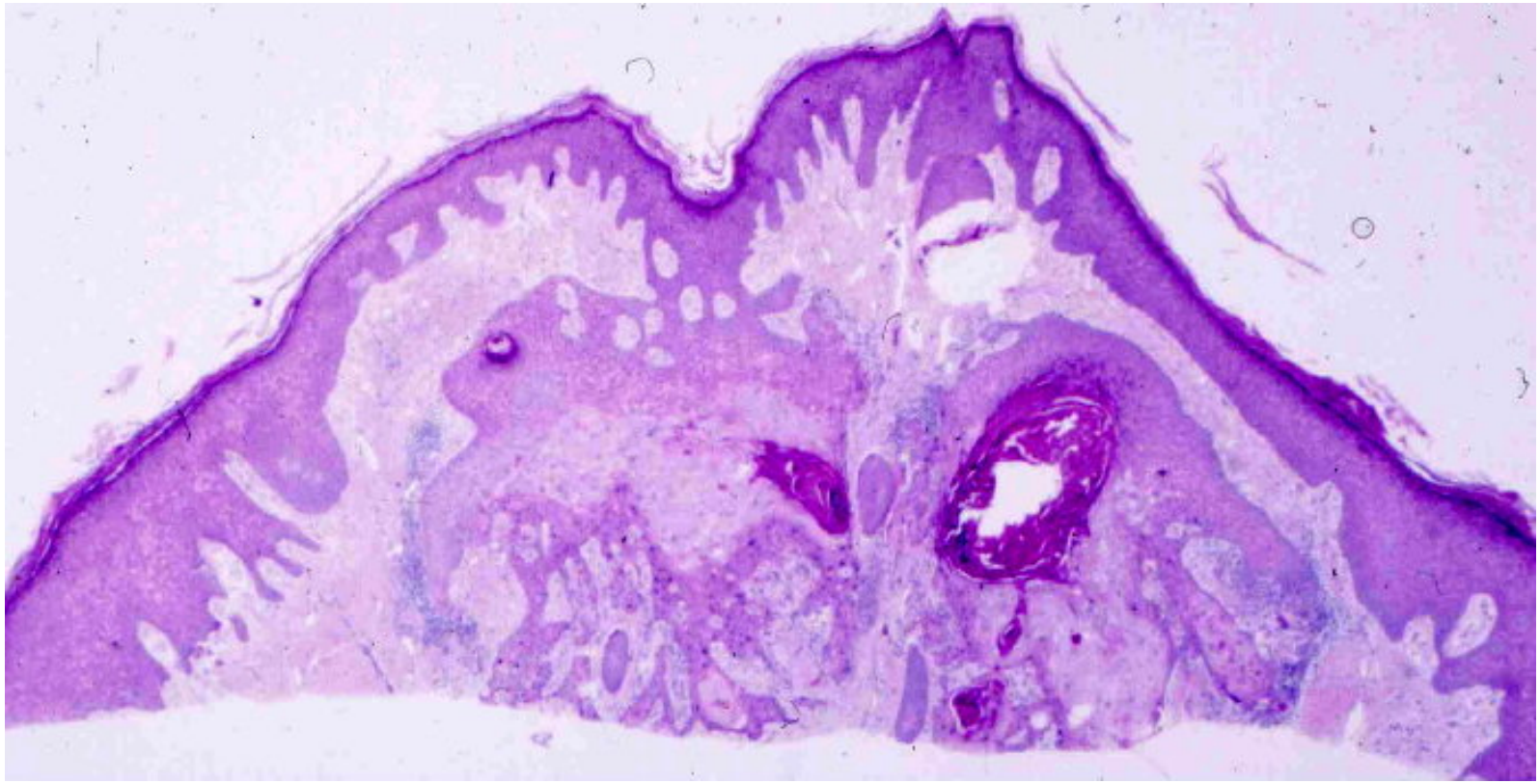
After Transplantation – Reduce Incidence of Skin Cancer

Aggressive C & D

- Base adequacy of treatment on several parameters
- Clinical
  - Tumor easily curetted and a firm base reached
  - Because of fragility of most OTR's skin, extending full-thickness in small areas does not necessarily require change to excision(and they will still heal well)

Aggressive C & D

- Histologic exam--look at the slides



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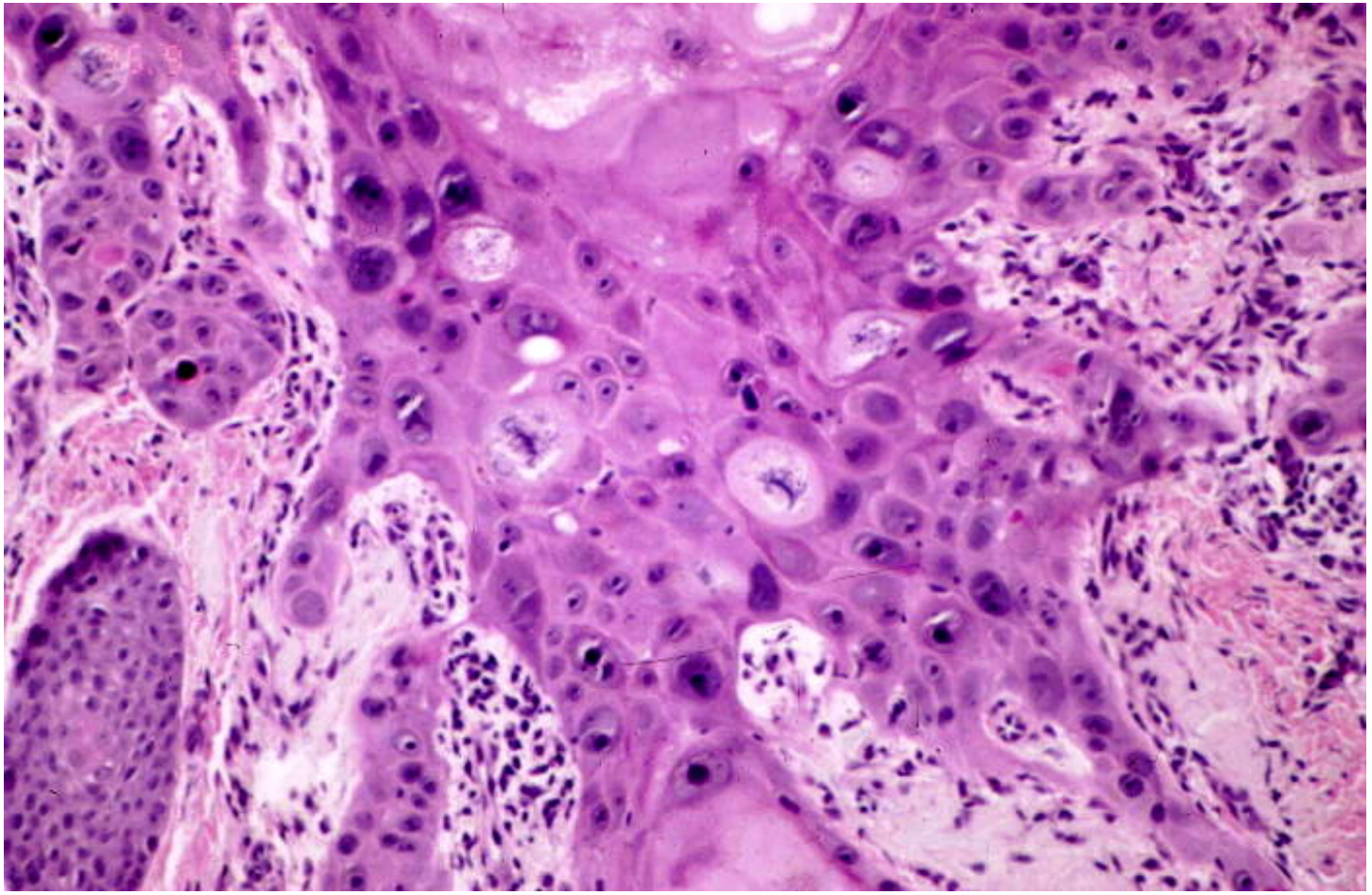
Marked cytologic atypia is very common in OTR



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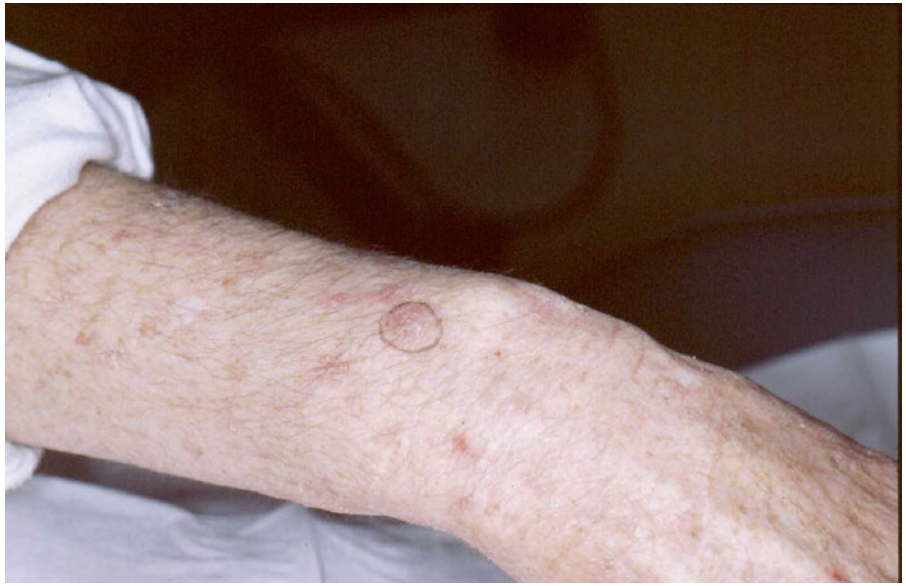
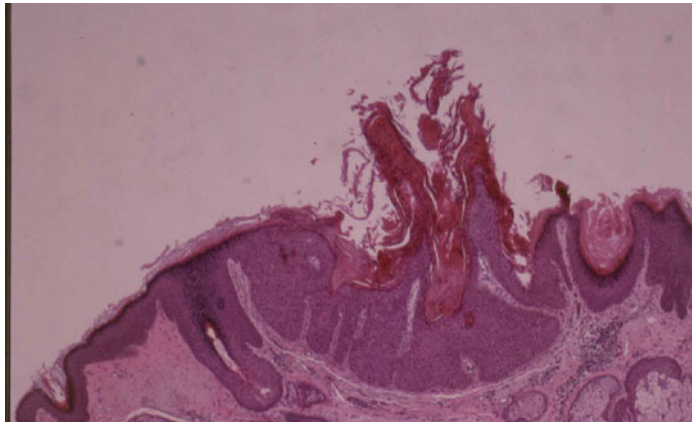
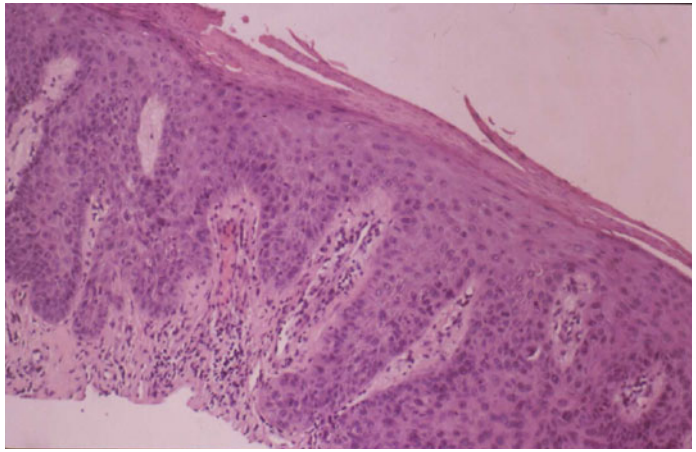
After Transplantation – Reduce Incidence of Skin Cancer

Aggressive C & D

- In spite of nodular appearance many lesions will be in-situ







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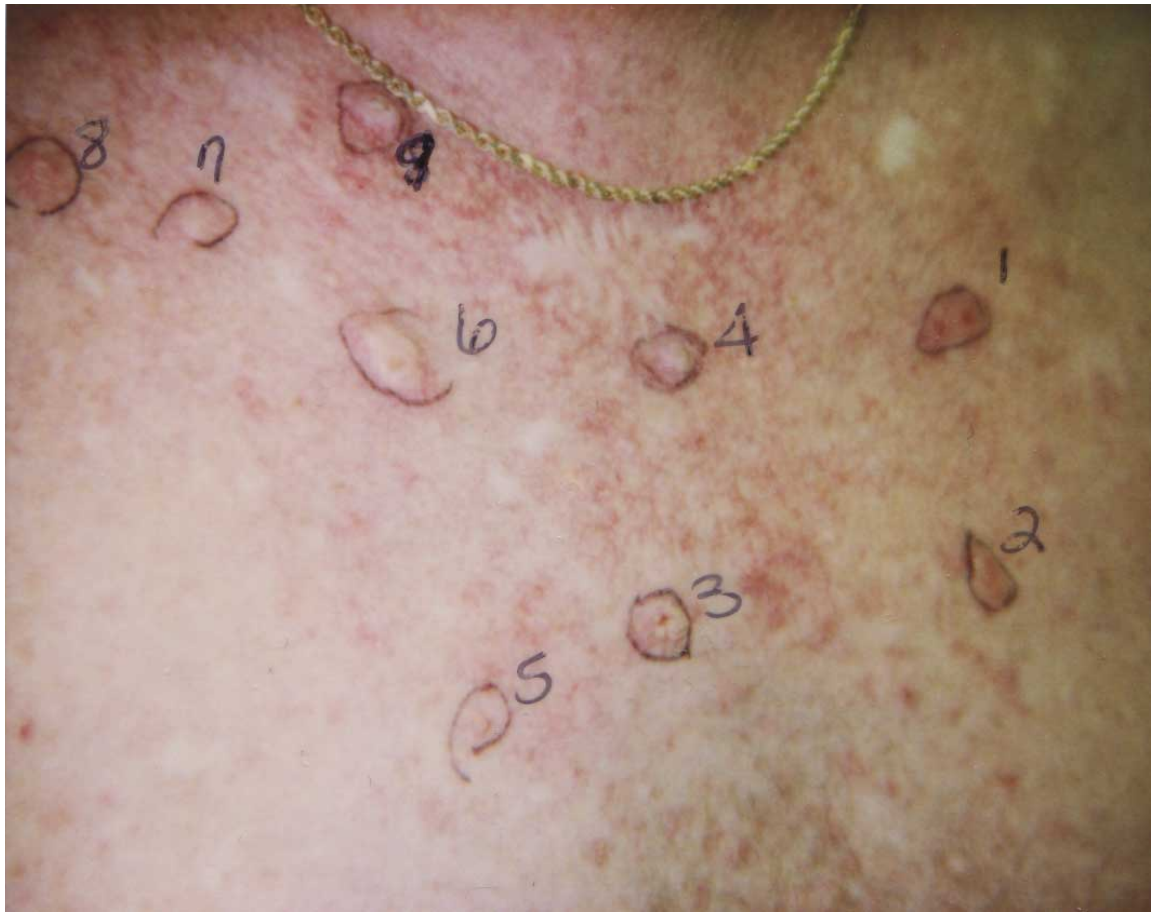
Aggressive C & D or Cryosurgery



Tumors may be too numerous for excision or Mohs

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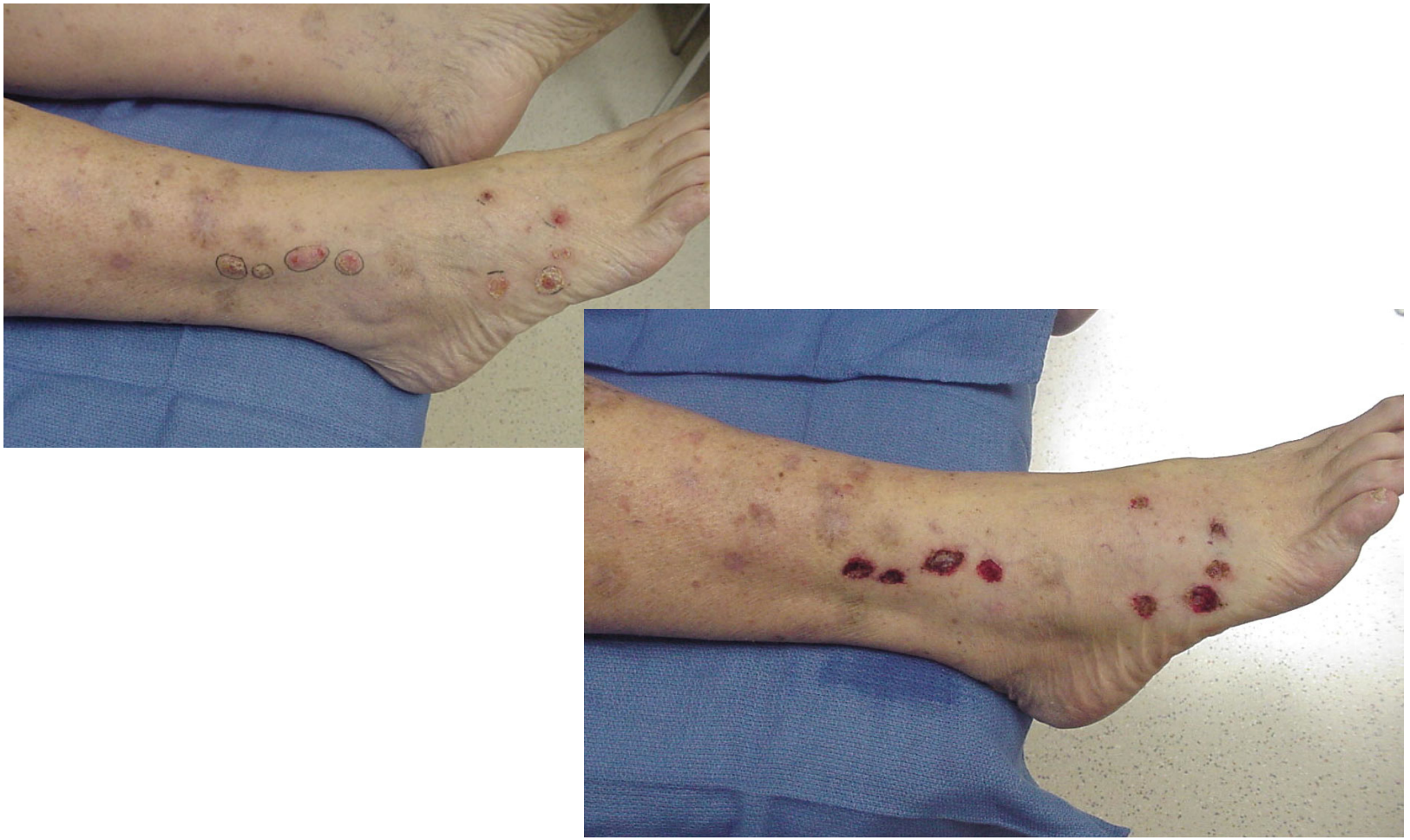
Aggressive C & D



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After Transplantation – Reduce Incidence of Skin Cancer

ED & C-Clinical Study

- 211 “low risk lesions” in 48 OTRs
  - Less than 2 cm
  - No clinical deep infiltration
- Mean follow-up 50 months
- Overall residual or recurrent 6%
  - 0% forearms
  - 11% head and neck
  - 7% dorsum of hands or fingers
  - 5% remaining areas
- Almost all recurrences in the first 12 weeks
- All recurrences treated easily with excision
  - The occurrence of residual or recurrent squamous cell carcinomas in organ transplant recipients after curettage and electrodessication.

De Graff YGL, Basdew VR, van der Zwan-Kralt, et al. Br J Dermatol 2006, 154, 493-497

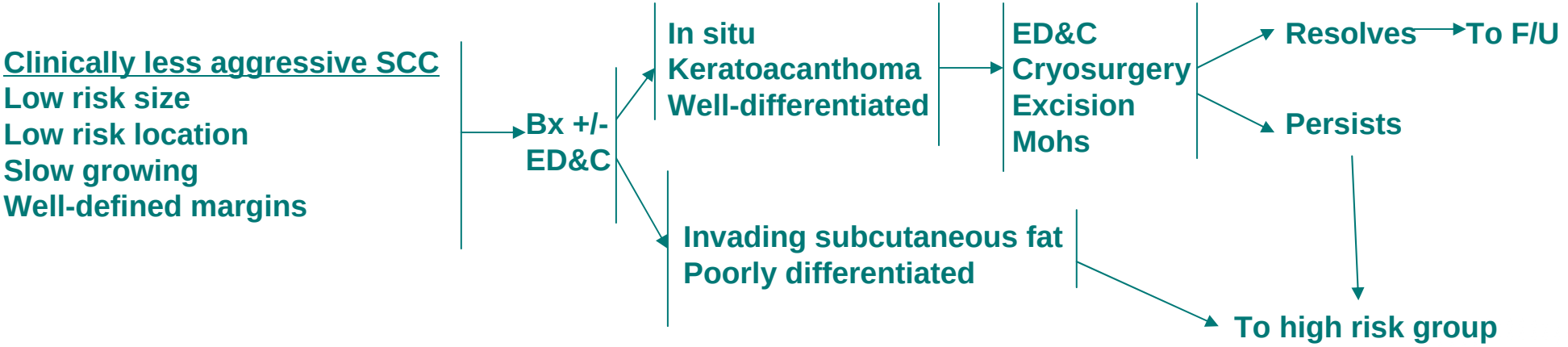
Survey

How would you treat an OTR with 5 clinically apparent keratoacanthoma-like SCC's(none clinically recurrent) on the right forearm and dorsal hand and a history of 10 previous similar lesions in the past 2 years all with KA/SCC histology?

- 13/23 Electrodesiccation and Curettage(or some variant)
- 13/23 Mohs or excision
- 3 suggested intralesional treatment
- Some suggested multiple treatments

Evaluation and Management of Squamous Cell Carcinoma

- All OTRs with suspected or proven SCC should have a thorough pretreatment evaluation.
- Less aggressive SCC in OTRs should be promptly managed with techniques including, but not limited to destructive modalities and excisional techniques. Histology should be obtained on all lesions.



*Size: < 0.6 cm, "mask" areas of the face(central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular areas, temple and ear), genitalia, hands and feet
<1.0 cm, cheeks, forehead, neck and scalp
<2.0 cm, trunk and extremities

**Location NOT on scalp, ear, lip, mid-face, genitalia, nail unit or within an anatomic fusion plane

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After Transplantation – Reduce Incidence of Skin Cancer

High Risk SCC

- Rapid growth or recurrence
- Ulceration
- Location: forehead, temple, ear, nose, lip, midface, genitalia
- Large size
  - >1.0 cm cheeks, forehead, neck and scalp
  - >0.6 cm other areas of face
  - >2.0 cm on trunk and extremities
- Poor differentiation
- Deep invasion (fat, muscle, cartilage, bone)
- Perineural/neural invasion

Mohs Micrographic Surgery

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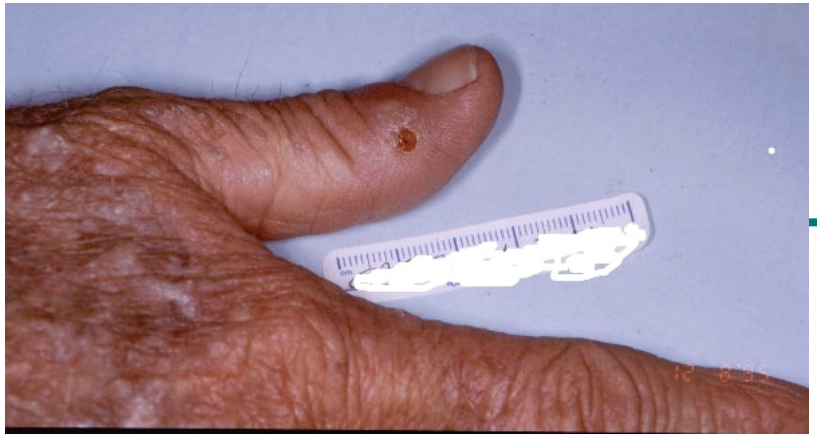
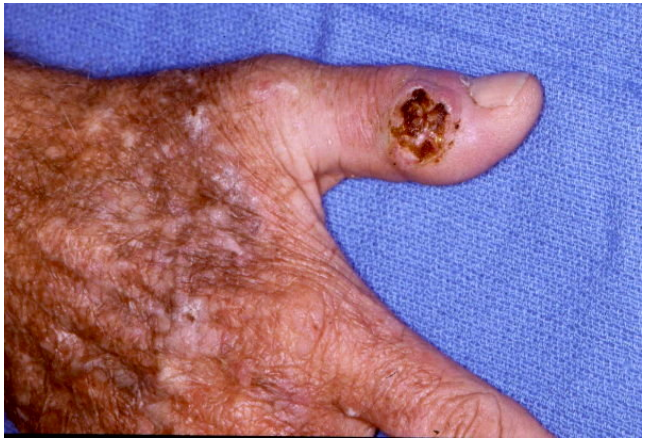
After Transplantation–Reduce Incidence of Skin Cancer

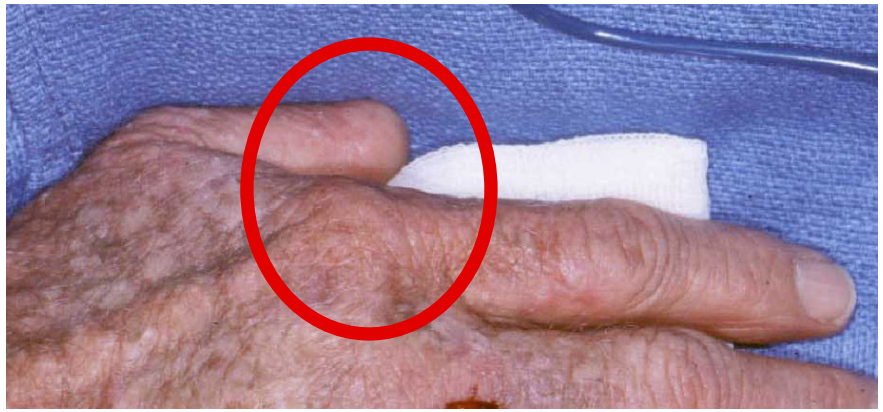
Rapid Growth

Tumor involved periosteum



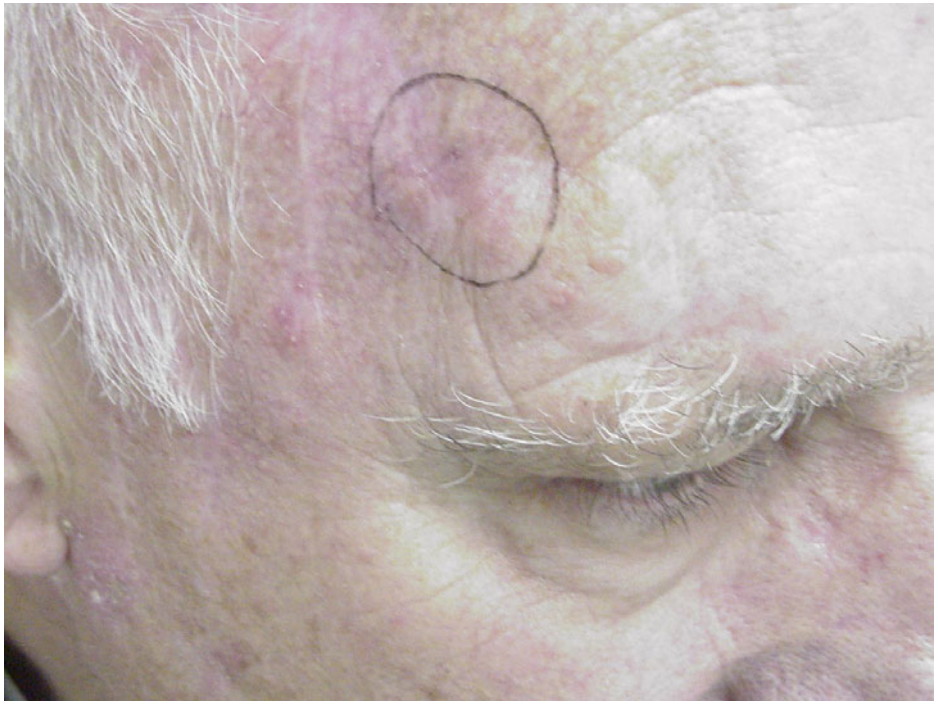
6 weeks

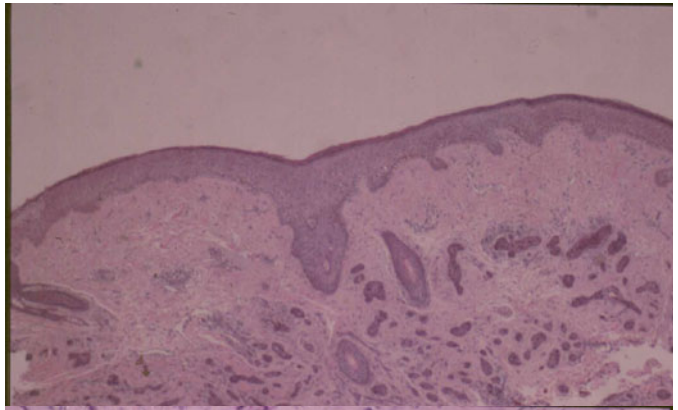


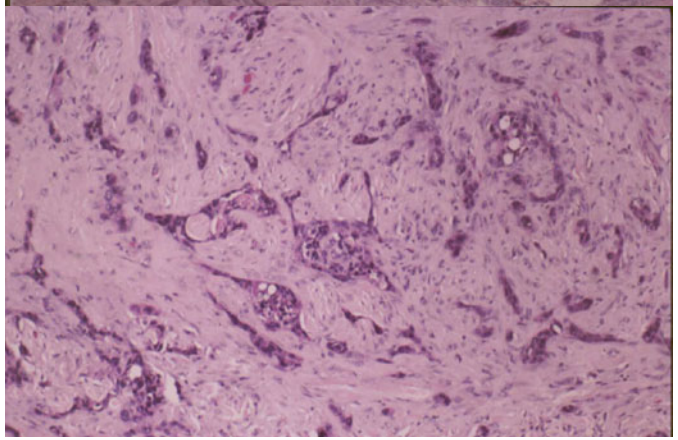


Forehead, palpates deeply

Poor differentiation, deep invasion







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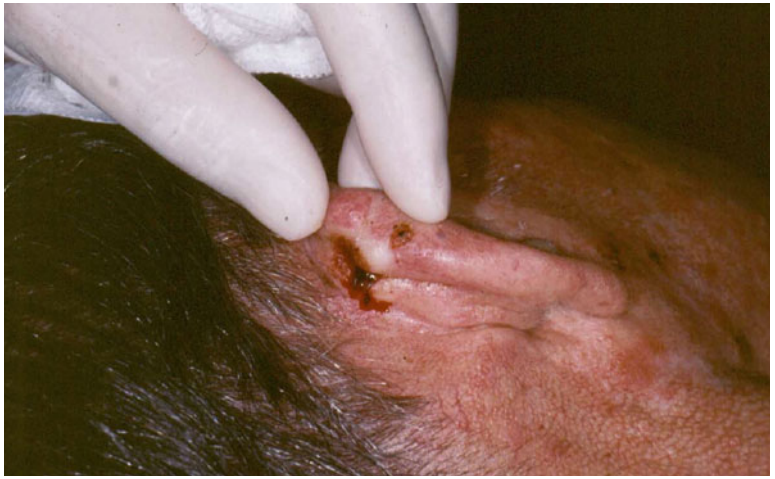
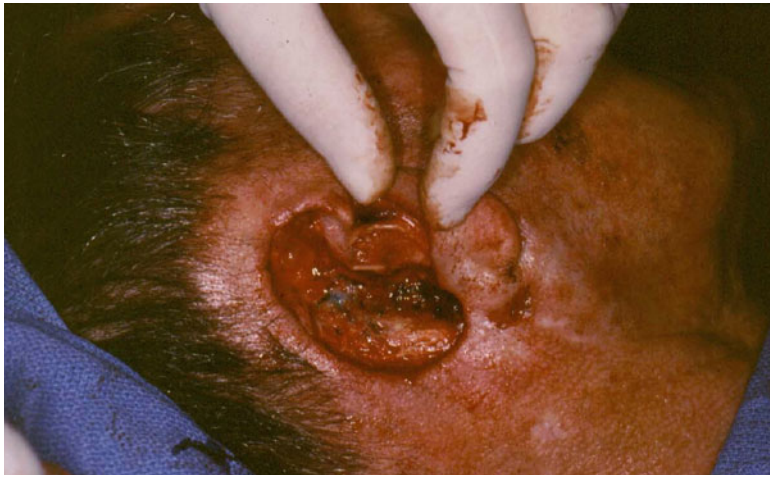
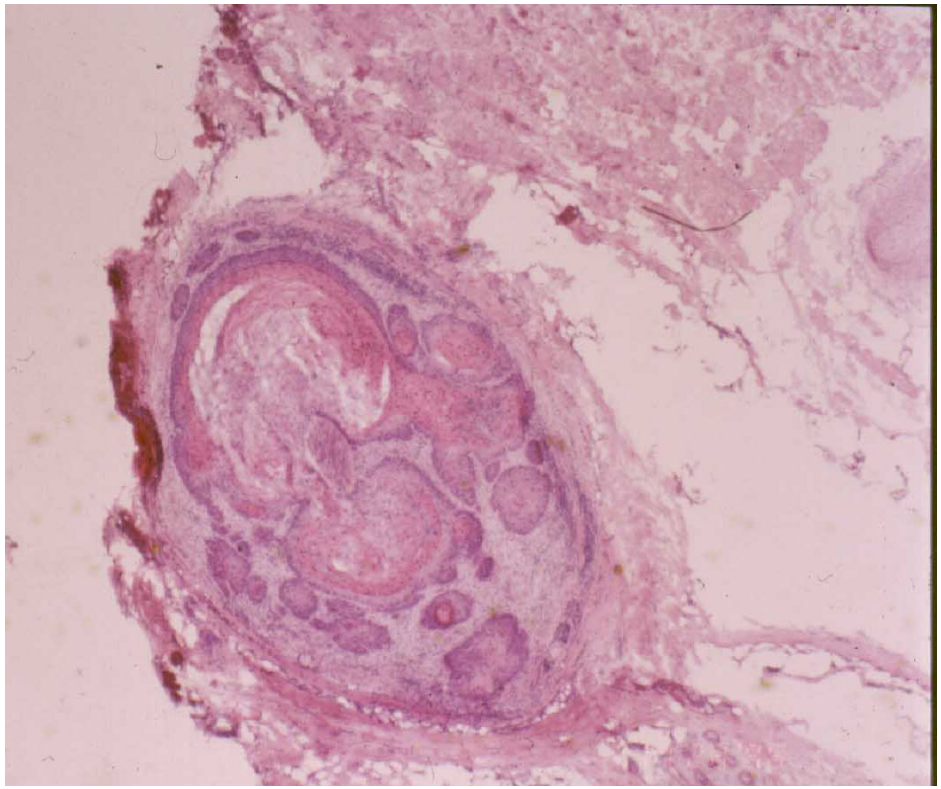
Perineural tumor invasion







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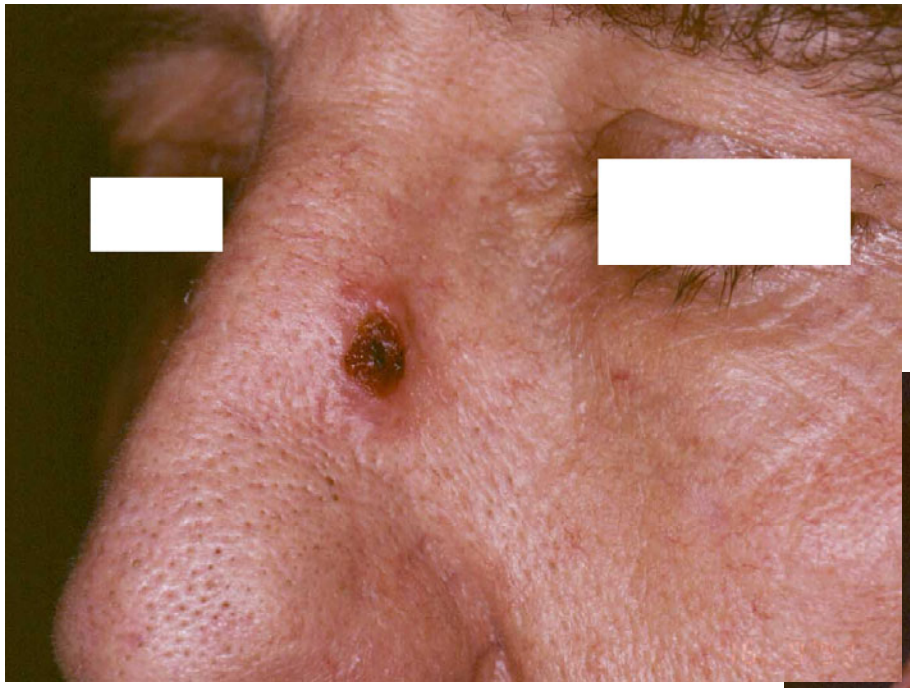
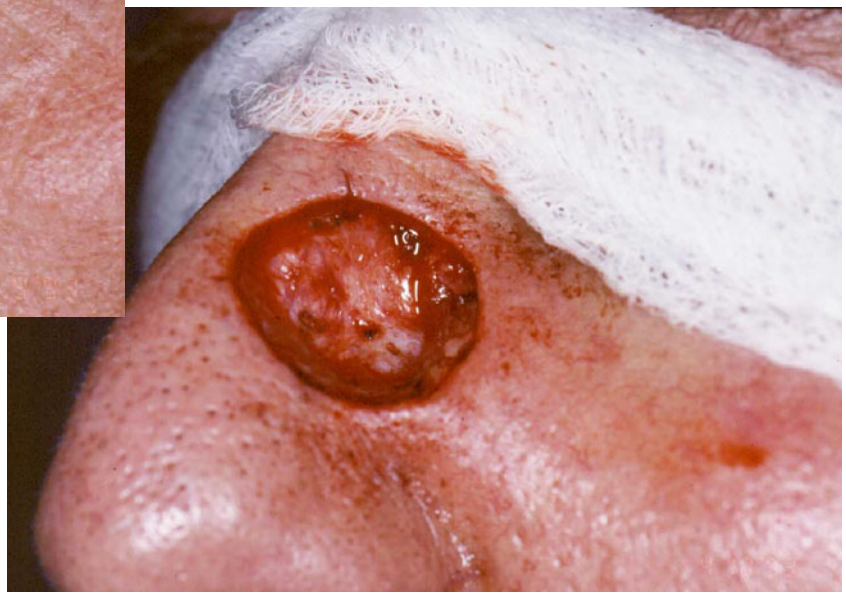
After Transplantation–Reduce Incidence of Skin Cancer

More aggressive growth patterns



Rapidly growing,
cyst-like appearance



Nasal location,
preauricular and
forehead

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After Transplantation–
Reduce Incidence of Skin Cancer

Mohs Surgery in Transplant Patients: How to define “Clear” margins?

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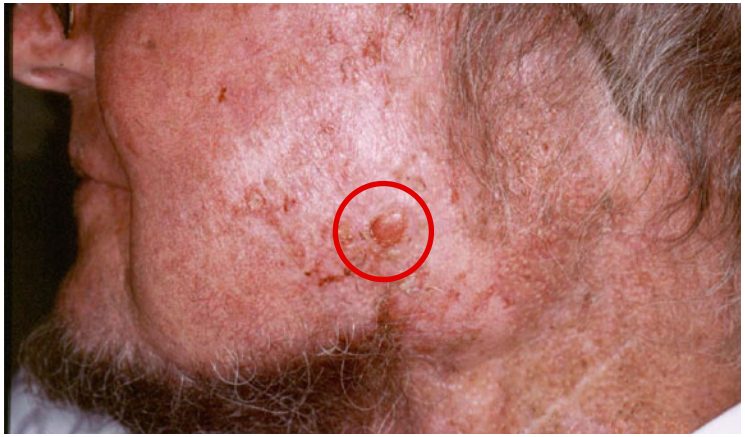
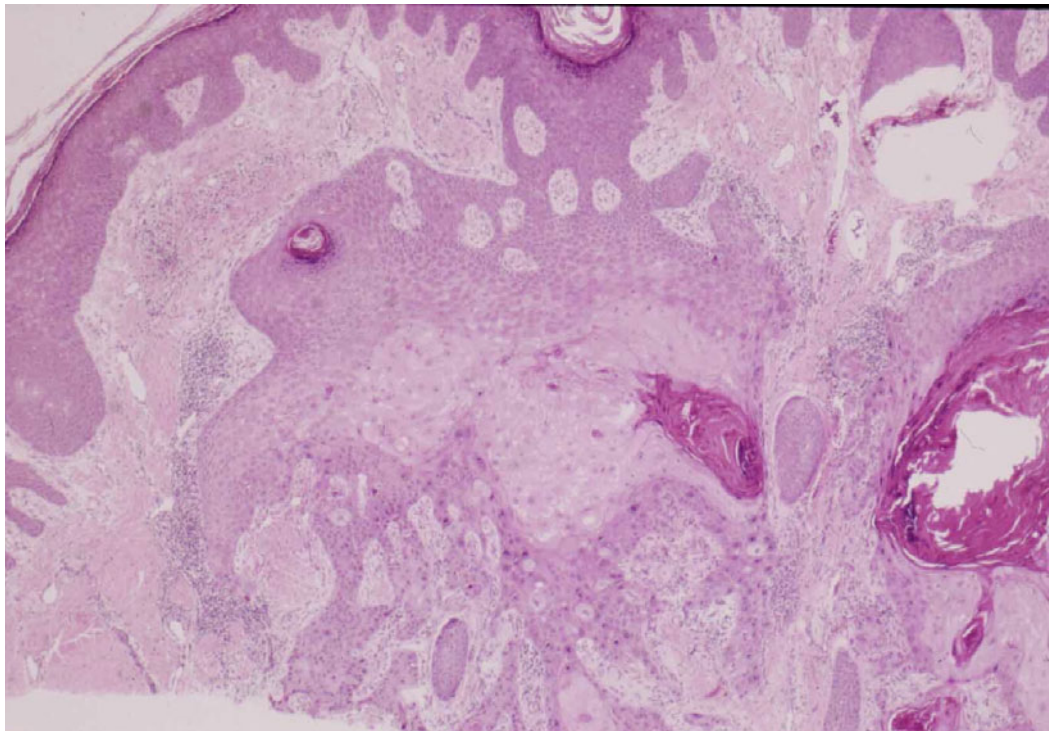
After Transplantation –
Reduce Incidence of Skin Cancer

Target lesion may be easy to define on frozen histology





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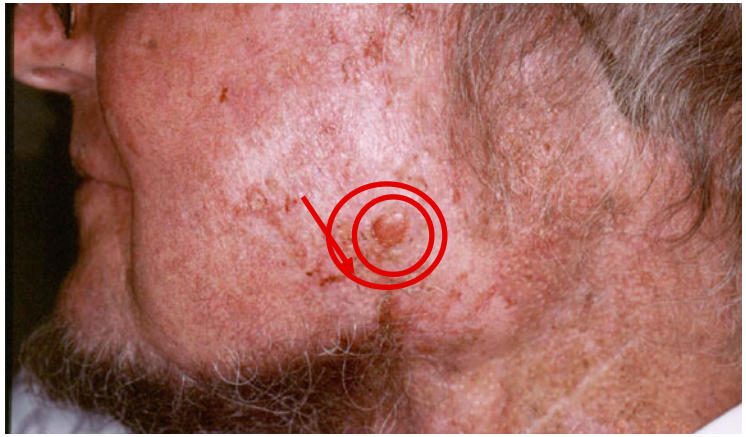
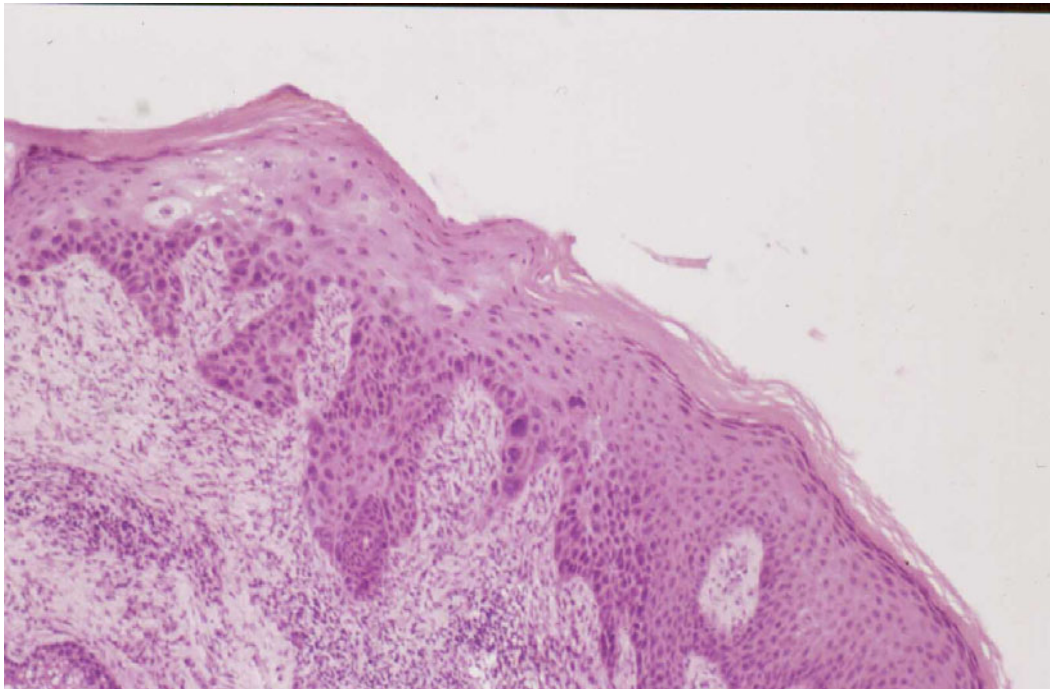
Skin margins may be difficult to determine





Additional lesions may be numerous and adjacent to to the treated lesion
Epidermal atypia can be diffuse and aggressive in appearance
Completely clear superficial margins may be difficult or impossible to obtain “Relatively” clear margins may need to be determined

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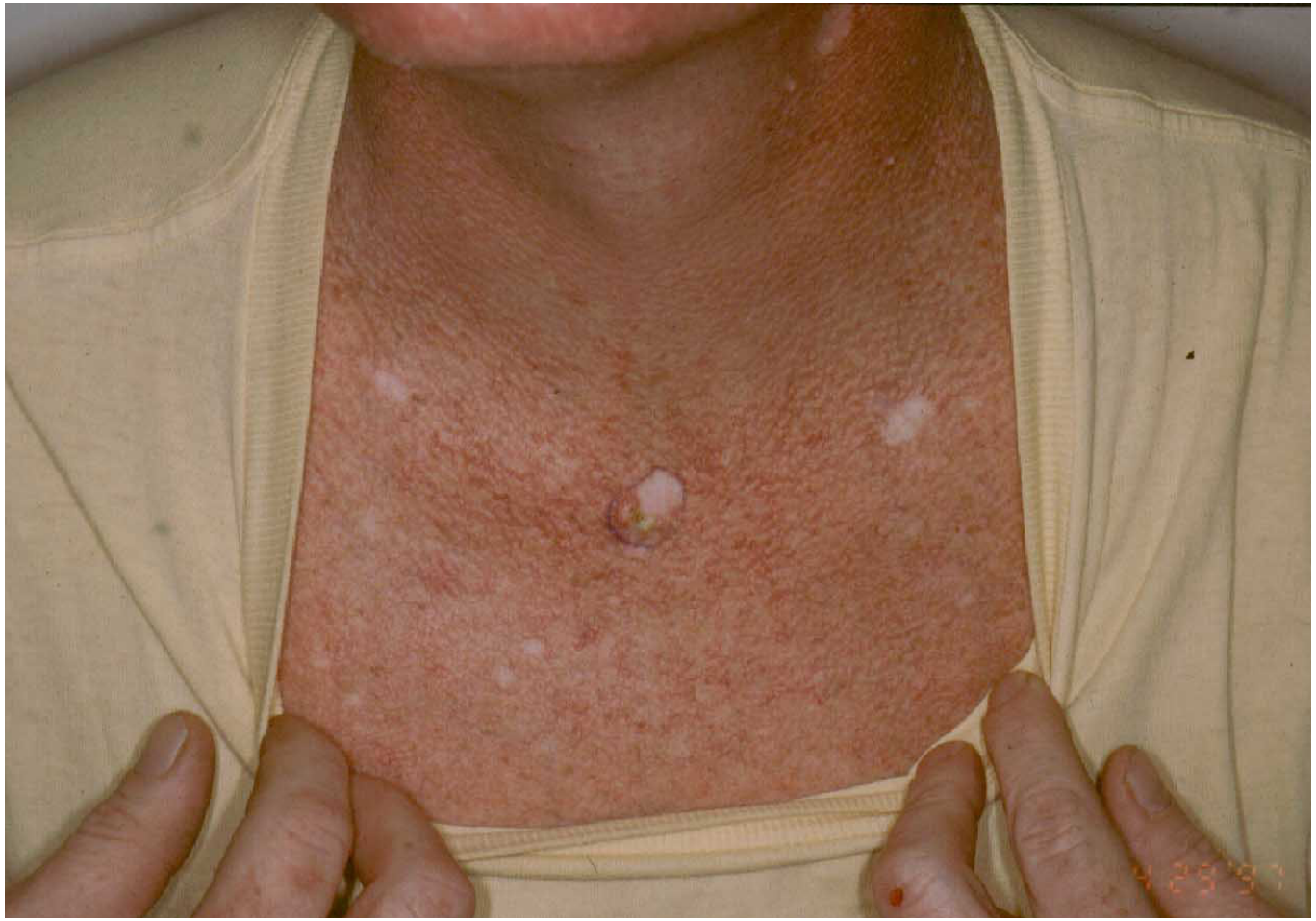
After Transplantation – Reduce Incidence of Skin Cancer

Clinical:
Recurrence After Previous Treatment



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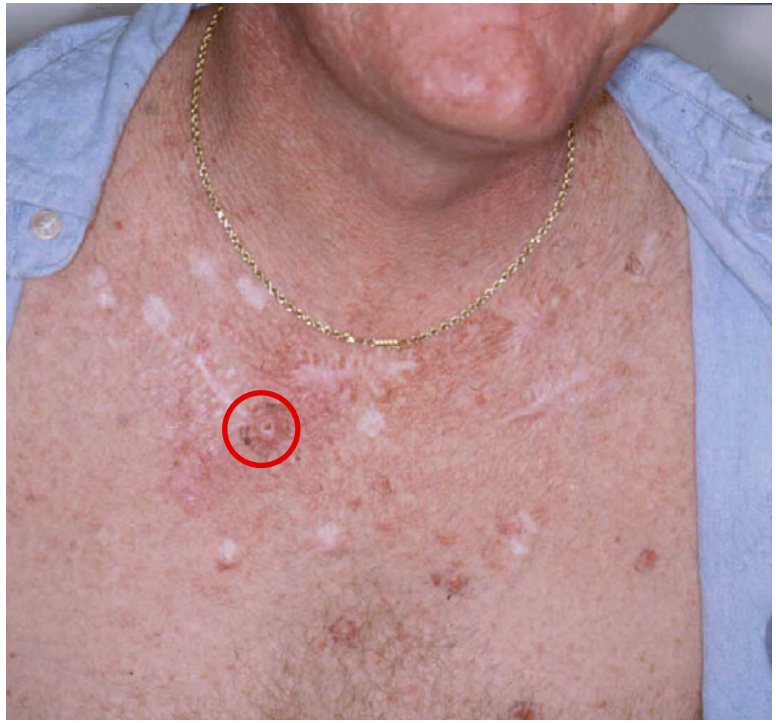
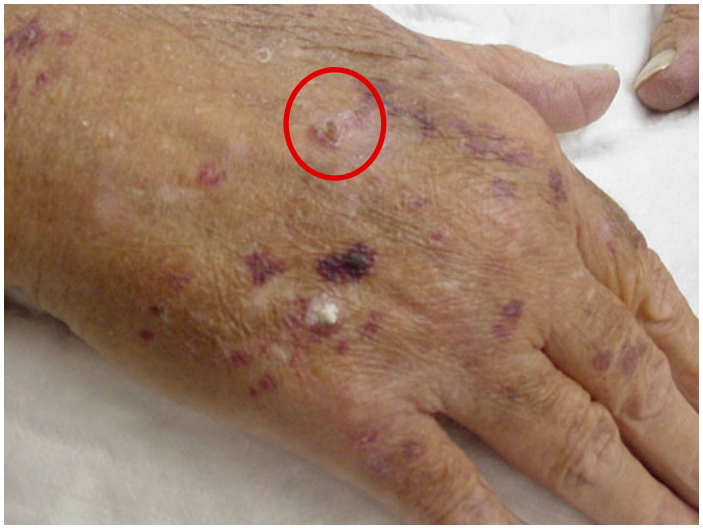
After Transplantation – Reduce Incidence of Skin Cancer

Recurrence rates

Patients may have hundreds of cutaneous premalignant and malignant lesions





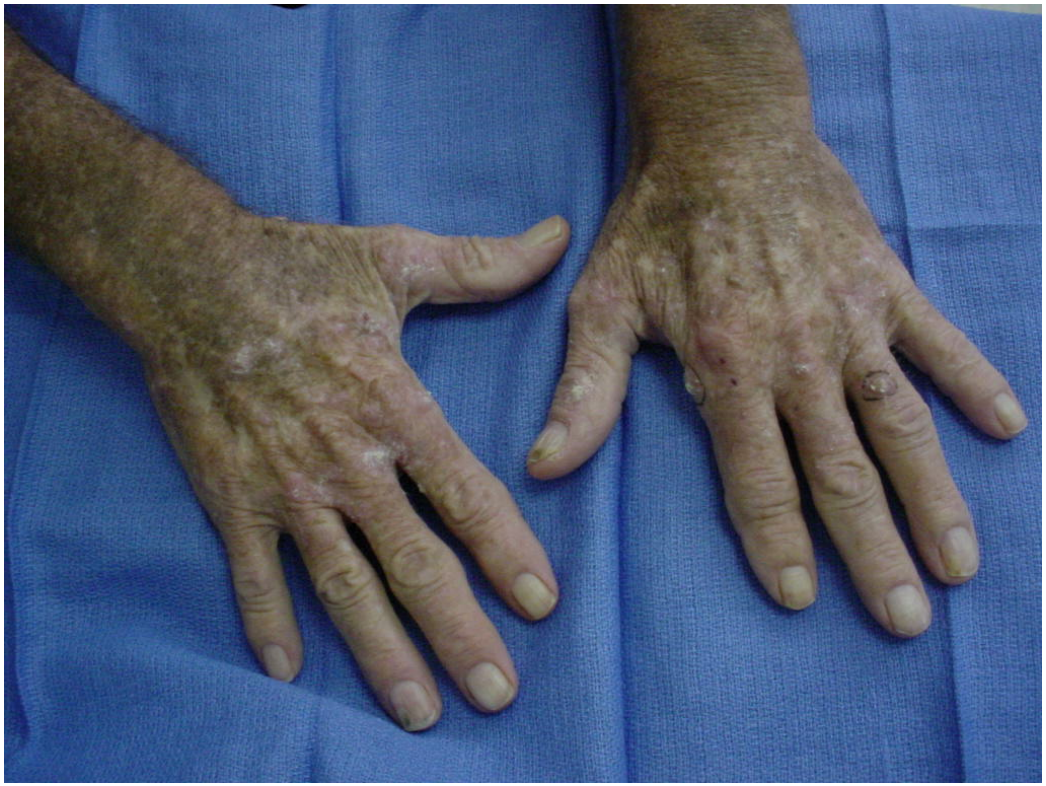
May be difficult or impossible to distinguish a recurrent lesion from a second primary

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

Special Situations: “Transplant Hand”

Dorsum of the hands and forearms – Dry and somewhat scaly skin

- Increased number of
  - verrucae
  - “actinic” keratoses
  - SCC



Blohme, et al. Skin lesions in renal transplant patients after 10-23 years of immunosuppressive therapy. Acta Derm Venereol 1990;70:491-494

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

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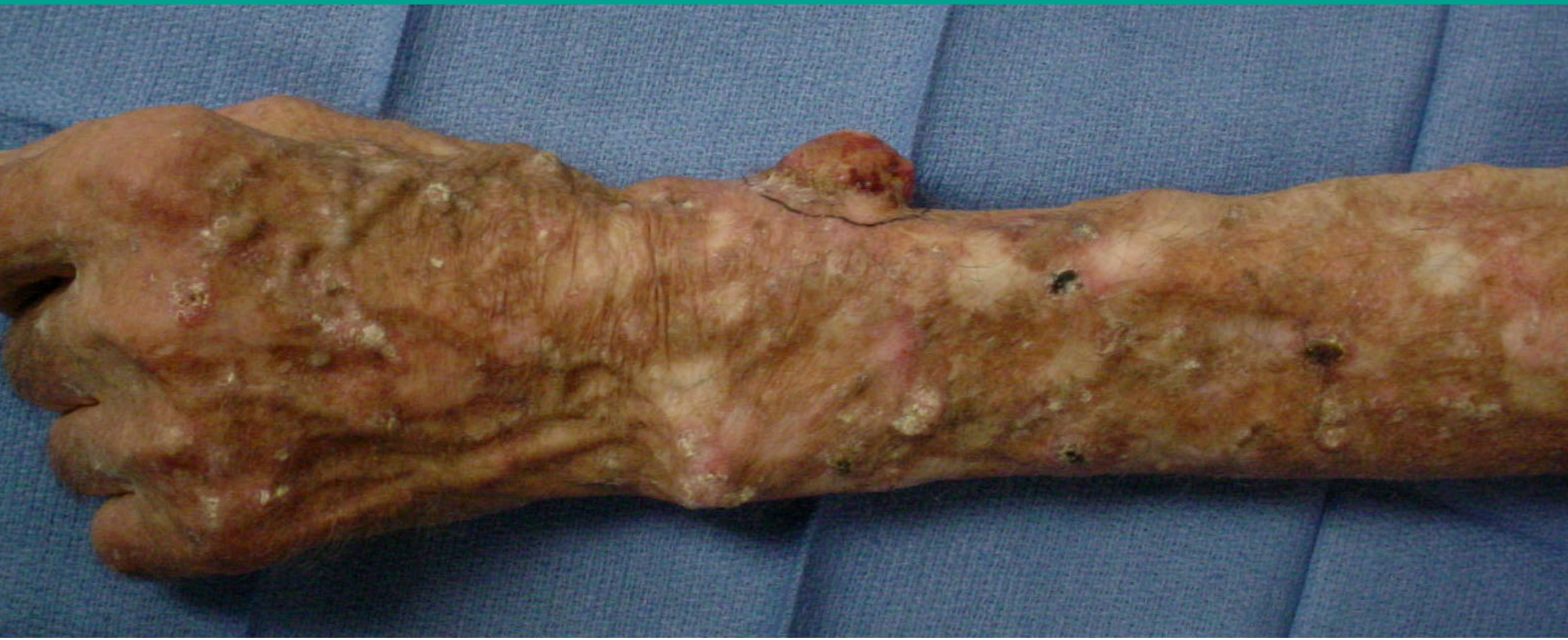

AT-RISC ALLIANCE

After Transplantation – Reduce Incidence of Skin Cancer

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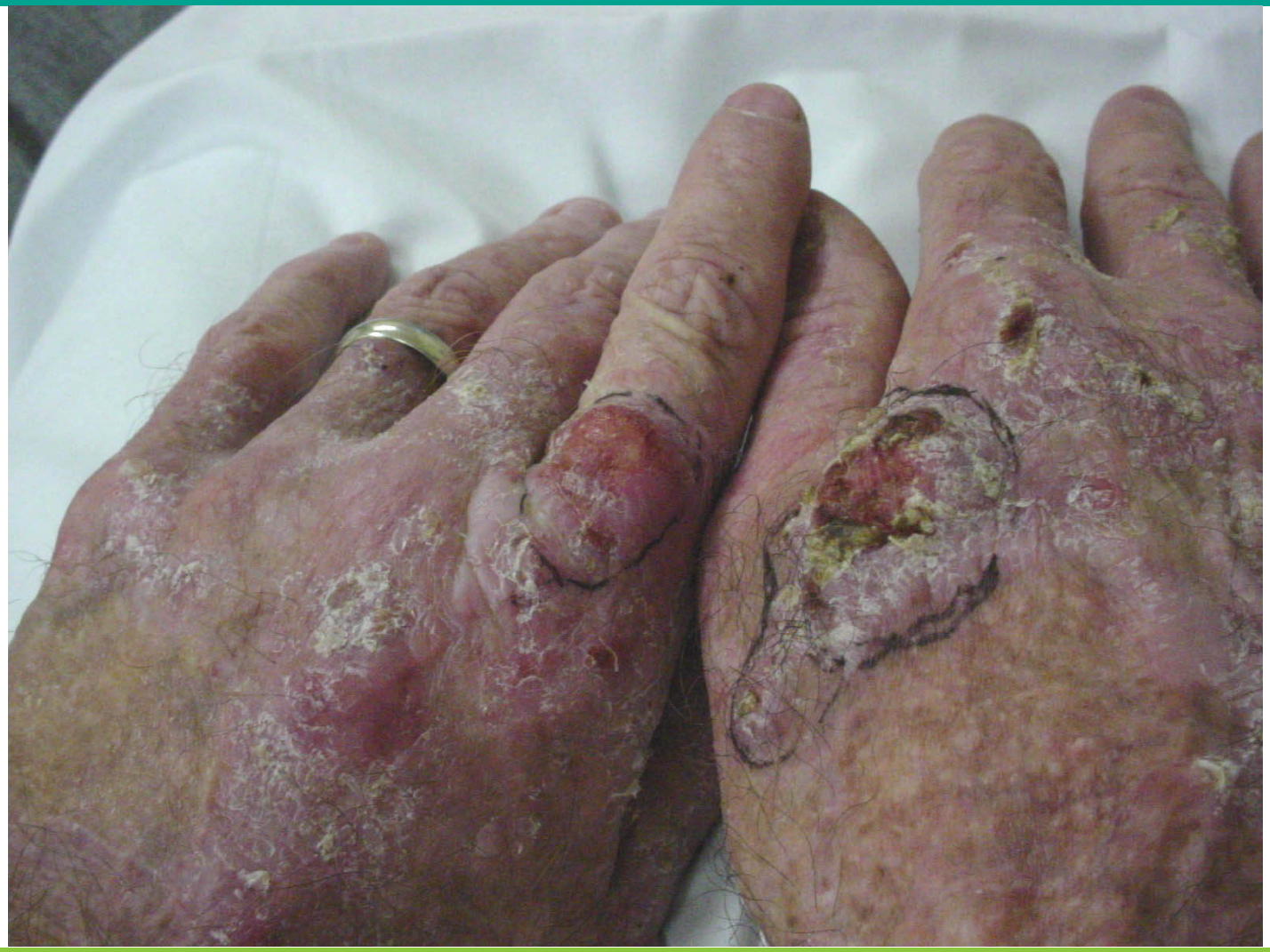

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After Transplantation – Reduce Incidence of Skin Cancer

Transplant Hand

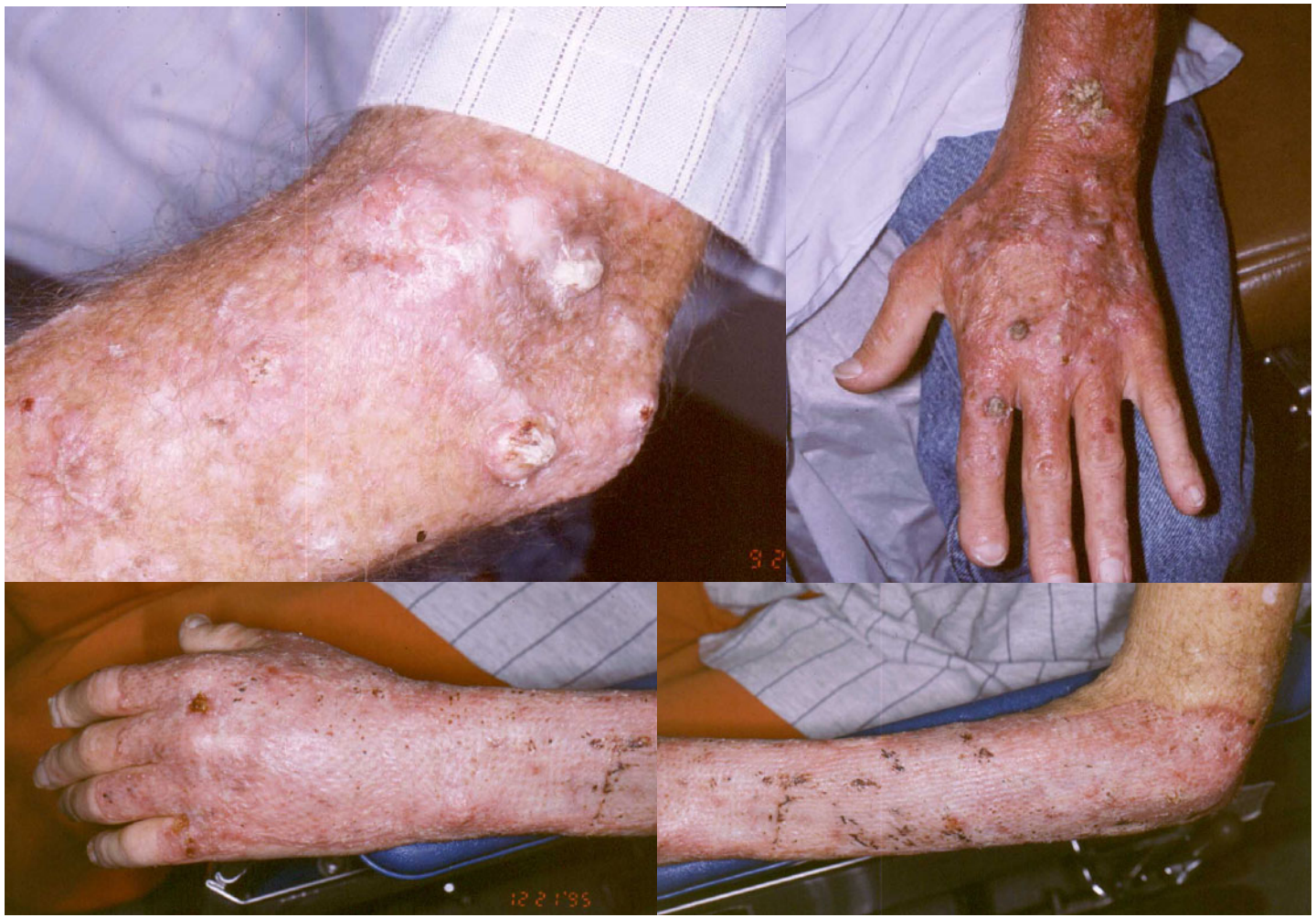
- Excision and grafting of entire back of hand
- 4 patients--no further SCC in 16 months*
- 11 patients--no further SCC--mean f/u 4.7 years#
- 14 patients since 1981--no recurrences°

*Glover, et al. Non-melanoma skin cancer in renal transplant recipients: the extent of the problem and a strategy for management. Br J Plast Surg 1994;47:86-89

#van Zuuren, et al. Resurfacing the back of the hand as treatment and prevention of multiple skin cancers in kidney transplant recipients. J. A. A. Dermatol 1994;31:760-764

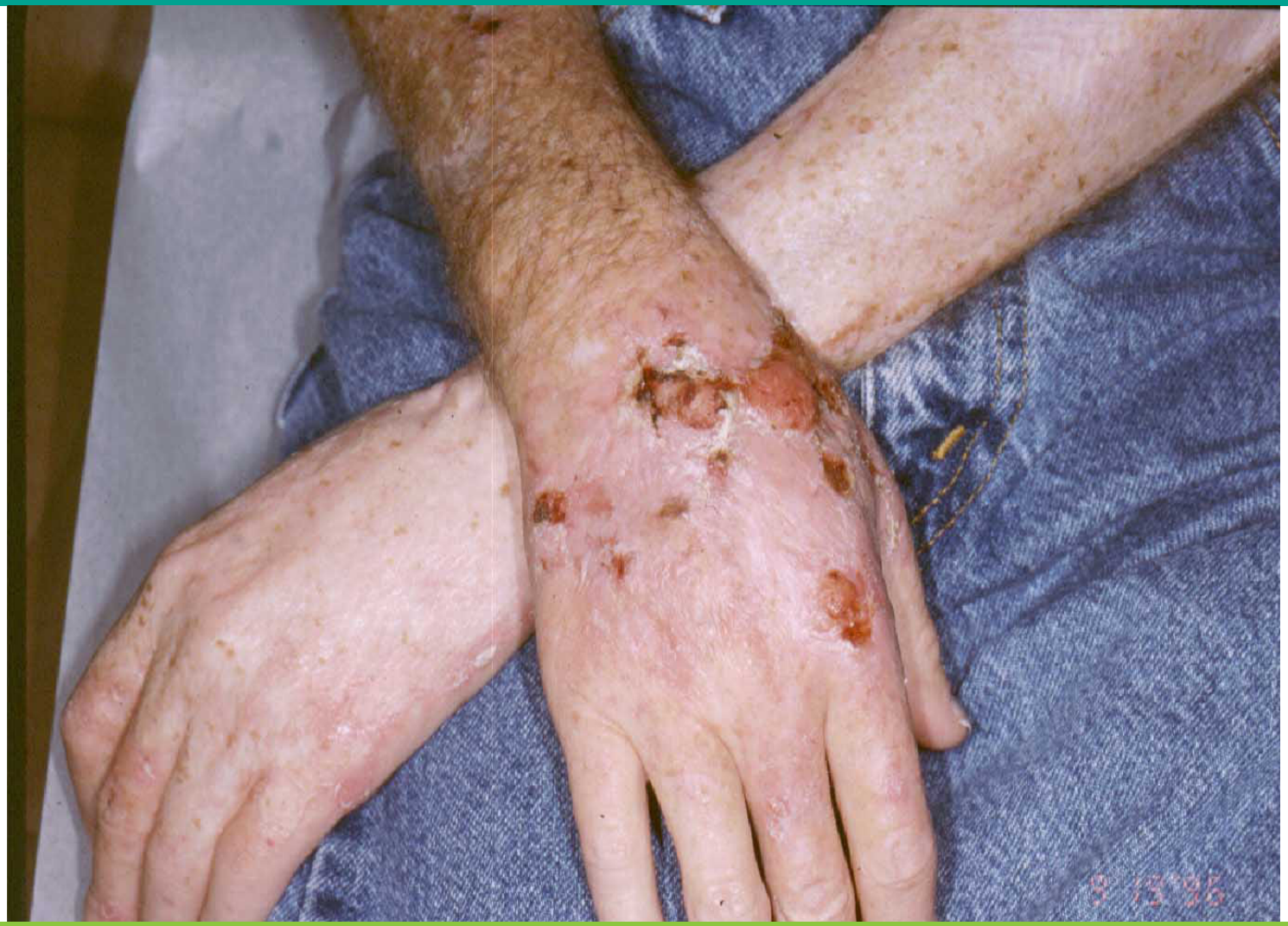
·Scholtens, et al. Treatment of recurrent squamous cell carcinoma of the hand in immunosuppressed patients. Journal of Hand Surgery, 1995:20.73-6

Transplant Hand
Treatment with excision and STSG



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

Transplant Hand
Treatment with excision and STSG



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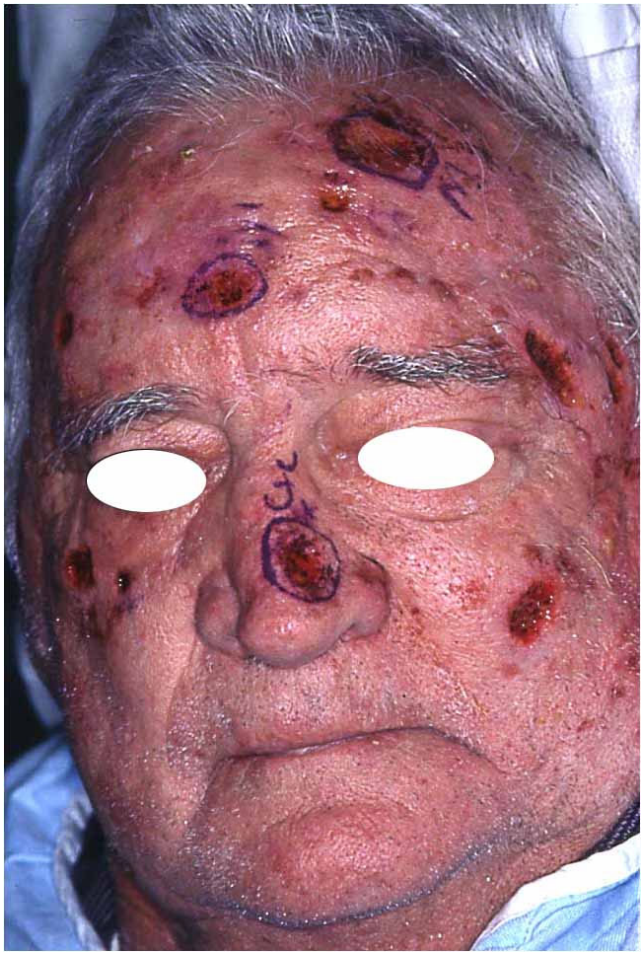
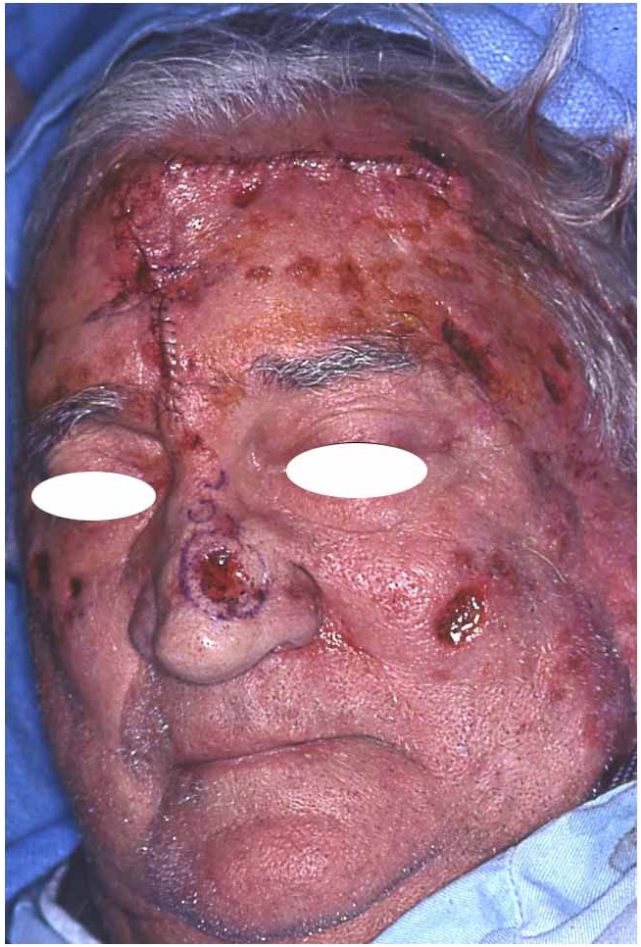
After Transplantation – Reduce Incidence of Skin Cancer

Special Situations: Multiple tumors may require multiple procedures at one setting





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

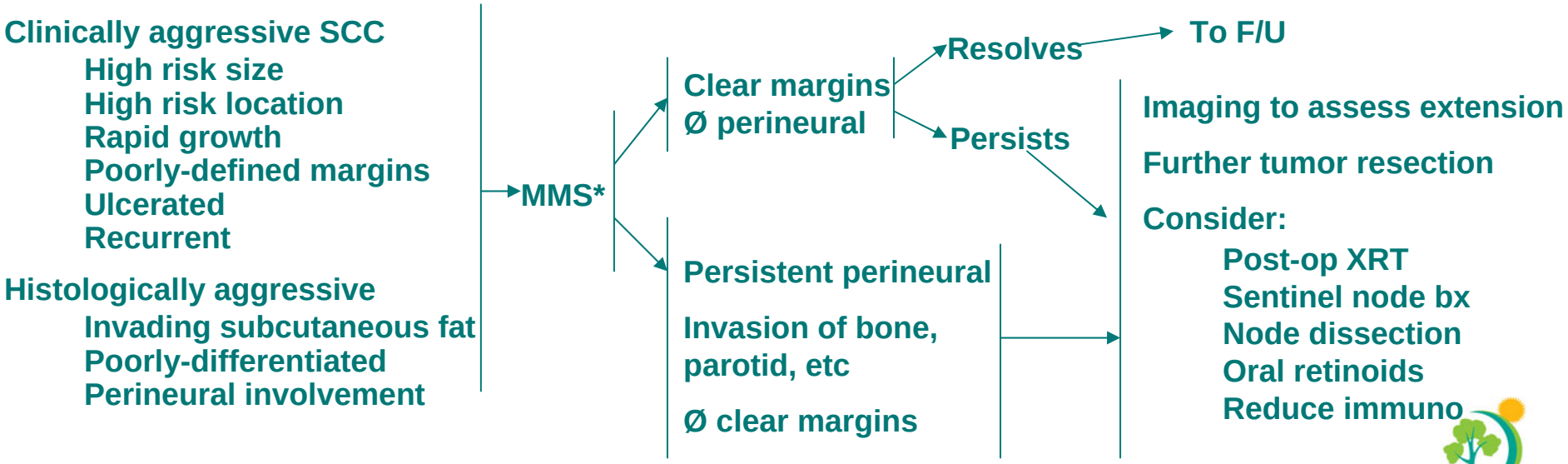
Therapy for High-Risk Patients

- Early and aggressive treatment is critical
  - Mohs' micrographic surgery
  - Surgical excision
  - Cryosurgery
  - Radiation therapy
  - ED&C
  - Possible adjuvant therapies
    - Systemic chemoprevention/suppression
    - Reduction of immunosuppression

Stasko T et al. *Dermatol Surg*. 2004;30(4 pt 2):642-650.
National Comprehensive Cancer Network. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nmsc.pdf. Accessed March 1, 2005.

Evaluation and Management of High-risk Squamous Cell Carcinoma

Aggressive SCC still confined to the skin and soft tissue in OTRs should be managed promptly with complete removal with excisional techniques. Additional modalities may be helpful in some situations.



*Or excision with margin control or primary radiation therapy in select situations

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After Transplantation – Reduce Incidence of Skin Cancer

Lymph Node Dissection

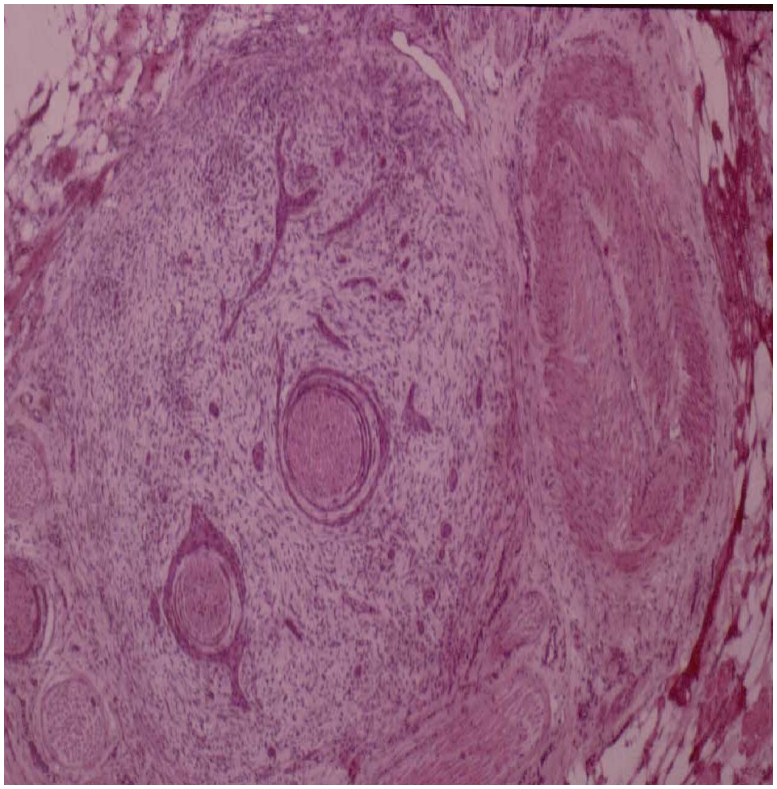
- No studies which document the role of LND in SCC in OTR
- Regard similar to non-OTR
  - No definitive studies/consensus as to the role of LND in SCC in non-OTR
  - Mounting evidence of the usefulness of SLN mapping and biopsy or FNA in head and neck SCC--rate of mets in ENT tumors is much higher

Lymph Node Dissection

- Palpable lymph nodes
  - Fine needle aspiration
  - Lymph node dissection
- Deep tumor in high risk areas
  - Consider CT/MRI to evaluate deep extension/nodes
  - Parotid and post-auricular areas
    - Consider node dissection with superficial/total parotidectomy

Radiation Therapy

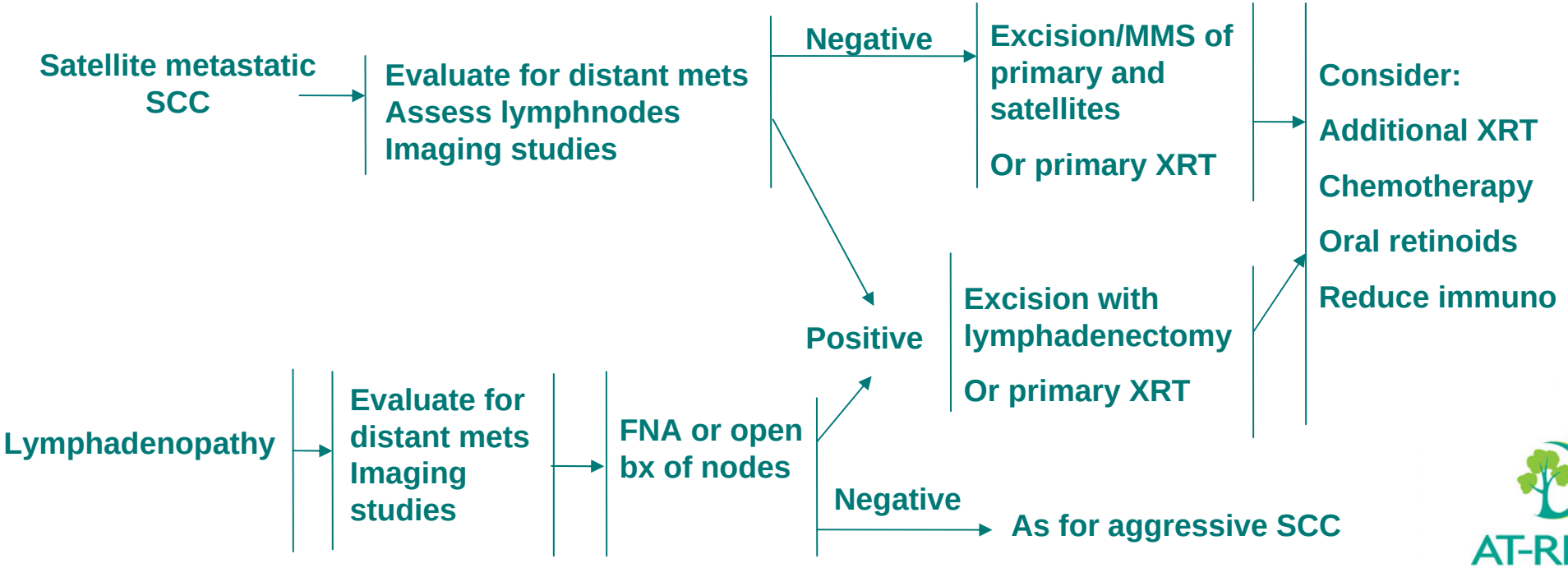
- Primary therapy
  - Rarely utilized
  - Non-surgical candidate
- Adjuvant therapy
  - Similar to non-OTR
    - Extensive lymph node involvement
    - Incomplete resection
    - Extensive perineural involvement



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

Evaluation and Management of Squamous Cell Carcinoma

- Satellite (in-transit cutaneous metastases) of SCC in OTRs require additional therapy and evaluation.
- OTRs with SCC and palpable lymphadenopathy or extensive tumor spread should be treated in the same manner as non-immunosuppressed patients with additional attention to reducing immunosuppression and chemoprophylaxis.



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After Transplantation – Reduce Incidence of Skin Cancer

Rationale for the Reduction of Immunosuppression

- 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

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After Transplantation – Reduce Incidence of Skin Cancer

Reduction of Immunosuppression for Transplant-Associated Skin Cancer: Rationale and Evidence of Efficacy

CLARK C. OTLEY, MD, AND SHERRY L. H. MARAGH, MD

Division of Dermatologic Surgery, Department of Dermatology, Mayo Clinic and Mayo School of Medicine, Rochester, Minnesota

BACKGROUND. Solid organ transplant recipients may develop numerous or life-threatening skin cancers. In addition to aggressive standard treatment of skin cancer, reduction of immunosuppression has been considered an adjuvant therapeutic strategy, albeit without direct proof of efficacy.

OBJECTIVE. To review the rationale for and evidence supporting the efficacy of reduction of immunosuppression for severe skin cancer in transplant recipients.

METHODS. Review of the literature regarding direct and indirect evidence on reduction of immunosuppression for transplant-associated skin cancer.

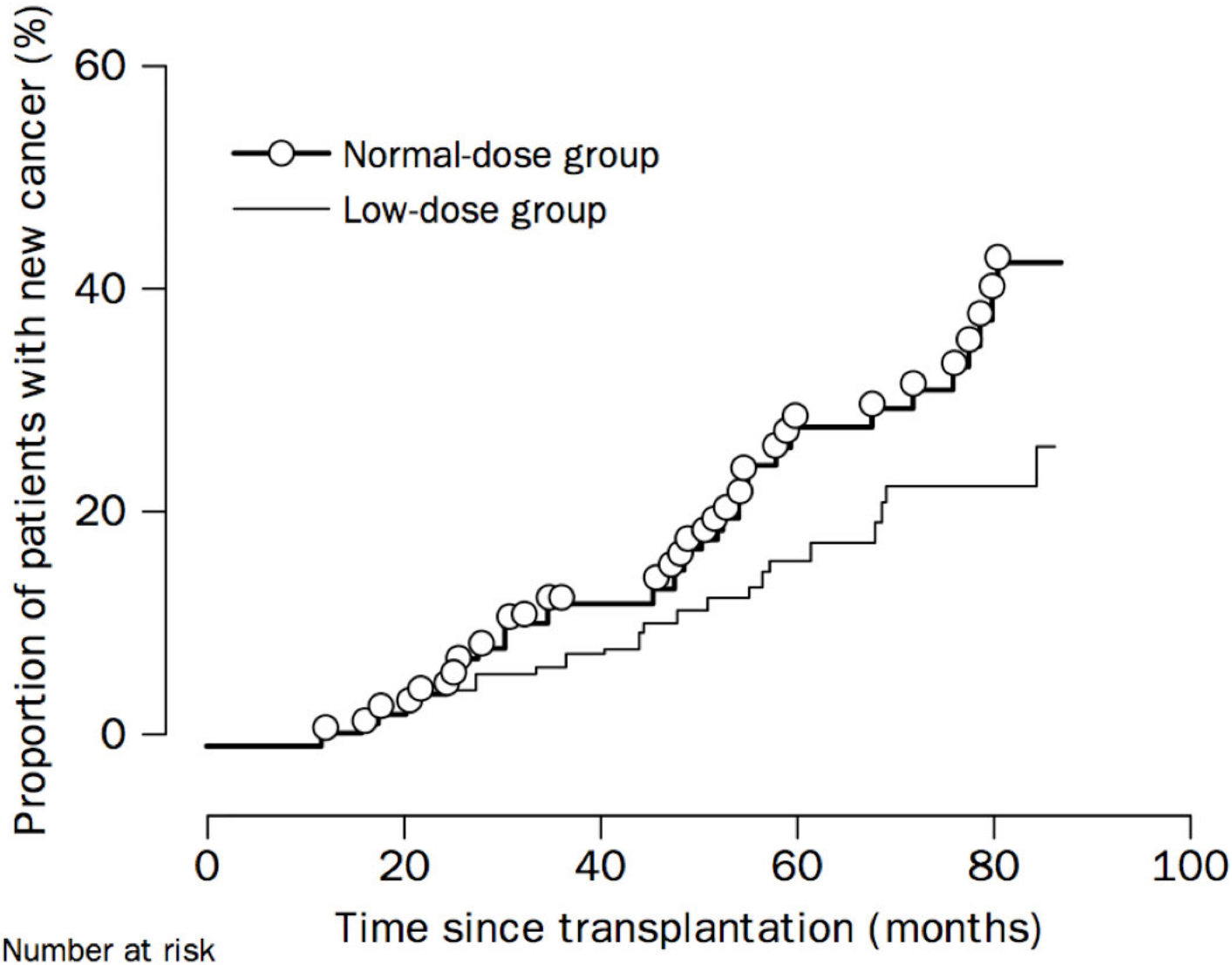
RESULTS. Although there are no randomized controlled trials of reduction of immunosuppression as a therapeutic intervention for transplant patients with skin cancer, multiple lines of evidence suggest that this strategy may be an effective adjuvant therapy. A randomized trial has demonstrated a lower incidence of skin cancer in transplant recipients after reduction of immunosuppression, albeit in a cohort not previously affected by skin cancer. Case series of reduction or cessation of immunosuppression demonstrate a lower incidence of skin cancer or improved outcomes of preexisting skin cancer. Lower overall immunosuppression is associated with a lower incidence of skin cancer. Multiple cancers affecting the skin have been shown to regress with reduction of immunosuppression.

CONCLUSIONS. Reduction of immunosuppression may be an effective adjuvant therapeutic strategy when confronting severe transplant-associated skin cancer. The risks of reduction of immunosuppression must be better defined, and randomized trials of this strategy are necessary.

Dermatol Surg 2005;31:163–168

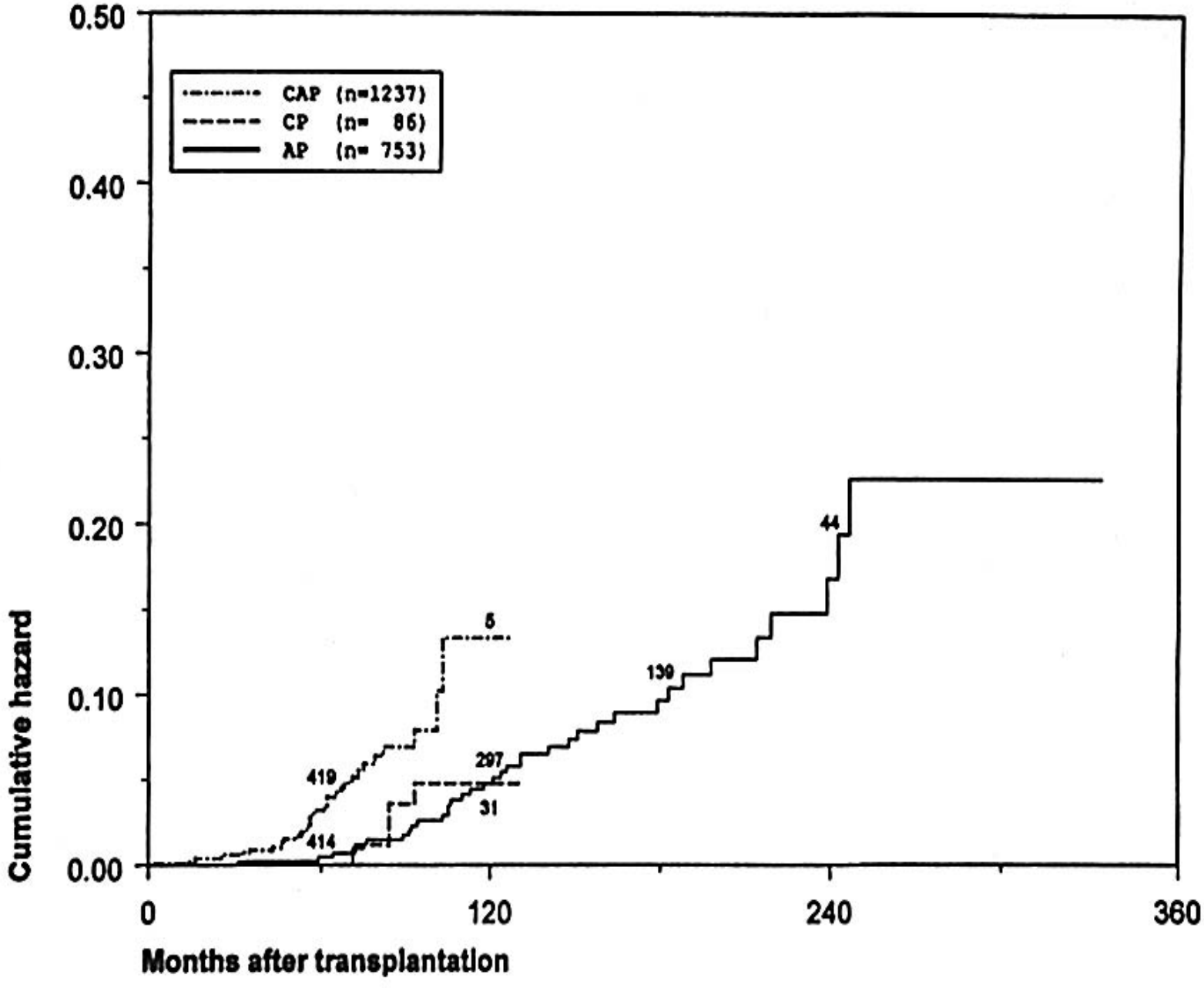
Evidence Supporting Reduction of Immunosuppression

- 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



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

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
419
414
297
31
139
44
6

Reduction or Cessation of Immunosuppression for Head-and-Neck SCC

- 9 OTR's with SCC--deeply invasive or metastatic
  - 5 patients no change in immunosuppression
    - All died from metastatic disease
    - All with functioning grafts
  - 4 patients with immunosuppression stopped or reduced
    - 1 died from metastatic disease (functioning graft)
    - 2 A&W w/o recurrence (functioning graft)
    - 1 A&W w/o recurrence (failed graft)

Moloney FJ, Kelly PO, Kay EW, et al. "Maintenance versus reduction of immunosuppression in renal transplant recipients with aggressive squamous cell carcinoma" Dermatol Surg 2004;30:674-678

Evidence Supporting Reduction of Immunosuppression

- Kaposi’s sarcoma regresses with RI
- PTLD regresses with RI
- Merkel cell carcinoma can regress with RI

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After Transplantation–Reduce Incidence of Skin Cancer

Support for the Reduction of Immunosuppression

Skin Cancer Scenarios – Transplant MD Opinion	Level of reduction of immunosuppression to consider		
	RENAL ALLOGRAF	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

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Candidates for reduction of immunosuppression

- Patients with a high risk(>20%) of metastasis from NMSC. Admittedly this risk is difficult to quantify.
- Patients developing many(5-10/year) NMSC.
- Patients with a high risk of melanoma or metastatic melanoma(>20%).
- Patients with Merkel cell carcinoma, atypical fibroxanthoma, malignant fibrous histiocytoma or Kaposi’s sarcoma.
- In combination with oral retinoids

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Reducing immunosuppression

- Dose reduction.
  - A simple gradual reduction of the overall amounts of immunosuppression may be helpful.
  - Done in small increments over a prolonged time course.
- Discontinuation of one or more immunosuppressive agents while maintaining immunosuppression with another agent.
  - Azathioprine.

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Reducing immunosuppression

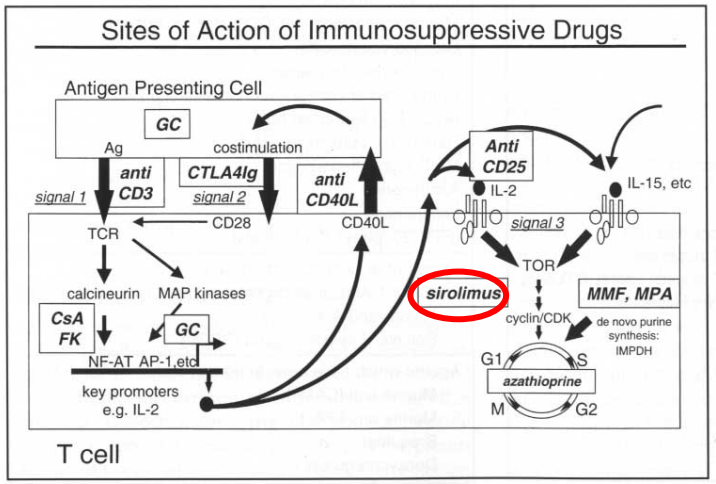
- Steroids seem to play little, if any, role in the development of skin cancers.
- Substitution of immunosuppressive agents.
- Mycophenolate mofetil for azathioprine
- Tacrolimus for cyclosporine

→For both -- an improvement if it allows for easier dosing and lower levels of immunosuppression

Sirolimus--Rapamycin--Rapamune

- Synergistic with cyclosporine(not a calcineurin inhibitor)
  - Used with cyclosporine in early trials
  - May be better in CsA sparing regimens
- Antiproliferative effects -- has been used in cardiac stents to prevent restenosis
- Induces permanent tolerance in some lab animals

Preliminary data suggests that introducing sirolimus with a reduction or cessation of cyclosporine may decrease the development of cancers.



Reducing immunosuppression

- In cases of severe morbidity or likely death from skin cancer, consideration can be given to withdrawing all immunosuppression.
  - Occasionally long-term liver transplant recipients can be weaned from all immunosuppression without adverse consequences.
  - Renal transplant patients can have immunosuppression withdrawn, but most will have graft failure and require dialysis.
  - Only the extraordinary cardiac transplant patient can survive without immunosuppression.

Reducing immunosuppression

- There is no reliable measure of adequate immunosuppression except organ rejection.
- Greatest risk for the development of rejection
  - First six months after transplantation,
  - Patients on cyclosporine or triple drug therapy.
- If rejection does develop during alterations of immunosuppression, it should be managed acutely with steroids and reintroduction or increased doses of other immunosuppressants.

Reducing immunosuppression

- Make changes in meds only through primary transplant physician
- Encourage transplant physician to reduce immunosuppression to lowest level possible in all patients at risk

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Chemoprophylaxis in Transplant Patients

Topical Retinoids, Acitretin and Isotretinoin

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Retinoids Mechanism of Action

- Growth arrest or apoptosis of tumor cells
- Arrests growth and replication of HPV
- Modulation of immune response
- Modulation of keratinocyte differentiation

De Graaf YGL et al. *Dermatol Surg.* 2004;30(4 pt 2):656-661.

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Topical retinoids provide modest benefit

- **0.05% tretinoin once daily**

  3 months--reduction in keratotic lesions compared to placebo (45% vs 23%)

  S. Euvrard, M. Verschoore, J. Touraine, et al. Topical retinoids for warts and keratoses in transplant recipients. Lancet, 1992:340.48

- **0.3% adapalene**

  6 months--decrease in Aks compared to placebo (32% vs 21%). No significant decrease with 0.1%

  Euvard S, Kanitkas J, Claudy A. Topical retinoids for the management of dysplastic epithelial lesions. In Skin Diseases after Organ Transplantation. Montrouge: John Libby Eurotext; 1998. P175-82

- **0.2% tretinoin (+/- calcipotriol)**

  6 weeks--no effect

  Smit JV, Cox S, Blokx WA, Actinic keratoses in renal transplant recipients do not improve with calcipotriol cream and all-trans retinoic acid cream as monotherapies or in combination during a 6-week treatment period. Br J Dermatol;147:816-8.

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

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All give a relative "holiday" while taking the drug in some patients, ie. fewer new lesions

- Acitretin--Double-blind study
  - 6 months--30mg per day
  - More than 10 keratotic skin lesions on the hands and forearms
- 2/19(11%) in treatment group developed 2 SCC's
- 9/19(47%) in placebo group developed 18 SCC's
- The effect was most pronounced in patients with a history of squamous cell carcinomas and basal cell carcinomas

J. N. Bavinck, L. M. Tieben, F. J. Van der Woude, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. Journal of Clinical Oncology, 1995:13.1933-8

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The effect and the rebound can be pronounced

4 patients, Etretinate 50mg per day

23 SCC	12 months before Tx
6 SCC	during Tx(8-13 months)
34 SCC	12 months after Tx

Kelly, et al. Retinoids to prevent skin cancer in organ transplant recipients. Lancet 1991;338:1407

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Many patients do not tolerate the side effects over long periods

Of 15 patients

- No significant systemic side effects
- 9 had cutaneous side effects — 5 decreased dose; 4 discontinued

Z. F. Yuan, A. Davis, K. Macdonald, et al. Use of acitretin for the skin complications in renal transplant recipients. New Zealand Medical Journal, 1995:108.255-6. Jun 28

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Table 4. Adverse Effects of Retinoids

Patient No.	Mucocutaneous Effects	Other Effects	Lipid Elevation		Lipid-Lowering Drug*	Retinoid Treatment Stopped or Reduced	Reason
			Pretreatment	Posttreatment			
1	Xerosis, alopecia	None	Yes	No	None	Stopped	Alopecia
2	Cheilitis, xerosis, pruritus, PPD, dry eyes	None	No	No	None	No	NA
3	Cheilitis, xerosis, epistaxis	Arthralgia	Yes	No	Pre	Reduced	Arthralgia
4	Cheilitis, xerosis	None	Yes	No	Pre	No	NA
5	None	None	Yes	Yes	Pre	No	NA
6	Cheilitis, xerosis, PPD	None	Yes	No	Pre	Reduced	Xerosis
7	None	None	No	No	None	No	NA
8	None	None	No	No	None	No	NA
9	Cheilitis, xerosis, PPD	None	No	No	None	No	NA
10	Cheilitis, xerosis	None	No	No	None	No	NA
11	Cheilitis, xerosis, PPD, nail fragility	None	Yes	No	Pre	No	NA
12	Cheilitis, xerosis, pruritus, PPD, alopecia	None	No	Yes	Post	Reduced	Itch
13	None	None	No	Yes	Post	No	NA
14	Cheilitis	None	Yes	No	Pre	No	NA
15	None	None	No	No	None	No	NA
16†	Cheilitis	Pseudoporphyria	Yes	No	Pre	Reduced	Pseudoporphyria
17	Cheilitis	None	Yes	Yes	Pre	Reduced	Lipids
18	Cheilitis, xerosis, PPD, dry eyes	None	No	No	None	No	NA
19	Cheilitis, xerosis, PPD	None	No	No	None	Reduced	Xerosis
20†	Cheilitis	None	No	No	None	No	NA
21	Cheilitis, dry eyes	None	Yes	Yes	Pre	No	NA
22	None	None	Yes	Yes	Diet	No	NA
23	Cheilitis	None	No	No	None	No	NA
24	Cheilitis, xerosis, pruritus, PPD, nail fragility	None	No	No	None	Reduced	Xerosis
25	Cheilitis	None	Yes	Yes	Post	Reduced	Lipids
26	Cheilitis, PPD	None	Yes	Yes	Post	No	NA
27	Cheilitis, PPD	None	Yes	Yes	Post	Reduced	Xerosis
28	Cheilitis	None	Yes	Yes	Post	No	NA

Retinoid Chemoprophylaxis

General Indications

- Numerous NMSCs per year (5-10/y)
- Innumerable actinic keratoses and multiple NMSCs
- Accelerating frequency of NMSCs
- Multiple NMSCs in high-risk locations (head and neck)
- Eruptive keratoacanthomas
- High-risk NMSC (>20% risk of metastasis)
- Metastatic NMSC
- In combination with a reduction in immunosuppression

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Dosage-Acitretin

- Response and side-effects are dose dependent
- Low/Slow may decrease side-effects
  - Start at 10mg/day (or 10mg qOD)
  - Advance by 10mg increments at 2-4 week intervals to desired effect
  - Manage mucocutaneous side-effects aggressively
  - Target dose: 20-25 mg/day
  - Some may tolerate only average of 10-15 mg/day
  - A few will tolerate 35-50 mg/day
- Some may develop “tolerance” after having been at a suppressive level--require increased dose, tolerate increased dose

Labs

- Monthly until stable, then at least every 3 months.
- Elevated lipids may require statins(or gemfibrozil)
  - Many patients are on them already.
- Bone density measurements--usually already being done by primary transplant physician.

Table 5. Routine Monitoring During Use of Retinoids

Time point	History	Physical examination	Lipids	LFTs	Hepatitis screen	Creatinine	Glucose	Urinalysis	CBC count	Spine radiography
Baseline	X	X	X	X	X	X	X	X	X	
2-4 wk	X	X	X	X		X†				
8 wk	X	X	X	X		X†				
12 wk	X	X	X	X		X†				
16 wk	X	X	X	X		X†				
Every 3 mo	X	X	X	X		X†				
Periodically as indicated	X	X	X	X		X	X	X	X	X

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Acitretin: Management of Lab Abnormalities — Hyperlipidemia

- Important to recognize and treat due to accelerated atherosclerosis in transplant recipients

Hypercholesterolemia	Repeat labs
	Prescribe statins
	Very effective
Hypertriglyceridemia	Repeat labs/fasting/no alcohol
	Prescribe gemfibrozil
	Lower dose for pancreatitis

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Acitretin: Management of Lab Abnormalities — LFT Elevations

- Discontinue other hepatotoxic agents (acetaminophen, ethanol)
- Check for hepatitis

Minor LFT elevation	Repeat labs
	Discontinue alcohol
	Lower dose
Elevation greater than 3x normal	Discontinue
	Repeat labs
	Consult hepatologist

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Acitretin: Mucocutaneous AE Prevention and Management

- Mucocutaneous effects: cheilitis, dry skin and hair loss may cause many discontinuations
- Early preventive management
  - Use emollients frequently from start of low-dose therapy
  - Apply Aquaphor® or petrolatum to lips 5 to 10 times daily and inside nares at bedtime
  - Moisturizing soap with tepid showers/baths
  - Artificial tears; avoid contact lenses
  - Consider decreasing dose by 25% for severe mucocutaneous AEs
- Hair loss can be a problem at higher doses

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Acitretin: Other AEs

- Arthralgia or myalgia
  - 25% dose reduction until resolved
- Myalgias
  - Dose reduction can be effective
- Arthralgias
  - Consider bone x-rays, but correlation of calcifications and symptoms poor

Retinoids

Rebound

- Will occur in all patients
- Plan on long-term/life-long therapy

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Retinoids

- Sencar mouse model
- Retinoic acid reduced the yield of papillomas and carcinomas
- After cessation of retinoic acid and reappliction of TPA the number of papillomas increased 2X
- Papillomas evolving during retinoic acid treatment exhibited a phenotype of high progression risk

Tennenbaum, T. et al. Topical retinoic acid reduces skin papilloma formation but resistant papillomas are at high risk for malignant conversion. Cancer Research. 1998(58): p. 1435-1443.

Retinoids

- Acitretin improves actinic keratoses via alteration of keratinization
- No effect on proliferation
  - May explain rebound
  - May explain the progression of some lesions

Smit, et.al J Am Acad Dermatol 2004;50:189-96

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Retinoid Safety

- Skin cancer chemoprophylaxis is not an FDA approved indication
- Warnings for use in females of childbearing potential
  - Only for nonpregnant women who are severely affected by NMSC and are unresponsive to other therapies or when there is no other therapy that may be used
  - 2 negative pregnancy tests before beginning treatment
  - 2 forms of contraception for at least one month prior to starting acitretin, during therapy, and for at least 3 years after discontinuing therapy
    - Not microdosed progestin

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Retinoids in transplant patients

- Isotretinoin
  - Reduces natural killer cell activity and number
- Etretinate
  - Increases natural killer cell activity and number
- Natural killer cells are involved in the initial phase of organ rejection. Suggests that isotretinoin is safer, particularly in the immediate post-transplant
- Small studies have shown no signs of increased chronic rejection with either drug

McKerrow, et al. The effect of oral retinoid therapy on the normal human immune system. B. J. Dermatol 1988;119:313-320

Risks of Chronic Retinoids

- Most patients will see you 5-10 years post graft
- There are no long-term safety studies with regards to graft survival

Organ and Survival Type		Follow-up Period				
		3 Months	1 Year	3 Years	5 Years	10 Years
Kidney: Deceased Donor	Graft Survival	93.9%	88.7%	78.4%	65.7%	36.4%
	Patient Survival	97.5%	94.2%	88.4%	80.7%	57.9%
Kidney: Living Donor	Graft Survival	96.8%	94.3%	87.7%	78.6%	55.2%
	Patient Survival	99.0%	97.5%	94.5%	90.1%	77.4%

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Retinoids

- **Coordinate all care with the primary transplant physician**

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

- Depends on specifics of cancer
- Provide the transplant team with available validated prognostic factors
- Accentuation of risk by immunosuppression is poorly quantified
- No clear data for re-transplantation in recipients already developing NMSC

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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

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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 car of organ transplant recipients at risk for skin cancer. Dermatol Surg 26;7: July 2000

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Role of Dermatologists in the Long-term Care of OTRs

- Repetitive education about importance of sun protection
- Implement preventive treatments to decrease future skin cancer formation
- Early recognition and treatment of skin cancers
- Work with transplant team in caring for patients with life threatening skin cancers

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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)

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