Non-Melanoma Cutaneous Malignancies

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No Related Financial Disclosures

or

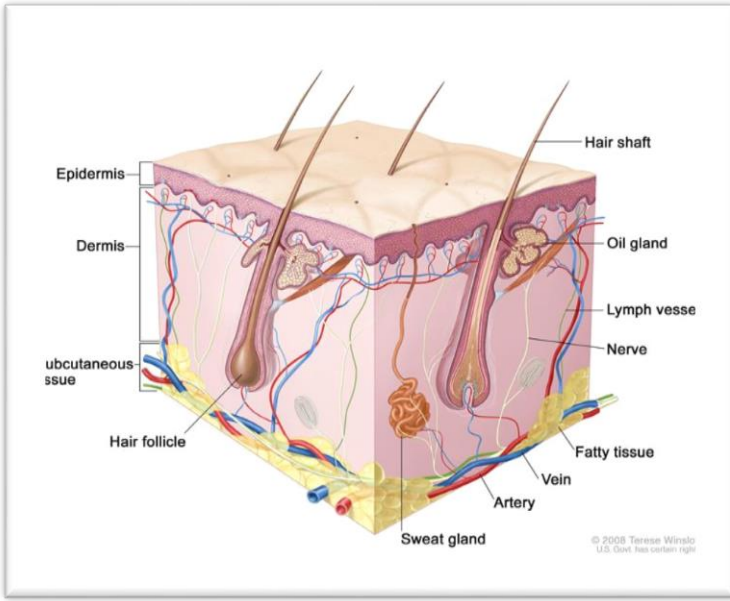
Conflicts of Interest

The Changing Face of Skin Cancer

The Changing Face of Skin Cancer

Overview

- Skin Cancer Epidemiology
  - Cost
  - Tanning Booths

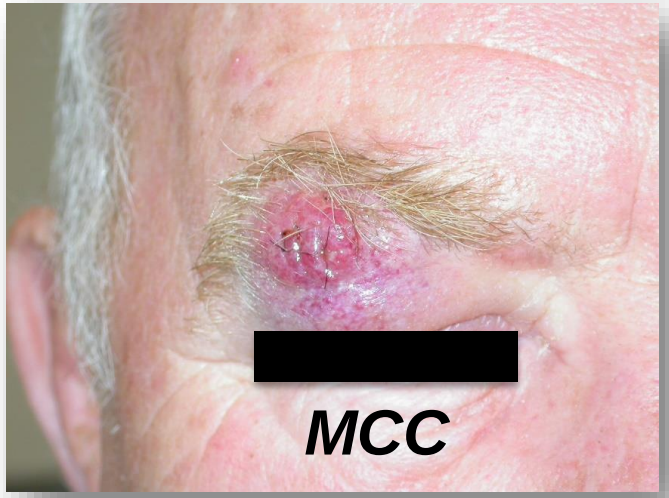


- Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (cSCC)
- Merkel Cell Carcinoma (MCC)

Non-Melanoma Skin Ca (NMSC)

> 80 different histologic types

- **Basal Cell Carcinoma (70 - 75%)**
- **Squamous Cell Ca (20%)**
- **Merkel Cell Ca (5%)**



NMSC incidence

- **BCC**
  - **Most common cancer**
  - **2.8 million cases year**
- **SCC**
  - **700,000 cases per year**
  - **Incidence increased 200% over past 30 yrs**
    (Karia PS, et al. J Am Acad Derm. 2013; 68(6):957)
- **40 – 50% Americans will have at least one SCC or BCC by age 65** *(NCI Cancer Trends 2009/2010)*

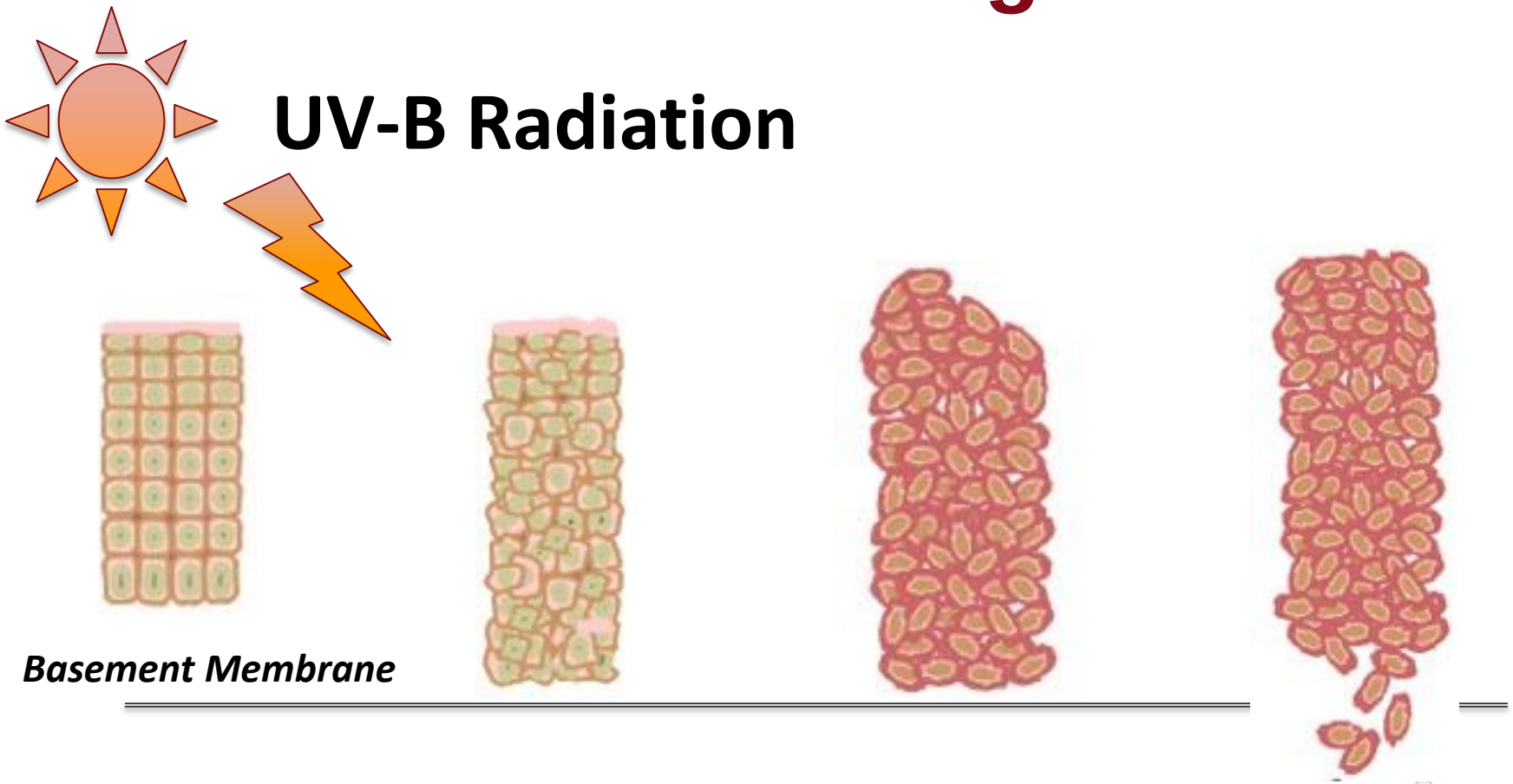
Non-Melanoma Skin Cancer *(NMSC)*

- **Overall excellent prognosis**
  90% 5-yr overall survival

- **Subset of aggressive NMSC**
  10% locally recurrent
  3-5% regional metastasis
  2,500 deaths per year

- **Prospective NMSC registries generally lacking**

cSCC Tumor Progression



Tanning Booths

- **Ultraviolet Radiation (UVR) = Carcinogen**

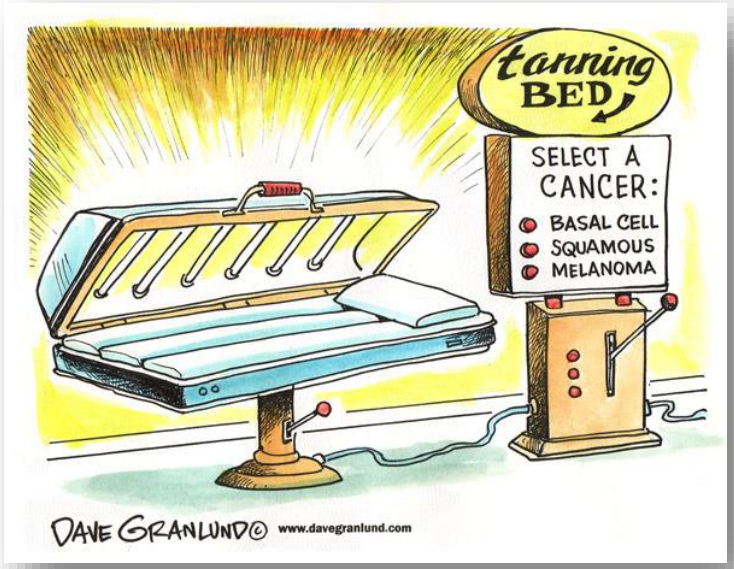
  Exceeds risk of Lung CA from smoking
- **1,957 ER visits from tanning bed burns**

- **Skin cancers from Tanning Beds**

  245,000 ~ BCC

  168,000 ~ SCC

  6,200 ~ Melanoma



Wehner M et al. JAMA Dermatol 2014; 150(4):390.

Tanning Booths

- **21 yr old: Tanned 4-5 times per wk**
- **1 tanning session**

  SCC risk increases 67%

  BCC risk increases 29%

  Melanoma risk inc. 75%
- **Outlawed in Brazil, Australia, and New South Wales**

http://www.skincancer.org/news/tanning/facebook

Circa 1947

Circa 1960

Coin dropped in slot . . . . . turns on sun lamp . . .

Skin Cancer Healthcare Costs

$8.1 Billion Dollars per year

$4.8 Billion NMSC

$3.3 Billion Melanoma

Guy GP, et al. Am J Prev Med. 2014; 104(4):e69.

I. Management of the Basal Cell Carcinoma (BCC)

BCC/SCC: Risk Stratification

	LOW RISK	HIGH RISK
Location/Size	< 20mm L Zone	≥ 20mm L Zone
	< 10mm M Zone	≥ 10mm M Zone
	< 6mm H Zone	≥ 6mm H Zone
Borders	Well Defined	Poorly Defined
History	Primary Tumor	Recurrent Tumor
Immunosuppression	No	Yes
Prior Radiation	No	Yes
Pathology		BCC: micronodular; infiltrative; sclerosing; morpheophorm
		SCC: adenoid; adenosquamous;desmoplastic
Perinerual /Vascular Invasion	No	Yes

Work-up: BCCA

- **Complete history & physical**

  Full body exam

- **Biopsy**

  If more than superficial, inclusion of deep reticular dermis preferred

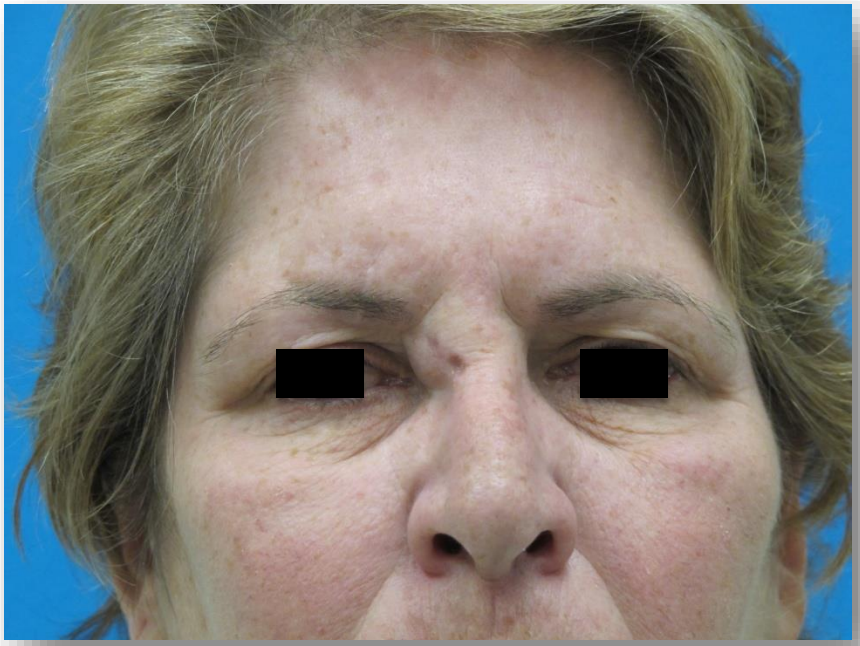
- **Imaging studies as indicated for extensive disease**

High Risk BCC Treatment

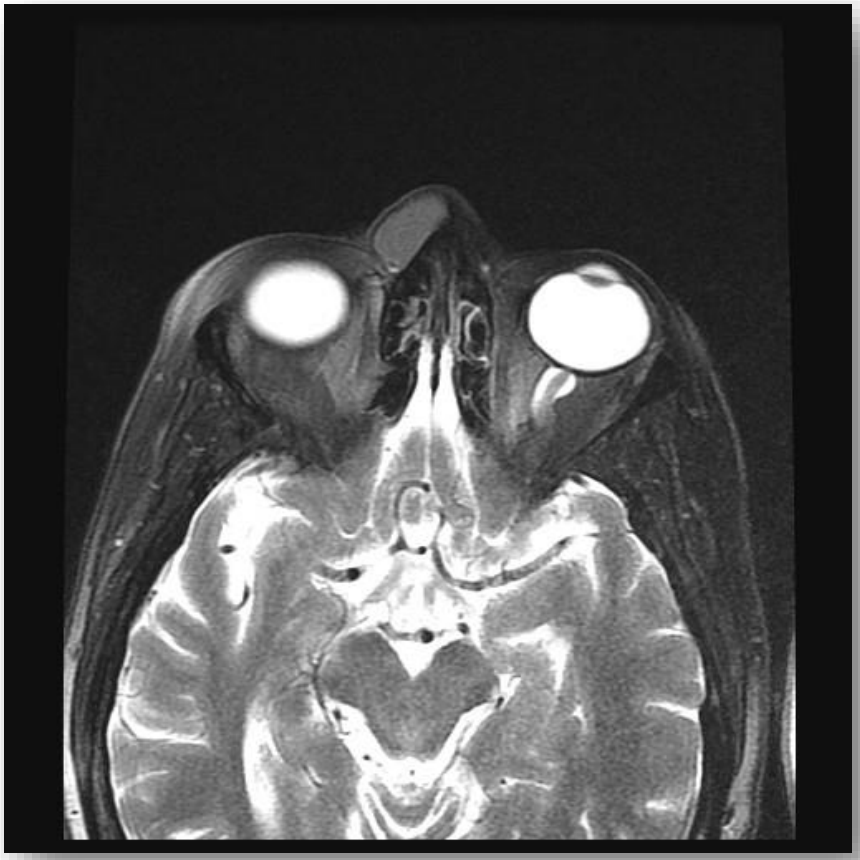
High-Risk

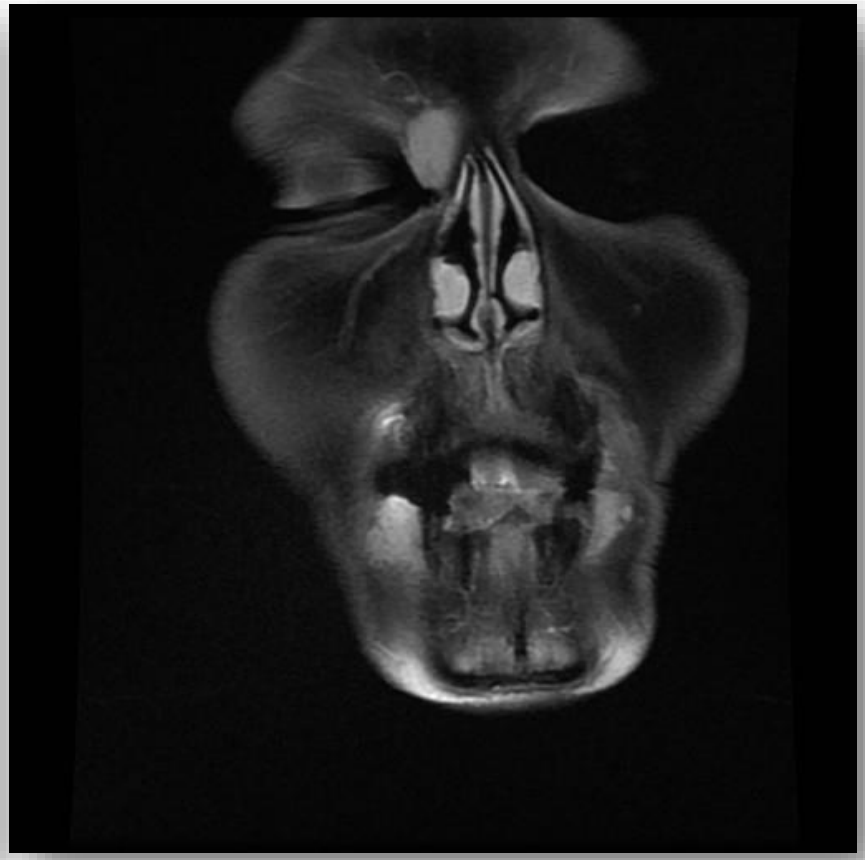
- Primary Excision (1 cm margin)
- MOHS
- Primary XRT – for Non-surgical Candidates
- Systemic Therapy – also not an XRT Candidate

I. Management of the Basal Cell Carcinoma (BCC)

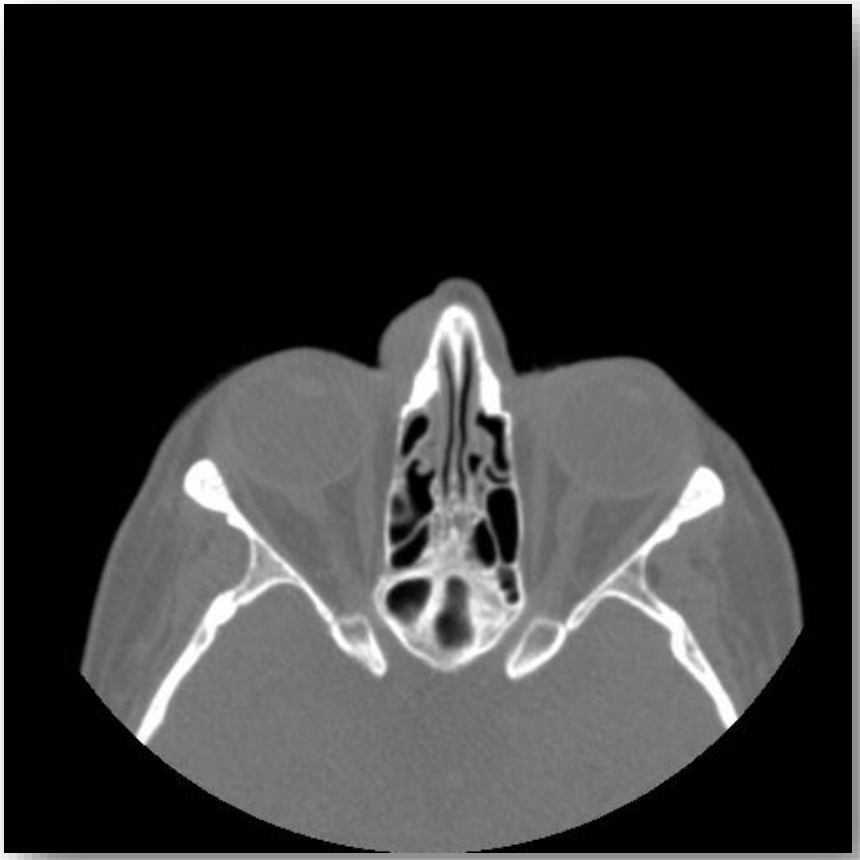


BCC: MRI – T2





BCC: CT Orbit



S/P MOHS: All Margins Clear

Local Advancement & FTSG

Advanced Basal Cell Carcinoma (BCC)

Hedge Hog (Hh) Inhibitor

Vismodegib (Erivedge)

Indications

- Metastatic BCC
- Locally advanced BCC recurring a/f surgery
- Patients who are not surgical/XRT candidates

Sekulic A, et al. NEJM. 2012;366:2171-9.

Vismodegib: Side Effects (150 mg PO QD)

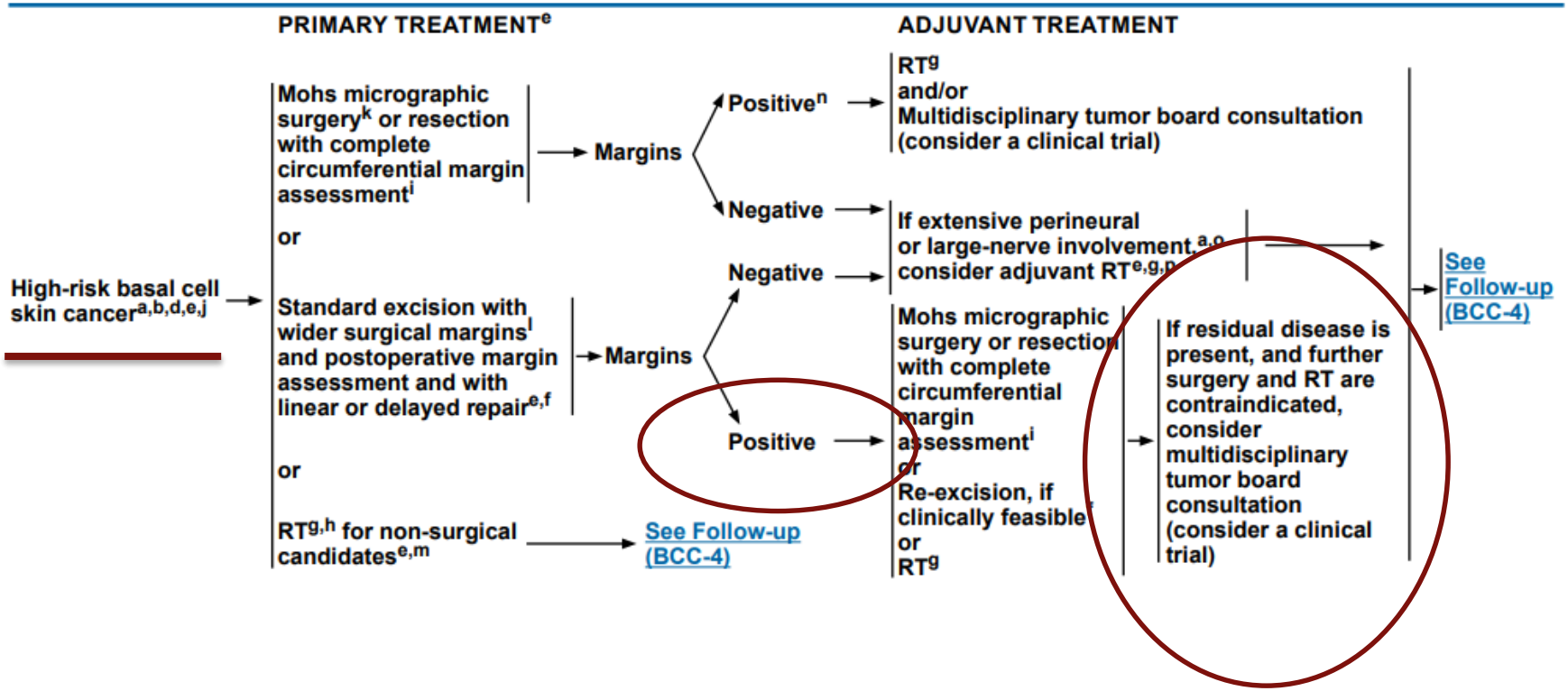
- Arthralgia
- Muscle Cramping
- Alopecia
- Diarrhea
- Fatigue
- Dysguesia/loss appetite/weight loss
- Teratogen****

} Hyponatremia

HHg Inhibitor: Indications

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Basal Cell Skin Cancer



HHg Inhibitor: Indications

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Basal Cell Skin Cancer

FOLLOW-UP

- H&P
  - Including complete skin exam every 6–12 mo for first 5 years, and then at least annually for life
- Consider imaging if clinical exam insufficient for following disease[t]
- Patient education:
  - Sun protection
  - Self-examination

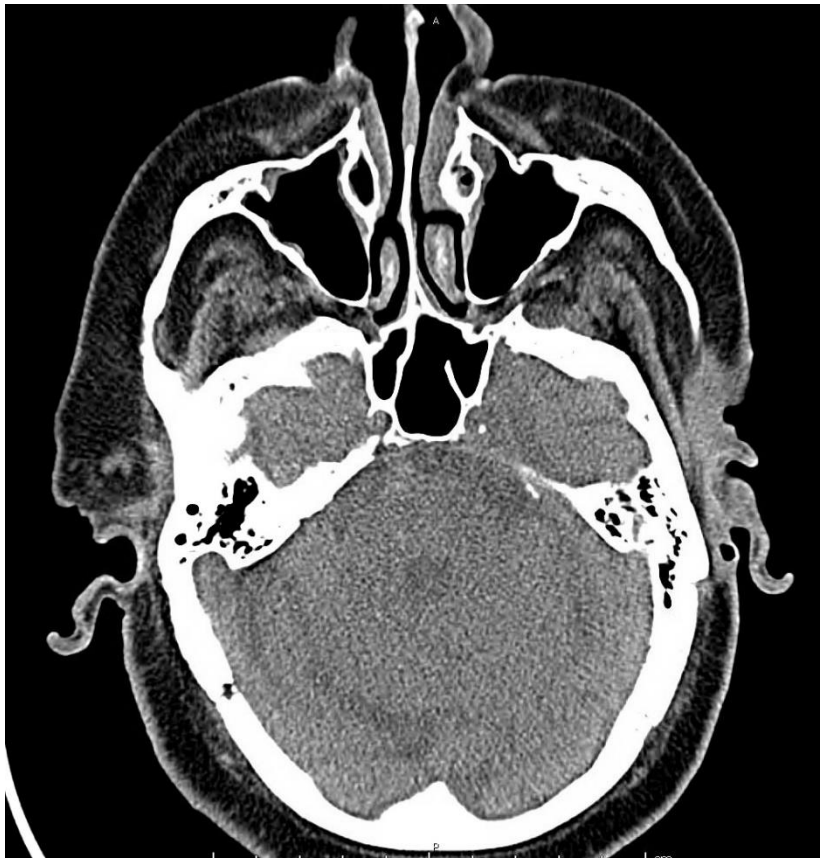
RECURRENCE OR ADVANCED DISEASE

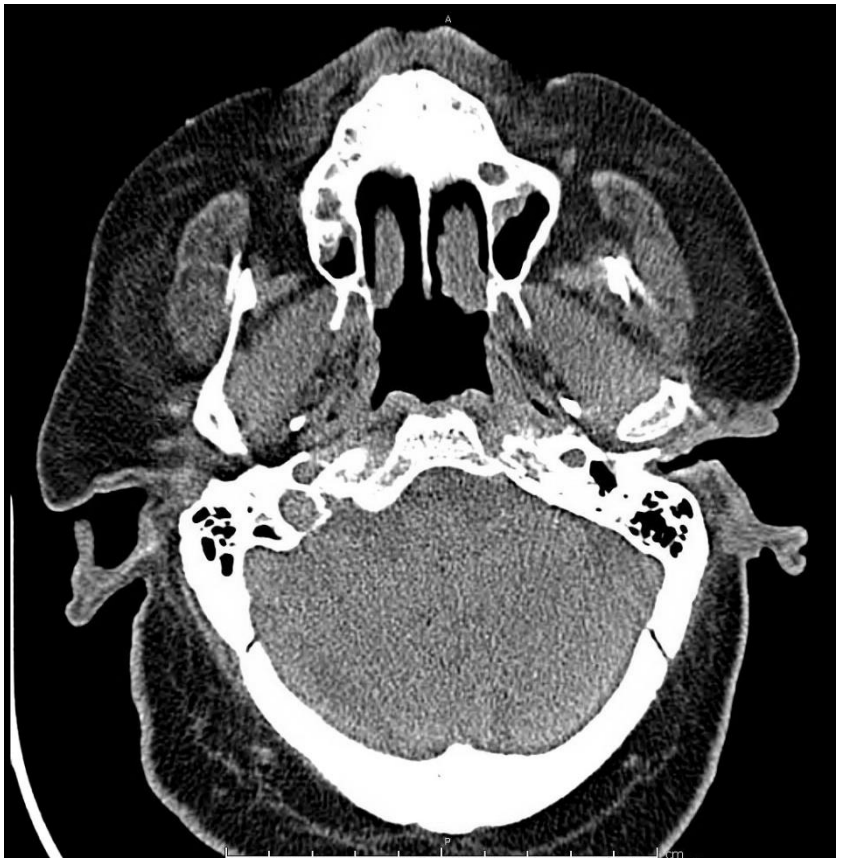
Local recurrence[t] → Follow Primary Treatment pathway for Local, high-risk disease (BCC-3)

Nodal or distant metastases[p] →

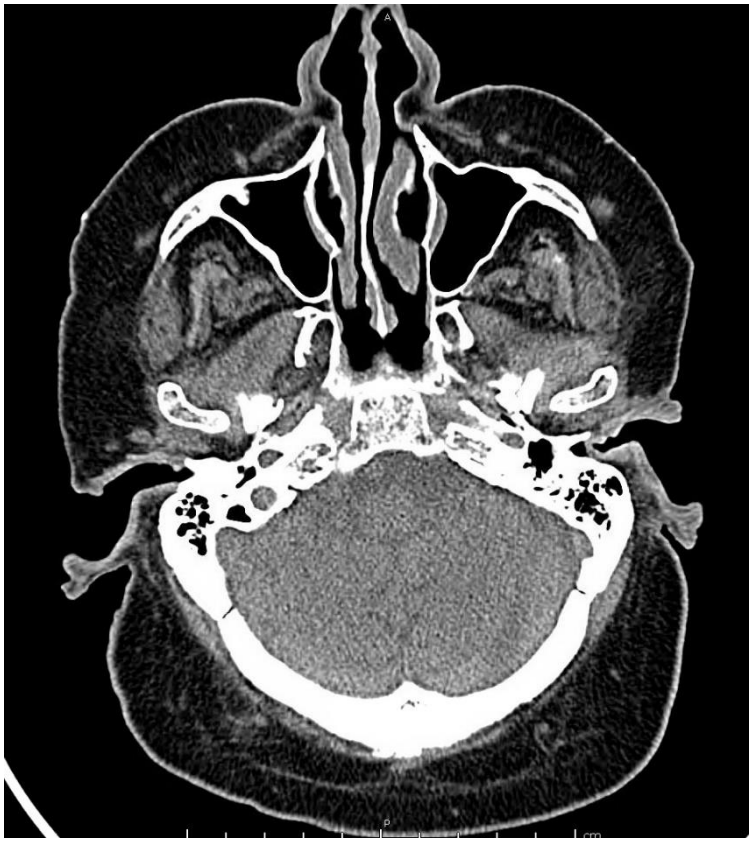
Multidisciplinary consultation to consider one or more of the following options:
- Surgery
- RT
- Hedgehog pathway inhibitor[p]
  - Vismodegib
  - Sonidegib (category 2B)
- Clinical trial

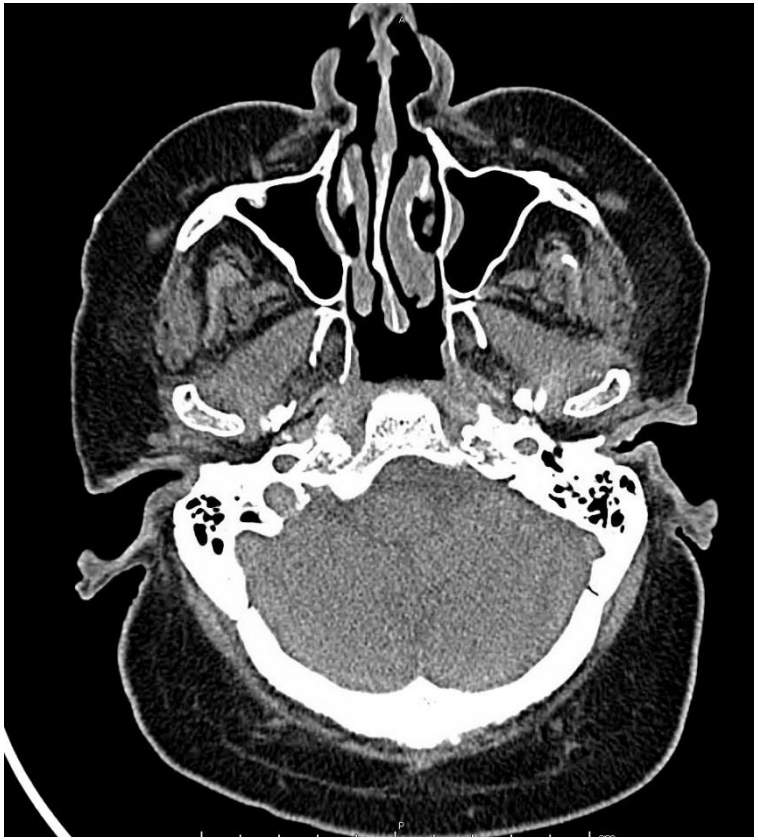
78 y.o. demented male presents with biopsy proven advanced BCC (present for > 3 yr)





5 Months Vismodegib





Neoadjuvant Vismodegib

June 4, 2014

Newly Diagnosed Advanced BCC

Pts not surgical/XRT candidates

Courtesy: Evans Bailey, MD, PhD

Sept 10, 2014

4 wks Neoadjuvant Vismodegib

Courtesy: Evans Bailey, MD, PhD

Oct. 29, 2014

11 wks Neoadjuvant Vismodegib

Courtesy: Evans Bailey, MD, PhD

Nov. 19, 2014

14 wks Neoadjuvant Vismodegib

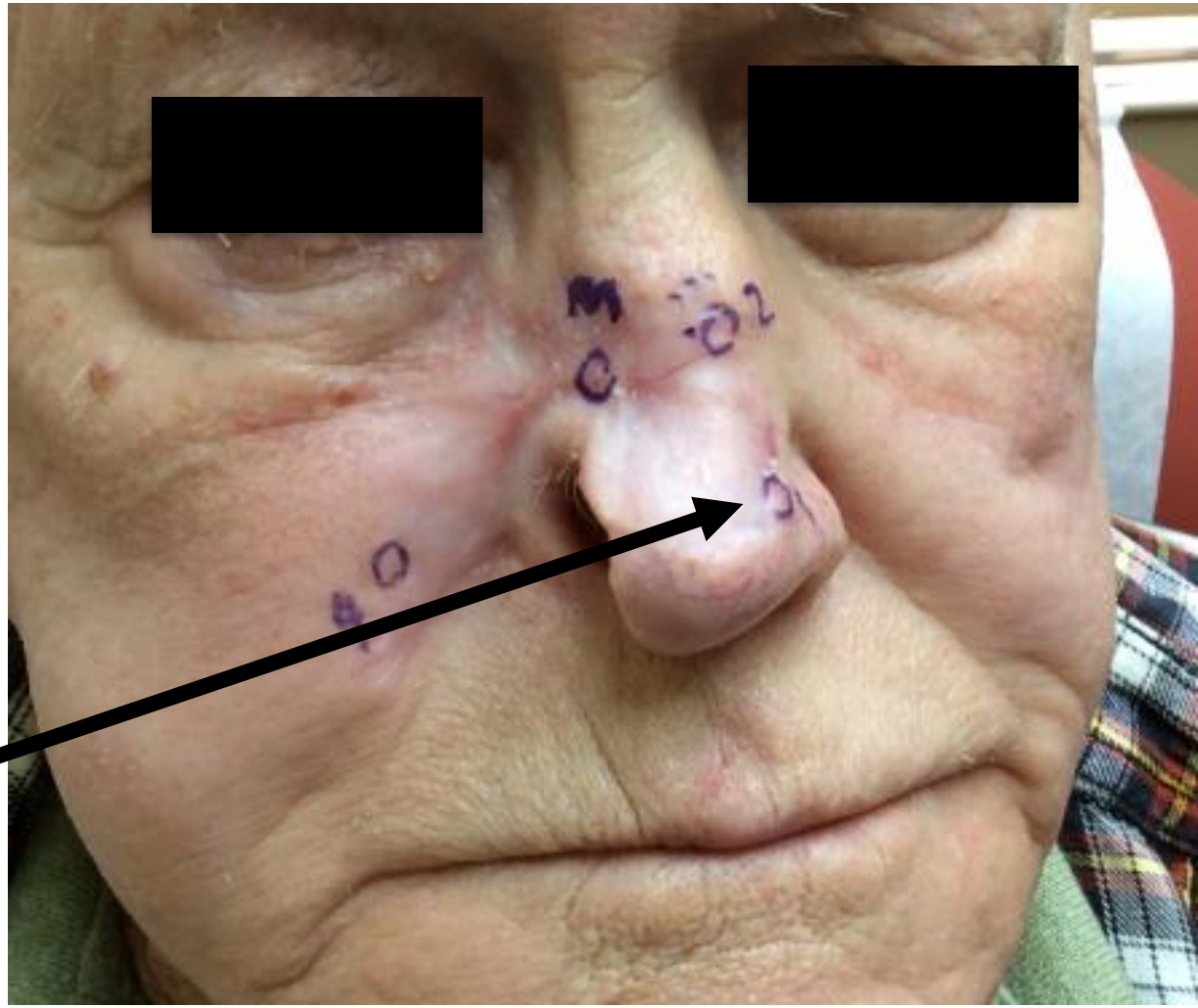
Courtesy: Evans Bailey, MD, PhD

Jan 28, 2015

24 wks Neoadjuvant vismodegib

#2, #3, #4 - Scar

#1 BCC



Courtesy: Evans Bailey, MD, PhD

March 10, 2015

30 weeks
(7.5 mons)
Neoadjuvant
Vismodegib

Day of
Cheek MOHS

Courtesy: Evans Bailey, MD, PhD

March 10, 2015

MOHS:
Cleared in 1 stage of Mohs

Perm Section pathology:
No BCC

Courtesy: Evans Bailey, MD, PhD

MAY 13, 2015

39 wks
Neoadjuvant
Vismodegib

Day Nasal
MOHS

Courtesy: Evans Bailey, MD, PhD

May 13, 2015

MOHS:
Cleared in 4 stages of Mohs

Perm Section pathology:
Central Focus BCC

Courtesy: Evans Bailey, MD, PhD

June 17, 2015

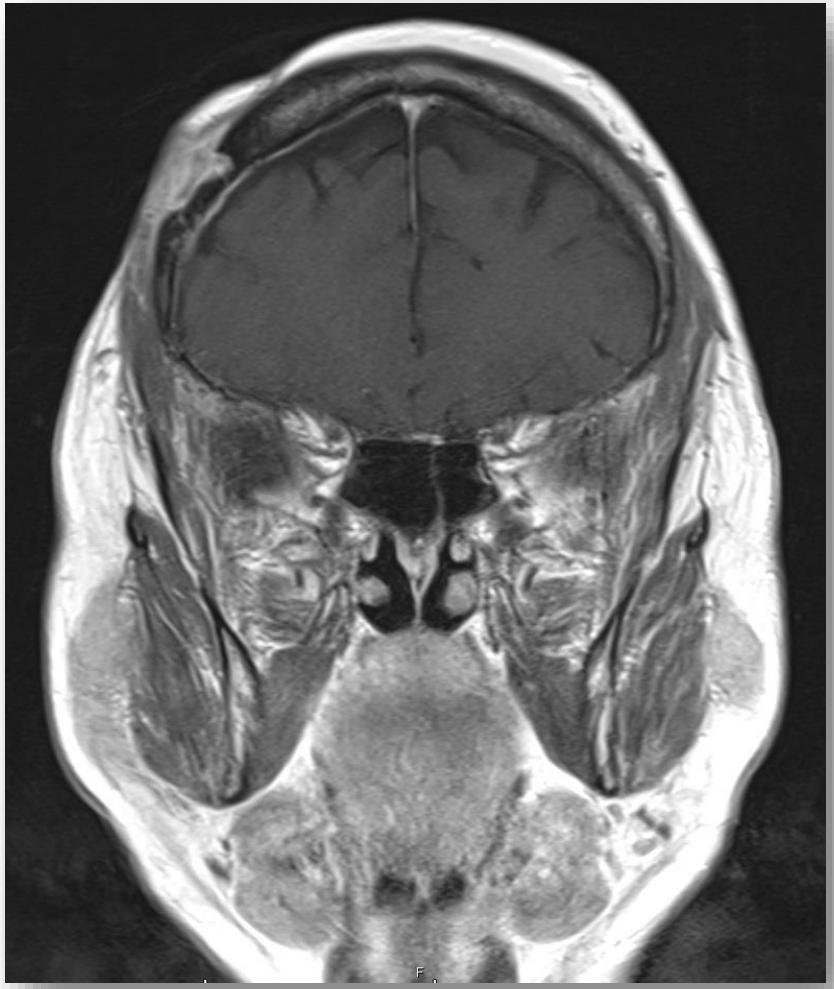
Courtesy: Evans Bailey, MD, PhD

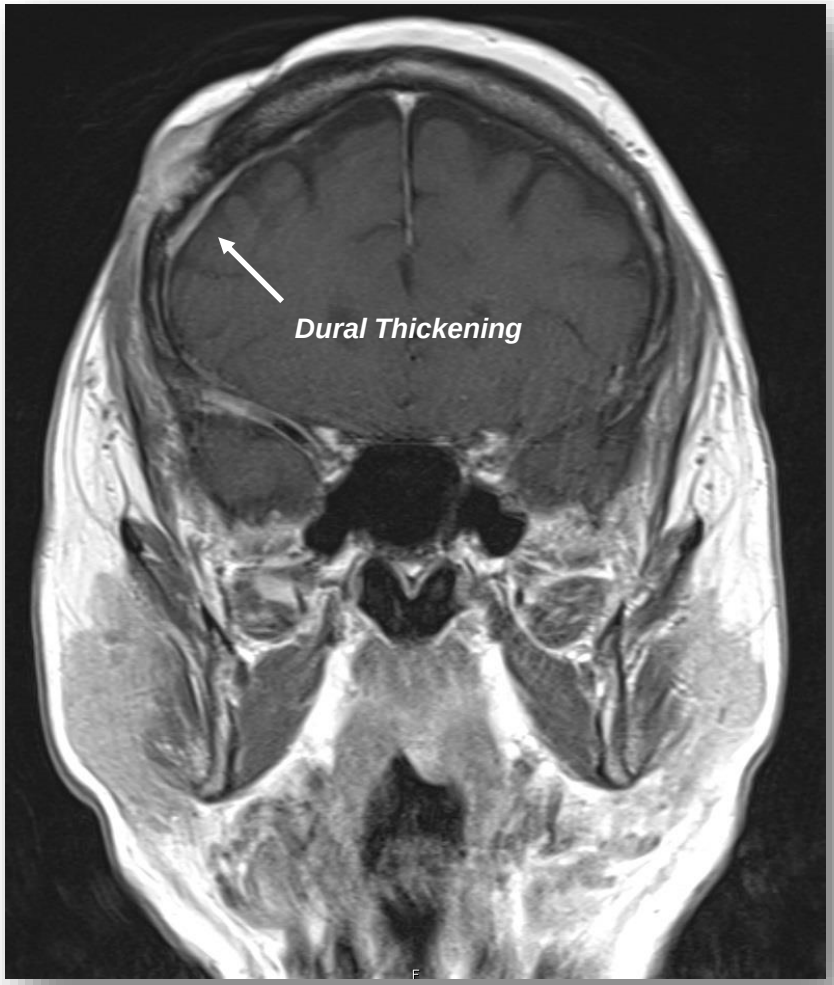
Pre-Vismodegib

7.5 months
Post-Vismodegib

73 y.o. Vismodegib, WLE with drilling of calvarium and regional flap, + deep margin and restarted on Vismodegib

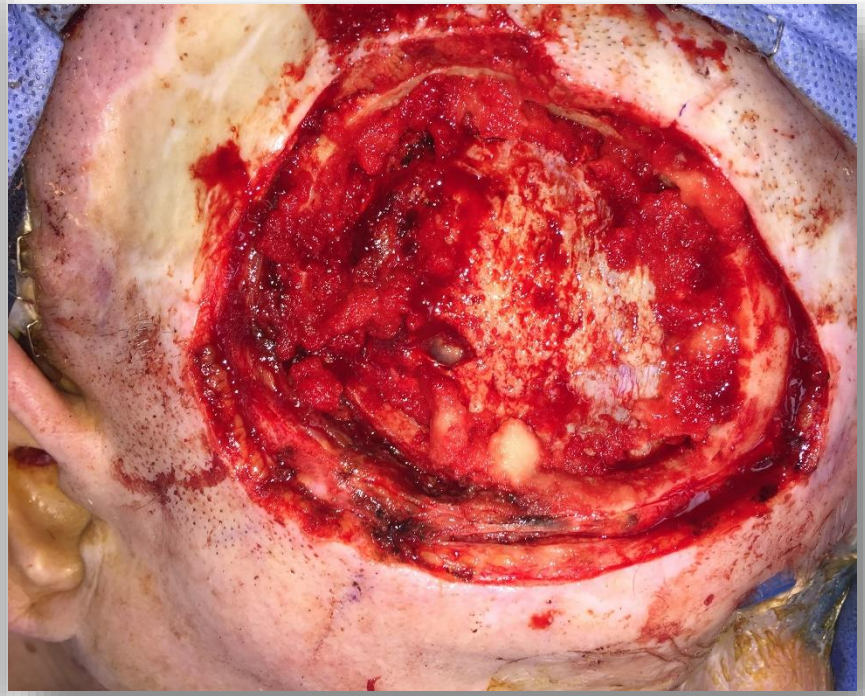
MRI with Gadolinium: BCC





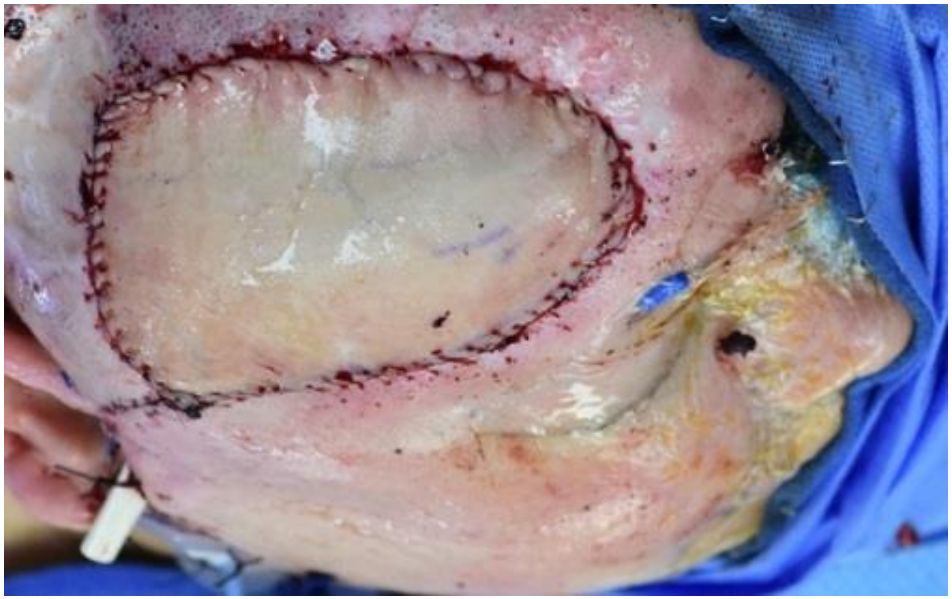
Cranial Erosion

Dural Involvement



Dural Resection

Mesh & RFFF



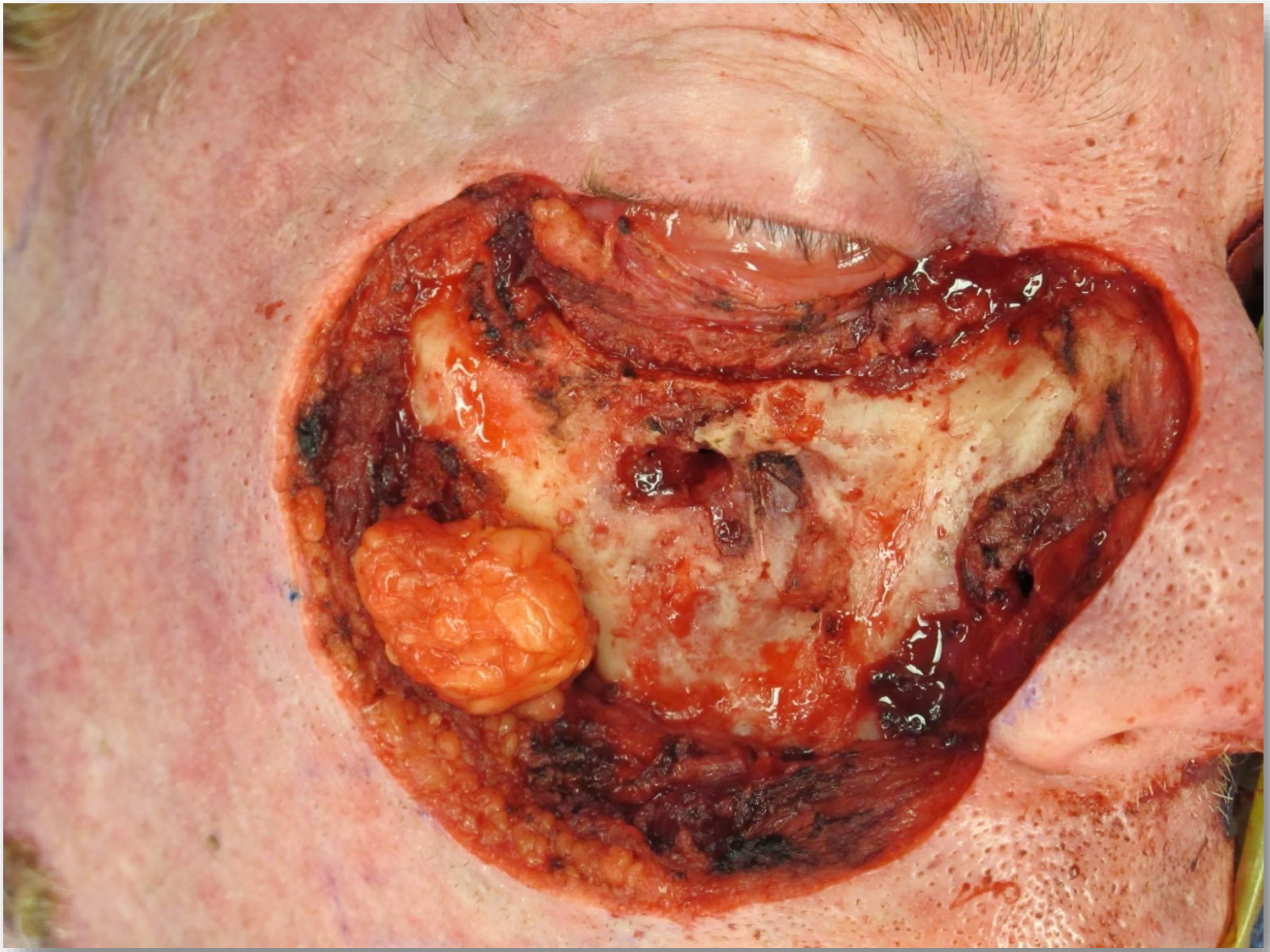
3 weeks post-op

9 weeks post-op

II. Management of the Squamous Cell Carcinoma (SCC)

Advanced cSCC

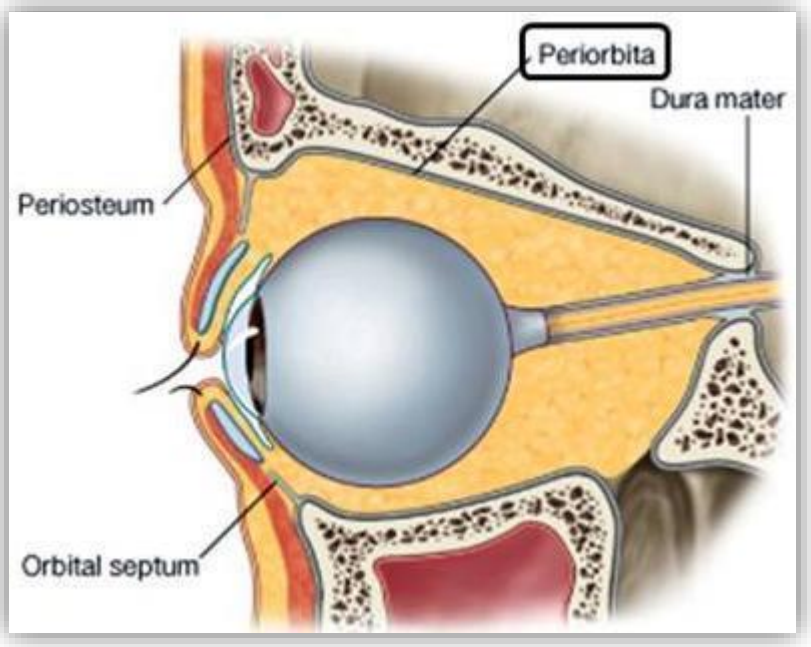
Surgical Management

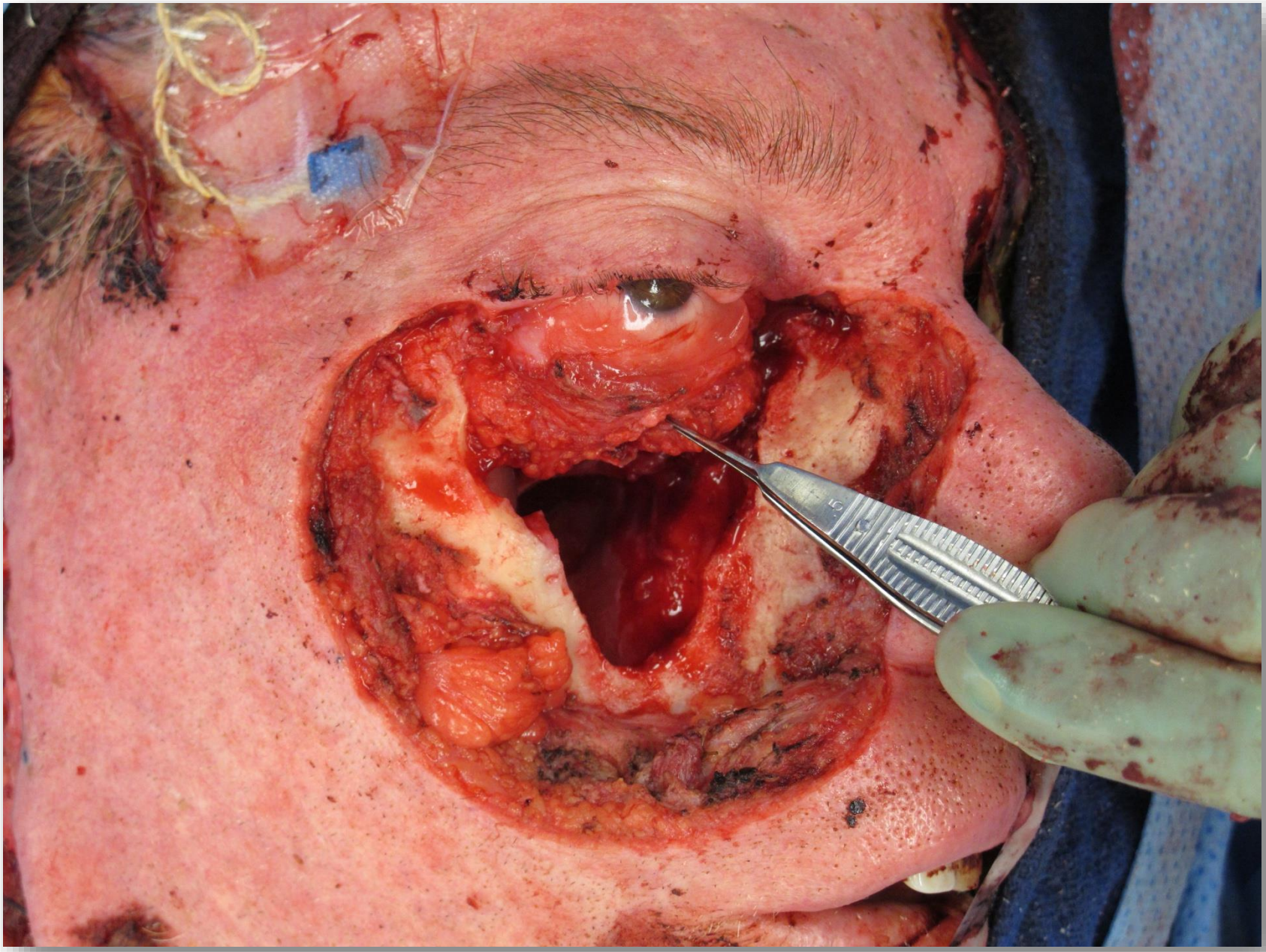


When do you Exenterate?

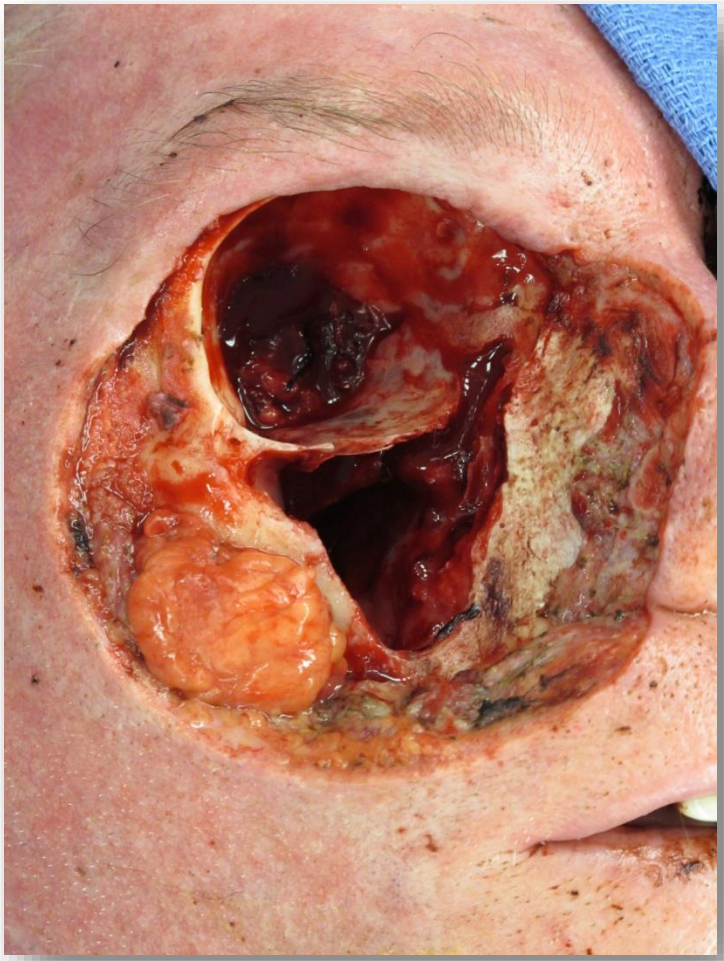
- **Intraoperative decision based on FS**
- **Only when Periorbital FAT is directly invaded.**
- **Periorbita involvement is not an indication**

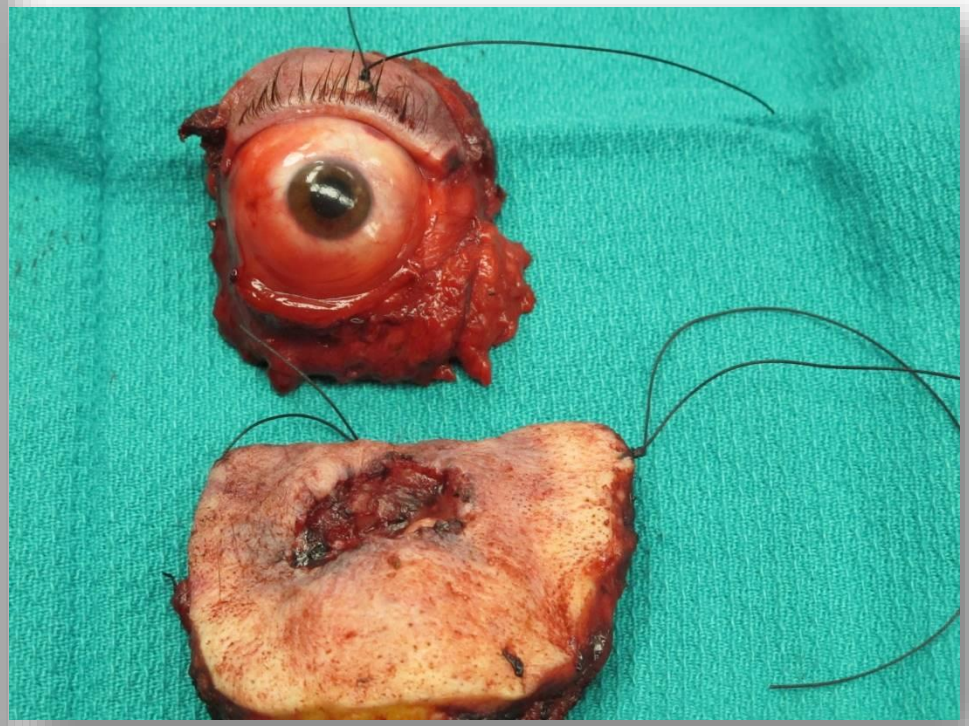
Perry et al. Preservation of the eye in paranasal sinus cancer surgery. Arch Otolaryn Head Neck Surg. 1988. Jun; 114(6):632





Orbital Exenteration





ALT FF

Final Pathology

- Invasive cutaneous SCCA (3.3 x 2 cm)
- Perineural invasion
- + Peri-orbital Fat
- All margins negative
- Intra-parotid LN (0/1) negative
- 2 + cervical LN, one with ECS

SCCA Adjuvant Therapy

Primary Tumor XRT

- **Positive Margin**
- **Perineural spread**
- **Large (named) nerve involvement**

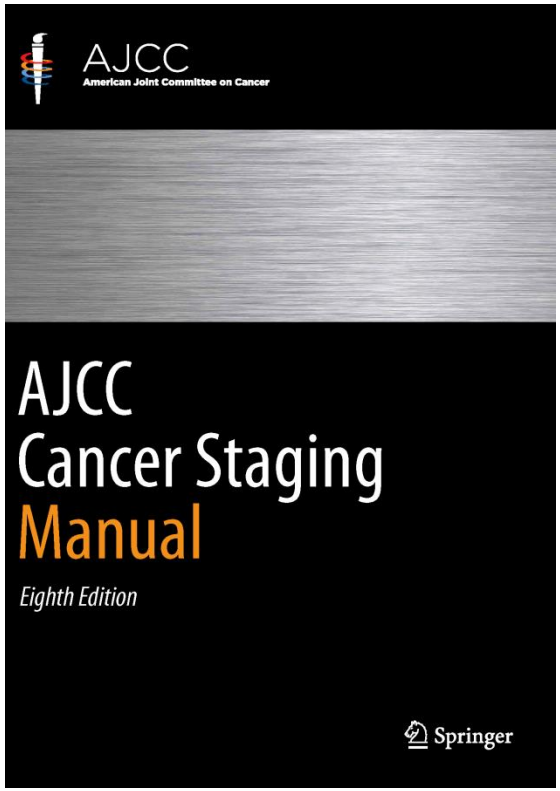
Regional Disease

• **1LN ≤ 3cm; no ECS**	***Optional***
• **≥ 2 LN**	**XRT**
• **1 LN > 3cm**	**XRT**
• **ECS**	**XRT +/- Chemo**
• **Incomplete excision**	**XRT +/- Chemo**

8th Ed AJCC Staging

January 2018

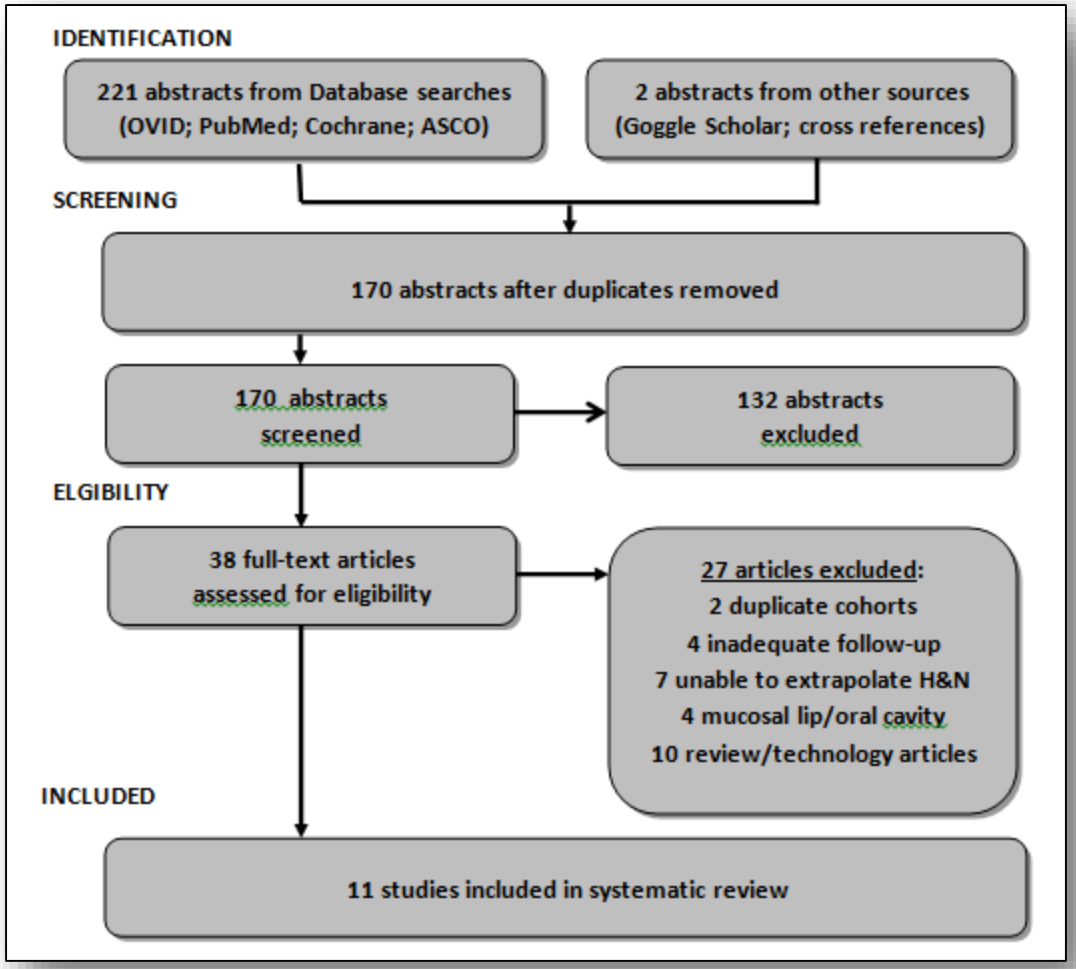
- **cSCC AJCC Task Force disbanded**
  - **cSCC now a subcategory in Head & Neck**
  - **Only applies to H&N**
- **TNM staging unchanged**
  - **Tumor diameter**
  - **Adjacent structure invasion**
  - **Risk Factors removed**



High Risk cSCC Patient

- Poorly defined borders
- Recurrent tumor
- Prior radiation
- Chronic inflammation
- Rapid growth
- Neurologic symptoms
- Pathology
  - Adenoid subtype
  - Desmoplastic subtype
  - Adenosquamous subtype (mucin)
  - Perivascular invasion

Utility of SLNB for cSCC



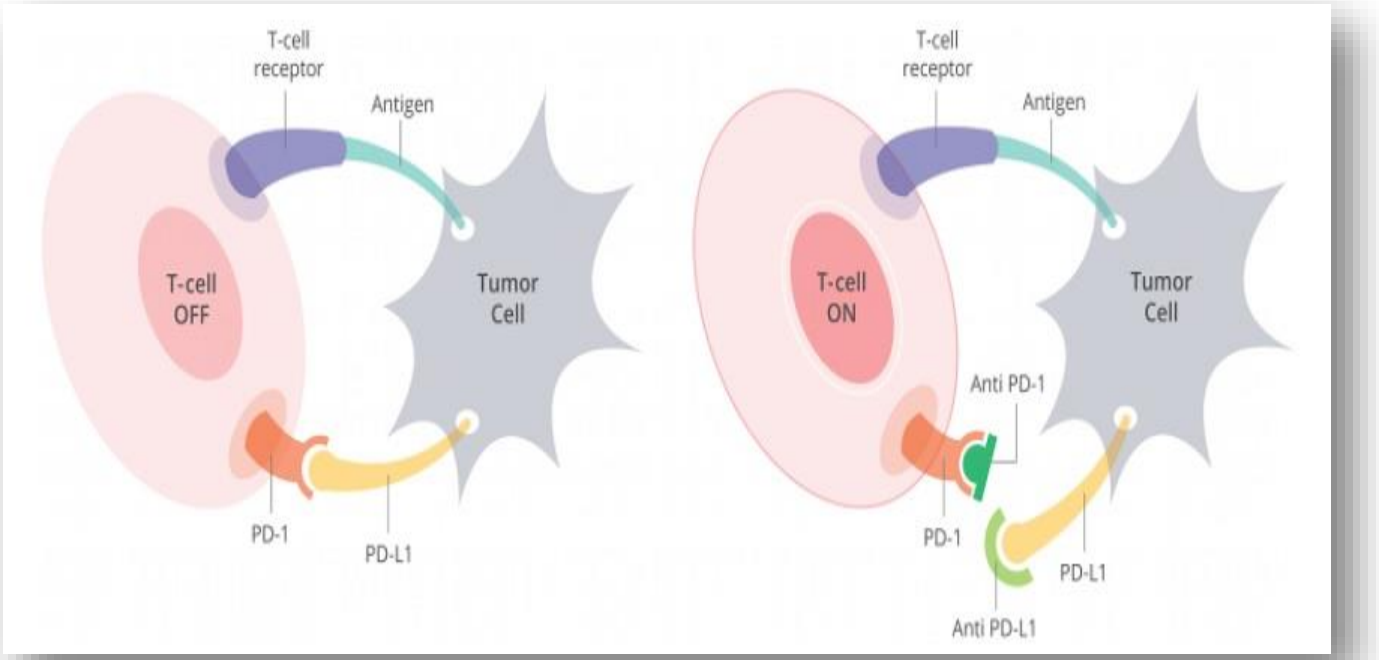
Ahmed MM, Moore BA, Schmalbach CE. Oto-HNS. 2014; 150(2): 180.

Utility of SLNB for cSCC

Author/Year	Country	No. Pts	No. +SLN Pts	Rate of False Omission‡ (No. Pts; %)	Median Follow-up (mon.)	SLN Technique£
Michl (2003)[12]	Germany	5	0	0	29	Colloid
Reschly (2003)[13]	USA	4	1 (25%)	0	14.5	Colloid + Dye
Wagner (2004)[8]	USA	5	2 (40%)	1 (33%)	14	Colloid + Dye
Nouri (2004)[14]	USA	8	1 (12.5%)	0	18	Colloid
Cecchi (2005)[15]	Italy	2	0	0	22	Colloid + Dye
Civantos (2006)[16]	USA	15	2 (13%)	0	16	Colloid
Sahn (2007)[17]	USA	4	0	0	27.5	NS
Resendez (2007)[18]	Mexico	11	3 (27%)	0	21	Colloid + Dye
Rastrelli (2011)[19]	Italy	11	1 (9%)	2 (20%)	24	Colloid + Dye
Kwon (2011)[20]	USA	2	0	0	13.65	Colloid
Demir (2011)[21]	Turkey	14	0	0	38.5	Colloid
Total		73	10	3 (4.76%)	21.5	

Ahmed MM, Moore BA, Schmalbach CE. Oto-HNS. 2014; 150(2): 180.

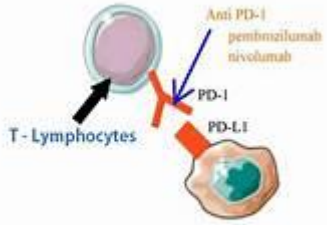
Checkpoint (PD-1) Inhibitors



Combat suppression of T cells

Cemiplimab-rwlc

- **FDA approved Sept 2018**
  - **Metastatic cSCC**
  - **Locally advanced cSCC not candidate for curative surgery or XRT**
- **Open-label multi-institutional trials (59pt)**
  - **Median FU 7.9 mon**
  - **Objective Response Rate: 47.5% (4% CR; 44% PR)**
  - **Dz Durable Response Rate: 61% for 6mons**
  - **Onset 1.9mon**

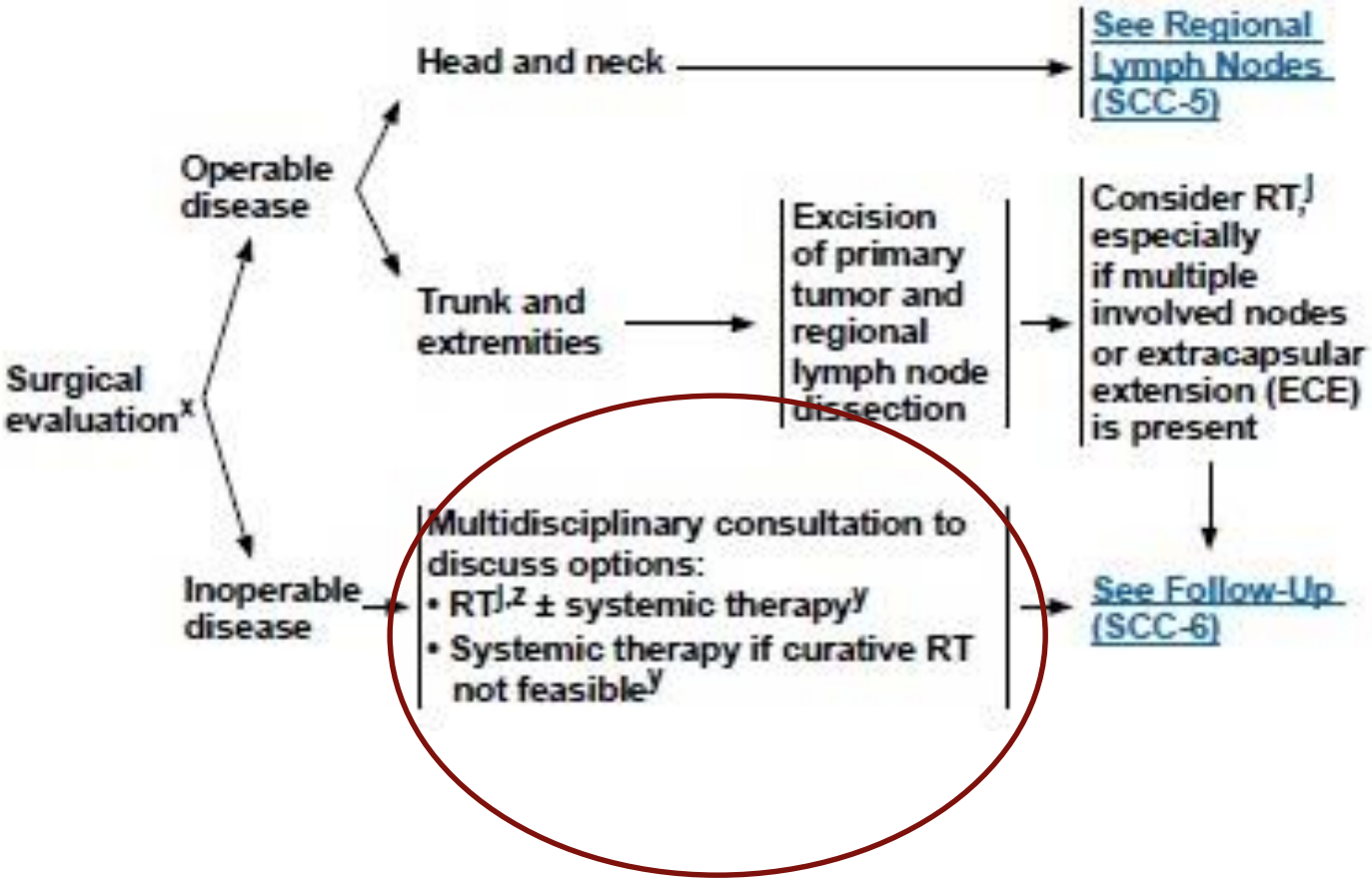


Pembrolizumab

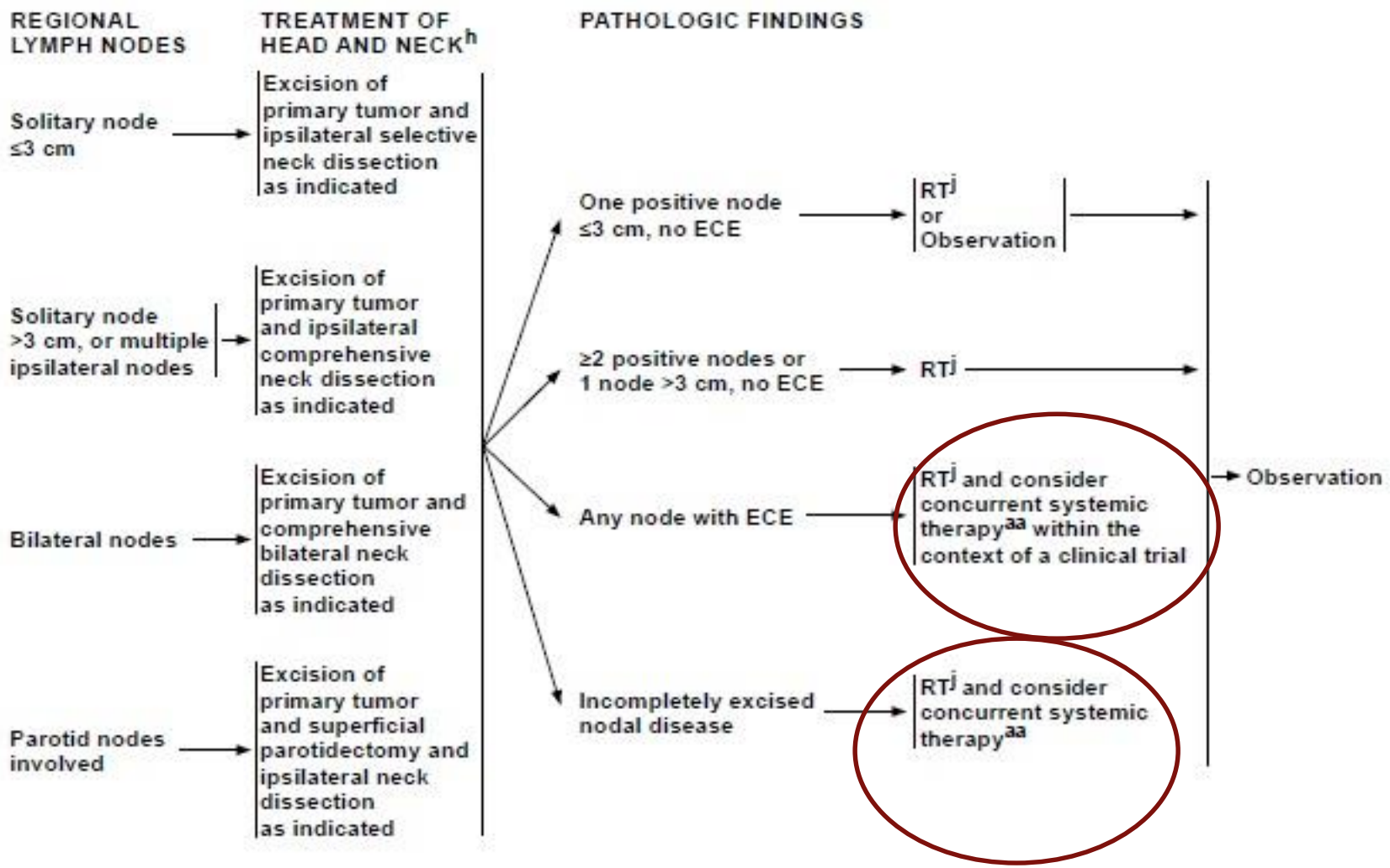
- FDA approved advanced cSCC June 2020
- KEYNOTE-629 (NCT03284424)
- Patients with recurrent or metastatic cSCC not amendable to surgery or XRT
- 105 pt
- FU 11.4 mon
- 34.3% response rate (4 CR)
- 52.4% disease control
- 6.9 mon progression free survival

J Clin Oncol. 2020; 38(25):2016

cSCC Adjuvant Systemic Therapy



cSCC Adjuvant Systemic Therapy



PD-1 Inhibitors for Transplant Pts

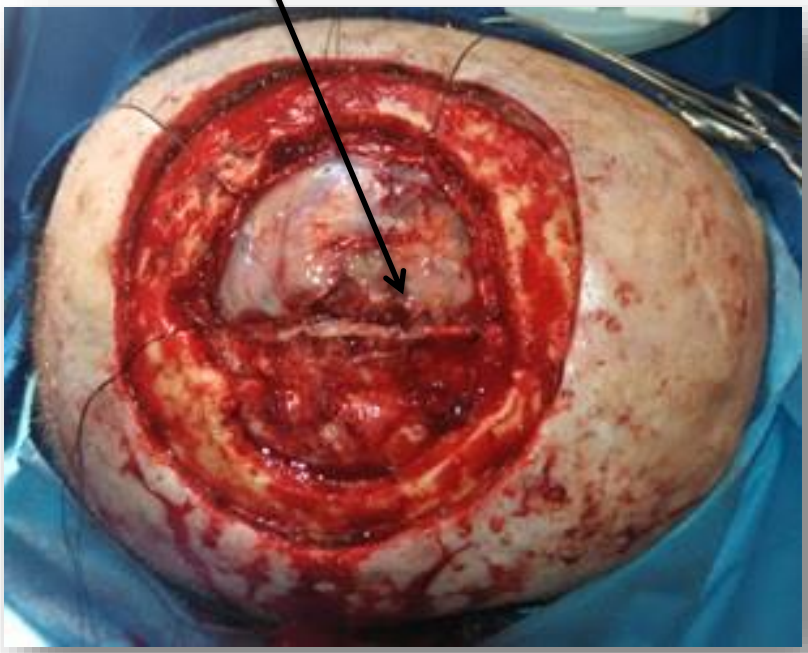
- **50-50 chance of transplant rejection with immune check point inhibitors**
  - **Fulminant rejection**
  - **Rapidly fatal**
  - **Heart, Lung, Liver: no plan B**

"Until we better understand how to use checkpoint inhibitors in transplant patients, cetuximab will remain the first-line choice"

~ C.D. Schmults, MD, MSCE, JNCC-360

Organ Transplant:
Risk Increases x 250

Sagittal Sinus Invasion



8th Ed AJCC Staging

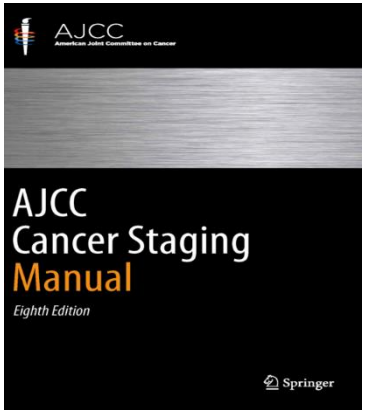
January 2018

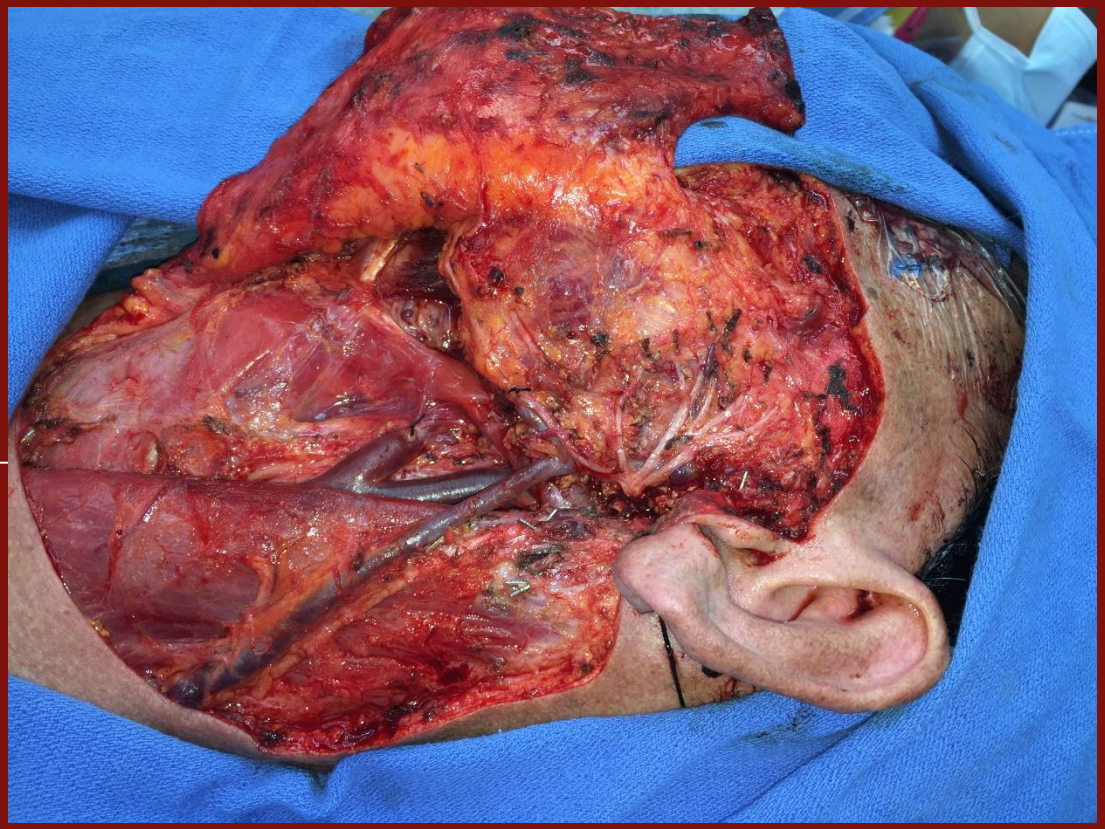
Strong consideration was given toward including immunosuppression as a risk factor

- **Only a single study cited demonstrating relationship between poor outcome and immunosuppression**

  Brantsch et al. Lancet Oncol. 2008.

- **Call for prospective cancer registry**





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DOI: 10.1177/0194599818808511
http://otojournal.org
SAGE

Immunosuppression Impact on Head and Neck Cutaneous Squamous Cell Carcinoma: A Systematic Review with Meta-analysis

Alhasan N. Elghouche, MD, MS[1], Zachary E. Pflum, MD[1], and Cecelia E. Schmalbach, MD, MSc[1]

Author (Year)	Country	Dates	Total Patients*	Median Age	Immunosuppressed patients (%)	Type(s) of Immunosuppression	Median follow-up (months)
Bachar (2016)	Israel	NS	71	NS, mean: 71	6 (8%)	OTR: 6	NS, minimum: 36
Brunner (2012)	Australia	1980 – 2010	603	NS, mean: 70	26 (4%)	NS	25
Ch'ng (2013)	NZ	1978 – 2010	239	68	33 (14%)	NS	37.2
Ebrahimi (2013)	Australia	1980 – 2010	229	98	19 (8%)	NS	45.6
Givi (2011)	USA	1993 – 2007	51	73	11 (22%)	OTR: 5, HM: 6	15
Kreppel (2013)	Germany	2003 – 2009	63	74	9 (14%)	NS	38
Manyam (2014)	USA	2000 – 2011	59	72	21 (36%)	OTR: 12, HM: 8, other: 1	17.7
McLean (2013)	Australia	1980 – 2010	95	NS, mean: 71	6 (6%)	NS	NS
Oddone (2009)	Australia	1980 – 2005	250	67	15 (6%)	OTR: 5, HM: 10	54
Palme (2003)	Australia	1987 – 1999	126	69	18 (14%)	OTR: 4, HM: 6, other: 8	NS, minimum: 24
Peat (2012)	NZ	1996 – 2001	170	NS, mean: 76	15 (9%)	NS	NS, minimum: 60
Schmidt (2015)	Australia	1998 – 2011	113	74	12 (11%)	OTR: 1, HM: 11	40
Shao (2014)	NZ	1989 – 2010	160	NS, mean: 78	28 (18%)	OTR: 10, HM: 16, other: 2	66
Southwell (2016)	Australia	1992 – 2002	49	NS, mean: 72	9 (18%)	OTR: 3, HM: 6	20
Tseros (2016)	Australia	1995 – NS	238	68	19 (8%)	OTR: 11, HM: 7, other: 1	55
Veness (1999)	Australia	1984 – 1995	17	52	17 (100%)	OTR: 17	21.5
Wermker (2014)	Germany	2005 – 2011	353	78	53 (15%)	NS	NS, mean: 43.4

Results

- **H&N SCC pts = 2,886**
  - **85% male**
  - **15% recurrent disease**

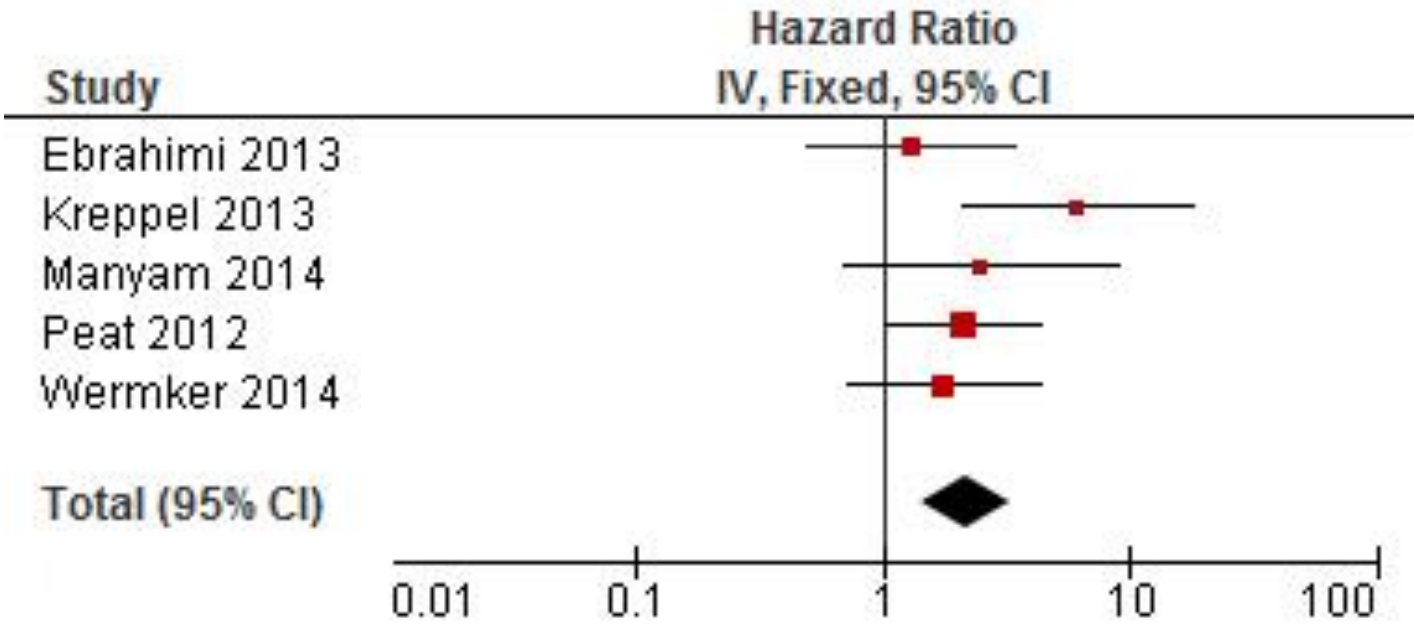
- **Treatment**
  - **Surgery + XRT (1,553; 74%)**
  - **Surgery alone (535; 25%)**
  - **Definitive XRT (21; 1%)**

Results: Systematic Review

- **Immunosuppressed cohort**
  - **n = 317 (11%)**

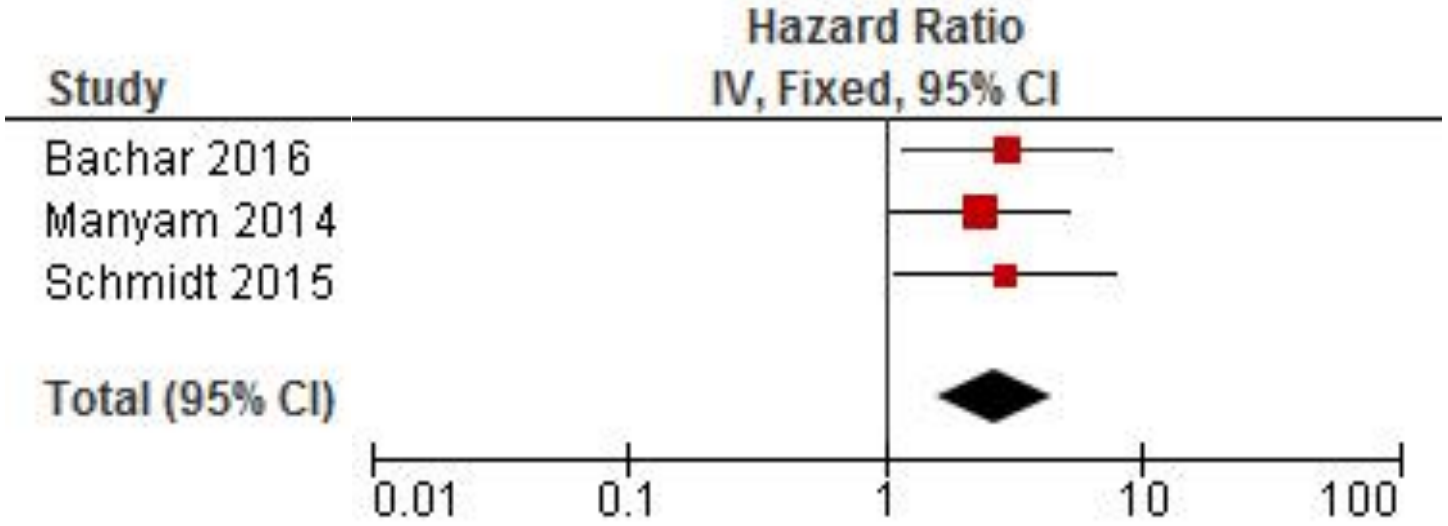
- **Etiology**
  - **Solid Organ (74; 23%)**
  - **Lymphoproliferative Disorders (70; 22%)**
  - **Chronic Immunosuppressive Tx (12; 4%)**
  - **Not specified (161; 51%)**

Meta-Analysis Results: Locoregional Recurrence (LRC)



Immunosuppressed pts are 2.20 times more likely to have local or regional failure

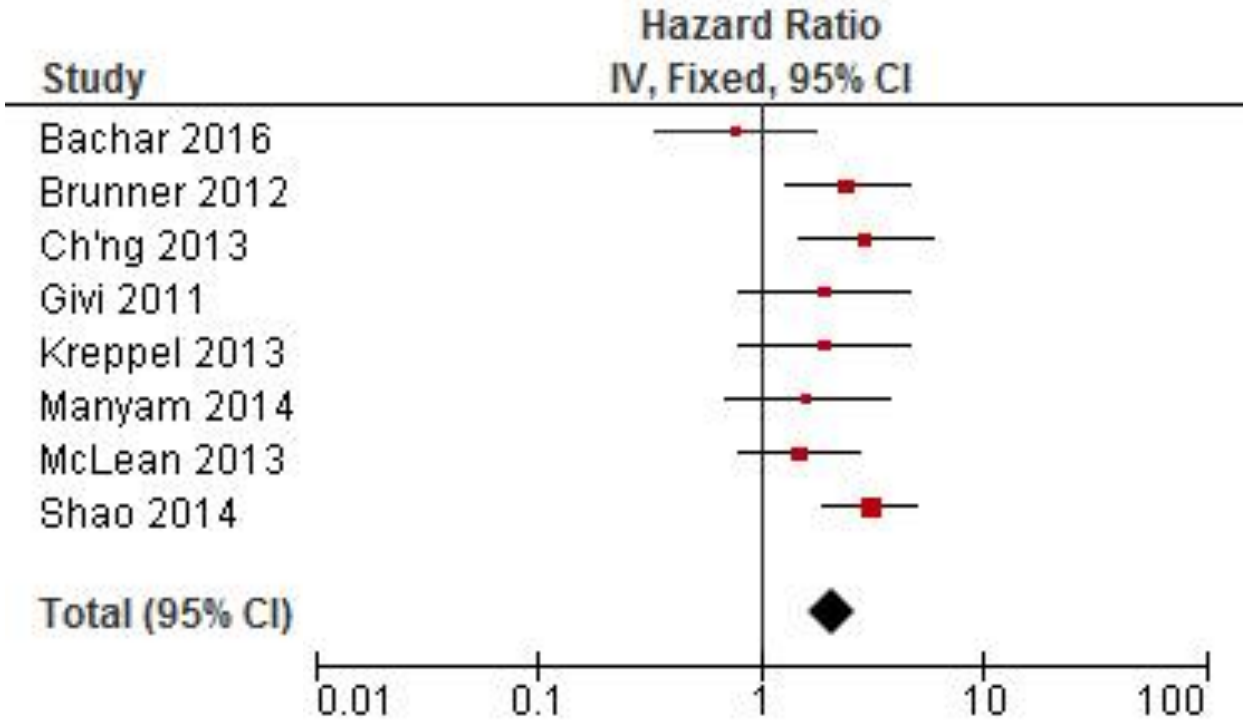
Meta-Analysis Results: Disease-Free Survival (DFS)



Immunosuppressed pts demonstrated worse DFS

(Pooled HR: 2.69)

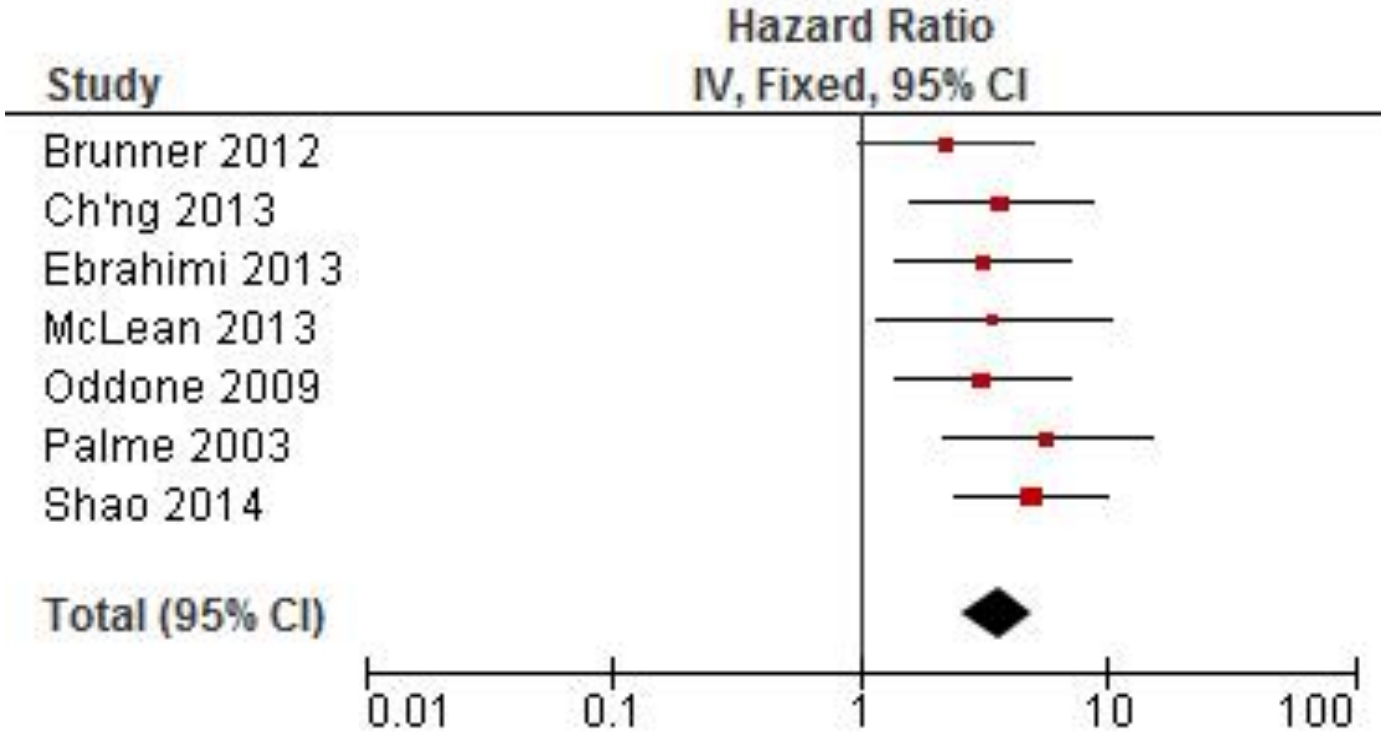
Meta-Analysis Results: Overall Survival (OS)



Immunosuppressed pts demonstrated worse OS

(Pooled HR: 2.09)

Meta-Analysis Results: Disease Specific Survival (DSS)



Immunosuppressed pts were 3.61 times more likely to die of their disease

Conclusions

- **Largest study of immunosuppressed cSCC H&N cancer patients**

- **Immunosuppressed cSCC H&N patients portend a:**
  - **Worse locoregional control rate**
  - **Worse disease-free survival**
  - **Worse disease-specific survival**
  - **Worse overall survival**

- **Provides scientific need for more comprehensive research and incorporation of immunosuppressed status into cancer staging systems**

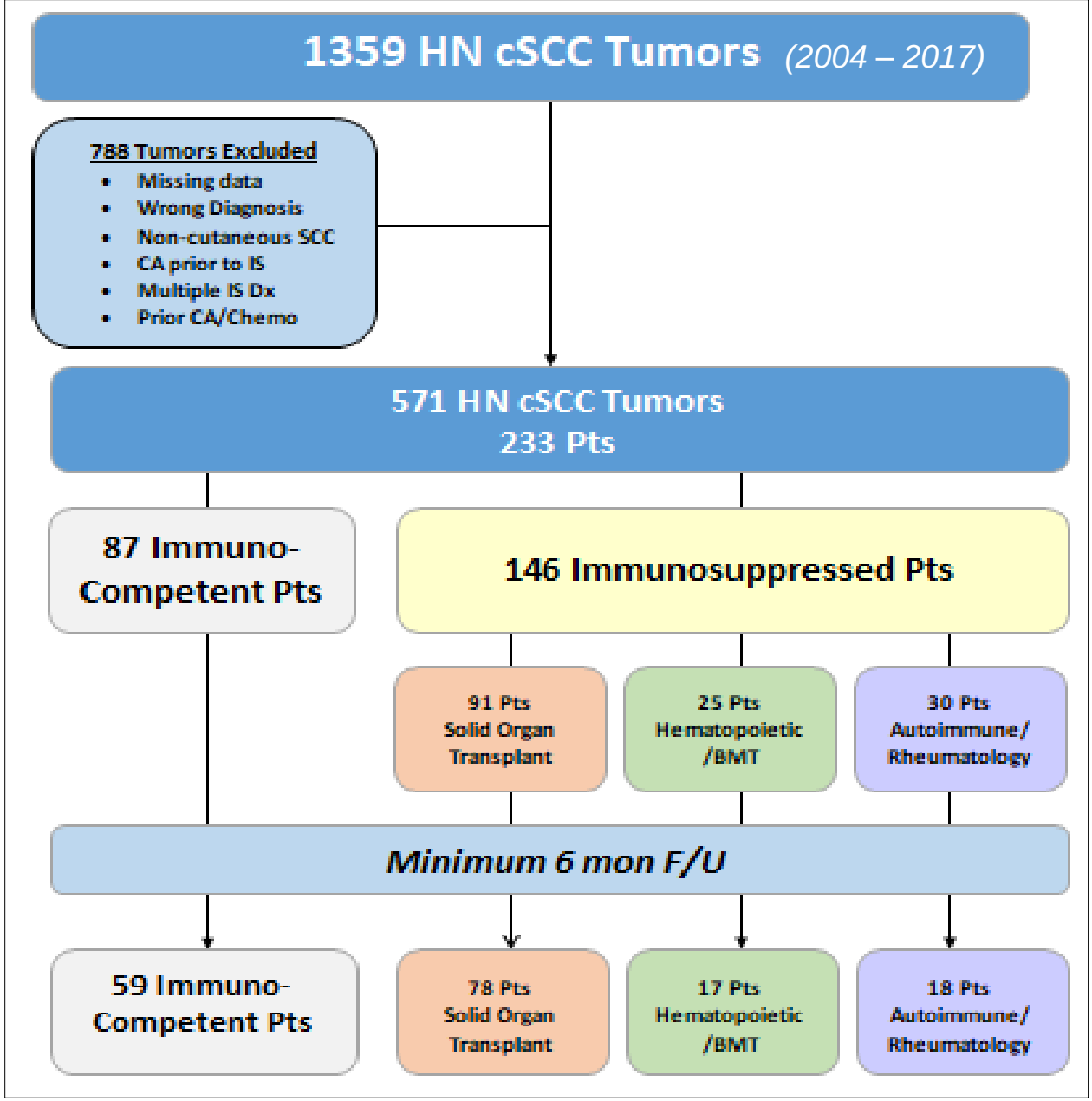
Impact of Immunosuppression on Cutaneous Head & Neck Squamous Cell Carcinoma

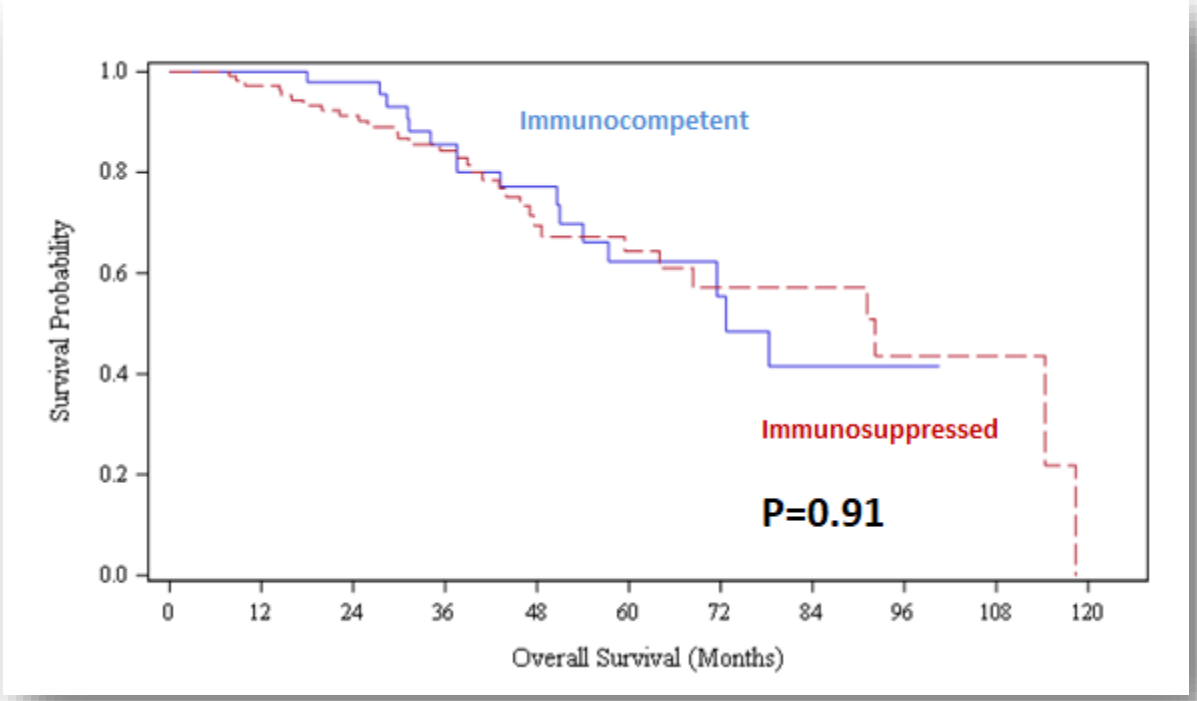
PI: C. Schmalbach, MD, MSc

Research Team: Z. Pflum, MD; **Alhasan Elghouche, MD, MPH; R. Graham, MD**

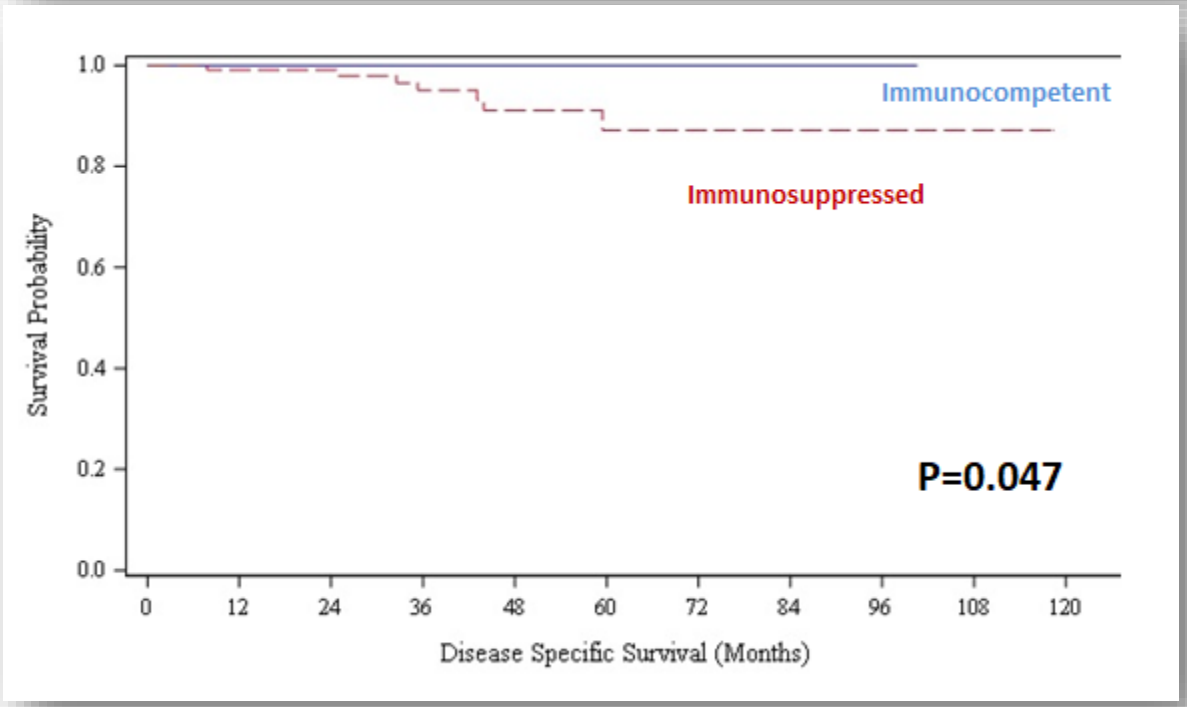
Biostatistician: D. Yu, PhD, MS

Otolaryngology-HNS
Temple University
Lewis Katz School of Medicine


1359 HN cSCC Tumors (2004 – 2017)
788 Tumors Excluded
Missing data
Wrong Diagnosis
Non-cutaneous SCC
CA prior to IS
Multiple IS Dx
Prior CA/Chemo
571 HN cSCC Tumors
233 Pts
87 Immuno-Competent Pts
146 Immunosuppressed Pts
91 Pts Solid Organ Transplant
25 Pts Hematopoietic /BMT
30 Pts Autoimmune/ Rheumatology
Minimum 6 mon F/U
59 Immuno-Competent Pts
78 Pts Solid Organ Transplant
17 Pts Hematopoietic /BMT
18 Pts Autoimmune/ Rheumatology

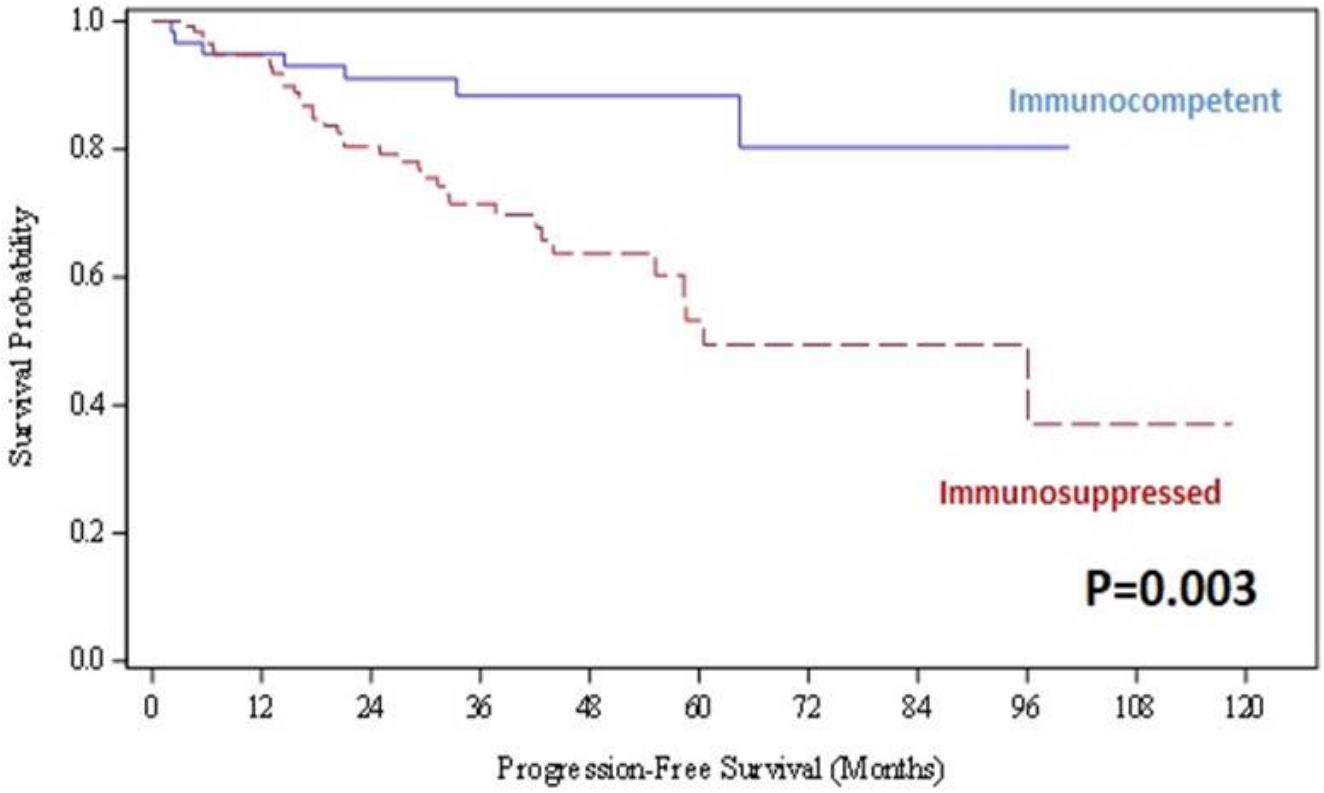


Overall Survival

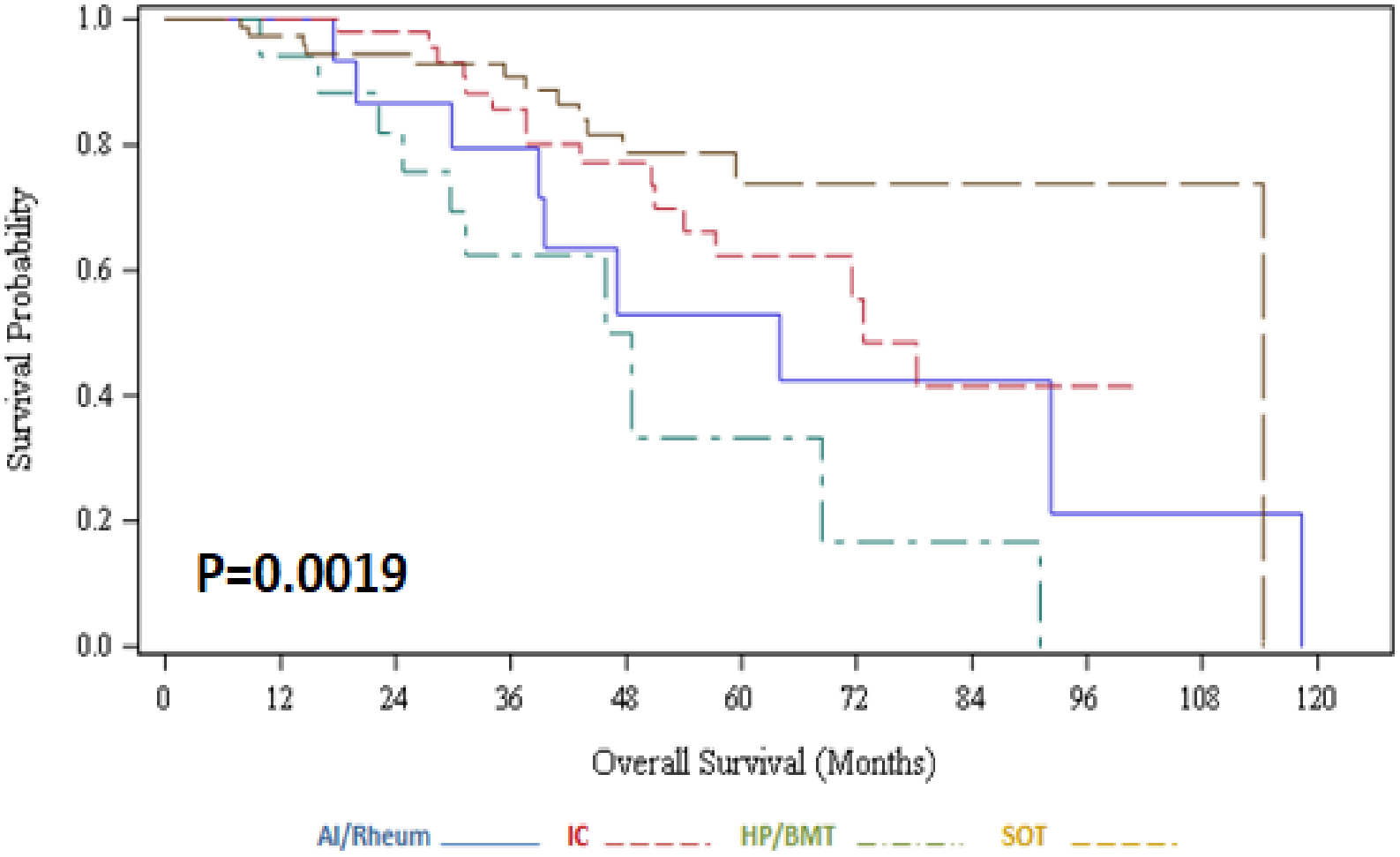


Disease Specific Survival

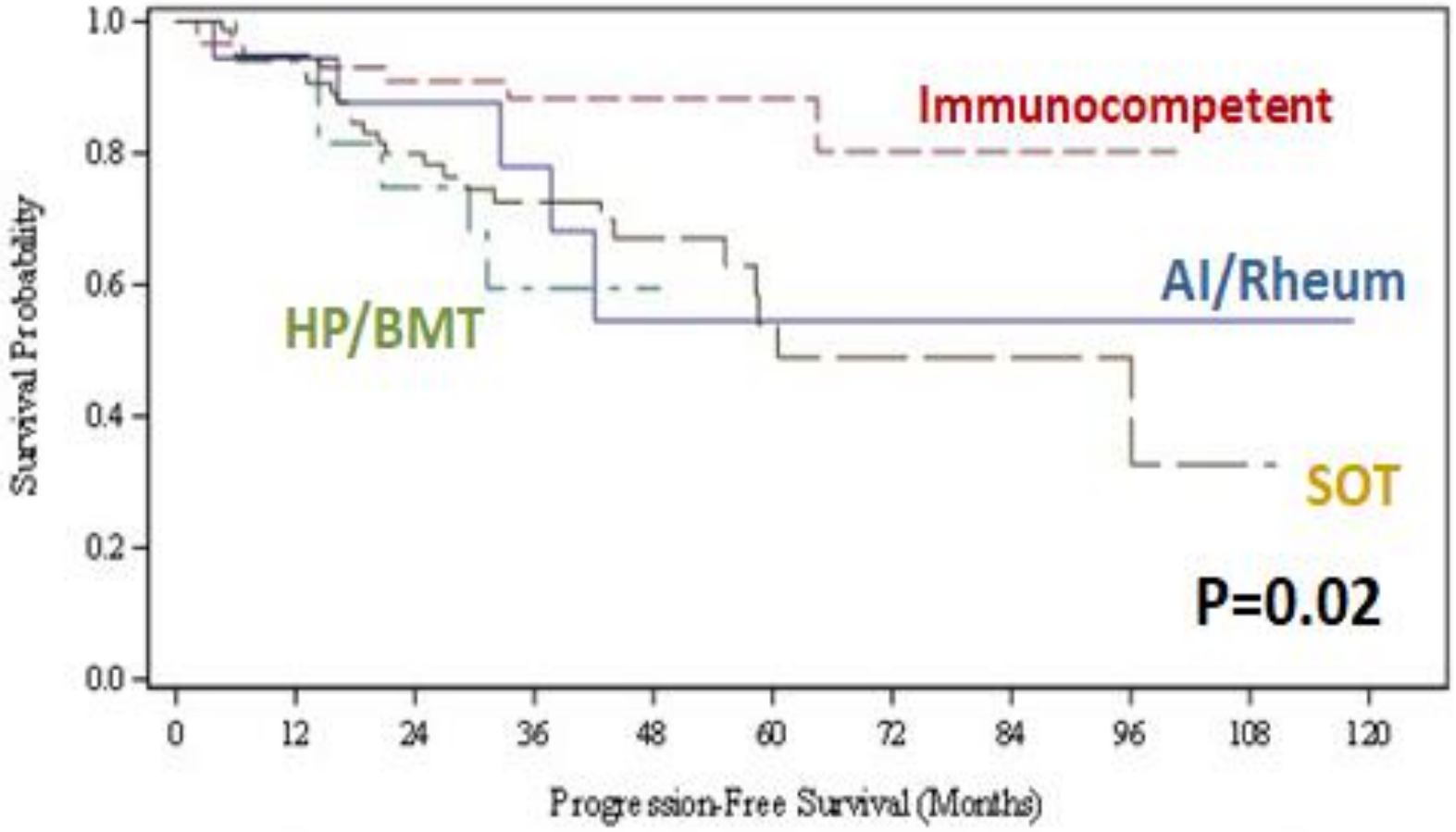
Progression Free Survival



Immunosuppression is Not All the Same



Immunosuppression is Not All the Same



Progression Free Survival
Best Fit Modeling
IS vs IC

Parameter	*DF*	*Parameter Estimate*	*Standard Error*	*Chi-Square*	*P-Value*	*Hazard Ratio*	*95% Wald CI*
Immuno-suppression	1	1.02007	0.49508	4.2453	**0.0394**	2.773	1.051, 7.319
Advanced Disease (Stage III & IV)	1	1.84467	0.81083	5.1759	**0.0229**	6.326	1.291, 30.966
Diameter > 2 cm	1	0.90625	0.34890	6.7466	**0.0094**	2.475	1.249, 4.904
Recurrent Disease At Presentation	1	1.16874	0.40233	8.4385	**0.0037**	3.218	1.463, 7.080

Conclusions

- **Immunosuppression identified as a significant predictor worse PFS**
- **Analysis of organ transplantation, hematopoietic, autoimmune and rheumatologic disorders revealed heterogeneous outcomes (SOT portending worst PFS)**
- **Call for the continuing research and consideration of immune status in future cSCC research and staging systems.**

III. Merkel Cell Carcinoma (MCC)

- **Rare neuroendocrine tumor**
  - **Local recurrence rate of non-melanoma skin ca**
  - **Regional & distant recurrence of melanoma**
  - **Mortality rate exceeds melanoma**
    - **5-year: 30-64%**
- **Elderly**
- **Merkel cell polyomavirus (MCV)**

Merkel Cell Carcinoma

Differential Diagnosis

Merkel Cell Carcinoma

Melanoma

Lymphoma

Neuroblastoma

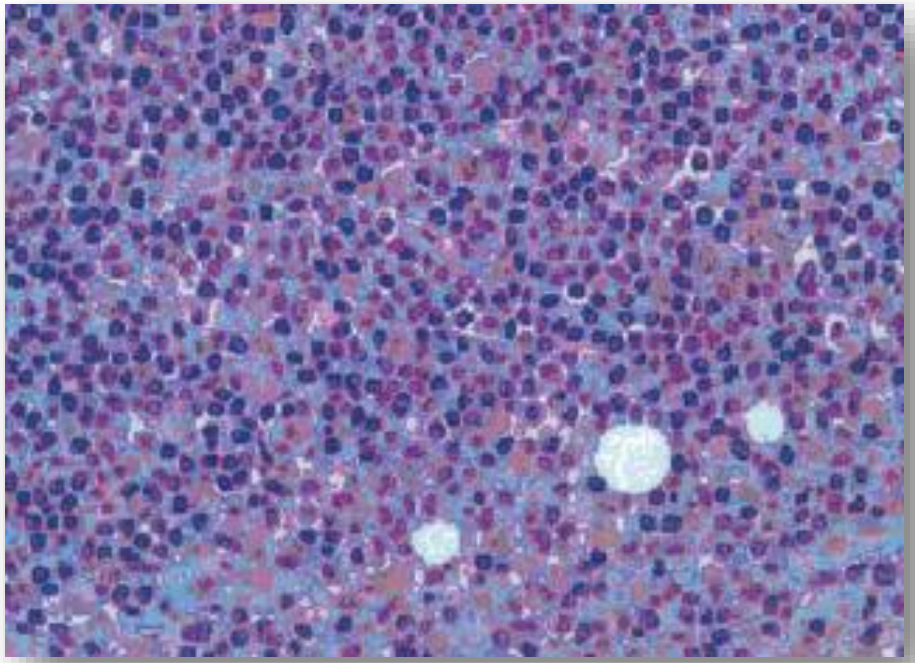
Carcinoid

Metastatic Small Cell Carcinoma of the Lung
Rhabdomyosarcoma

Extraskeletal Ewing's Sarcoma

Primitive Neuroectodermal Tumor (PNET)

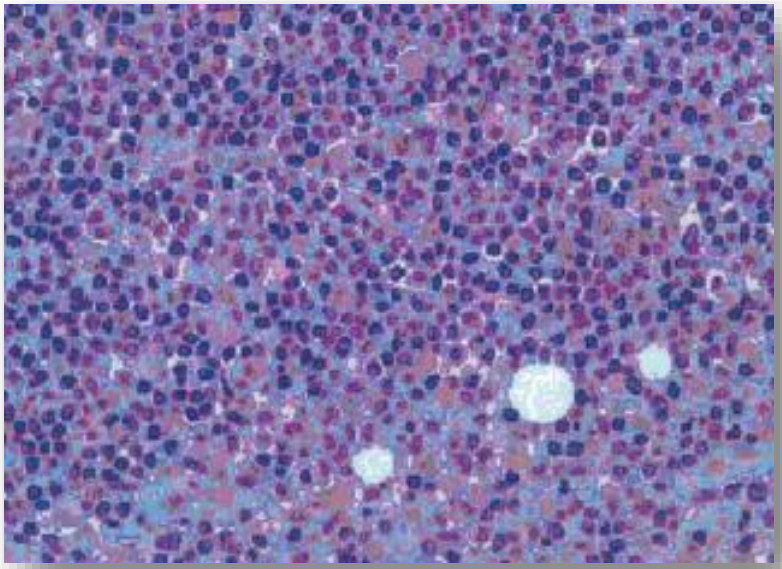
Small Round Blue Cells



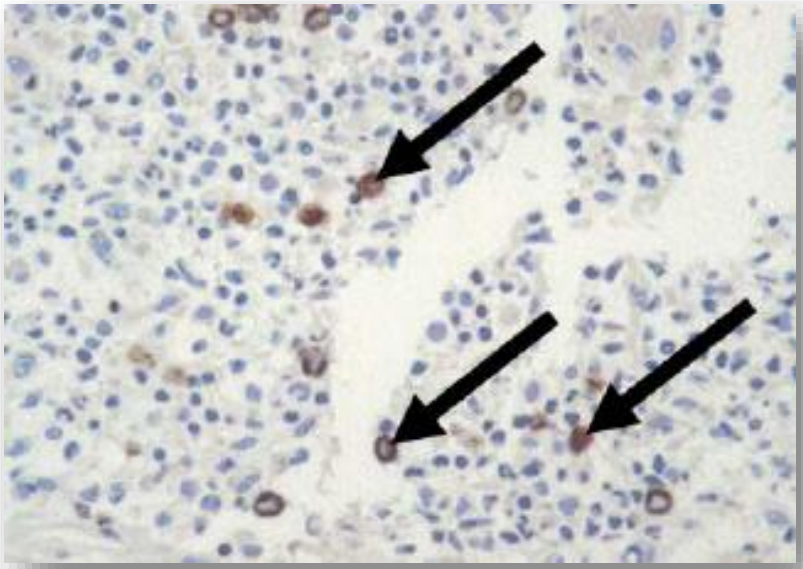
SLN Histologic Evaluation: MCC

H&E Staining

Small Round Blue Cells



CK-20 IHCS



Schmalbach CE, et al. Archives Otolaryngol. 131:610, 2005.

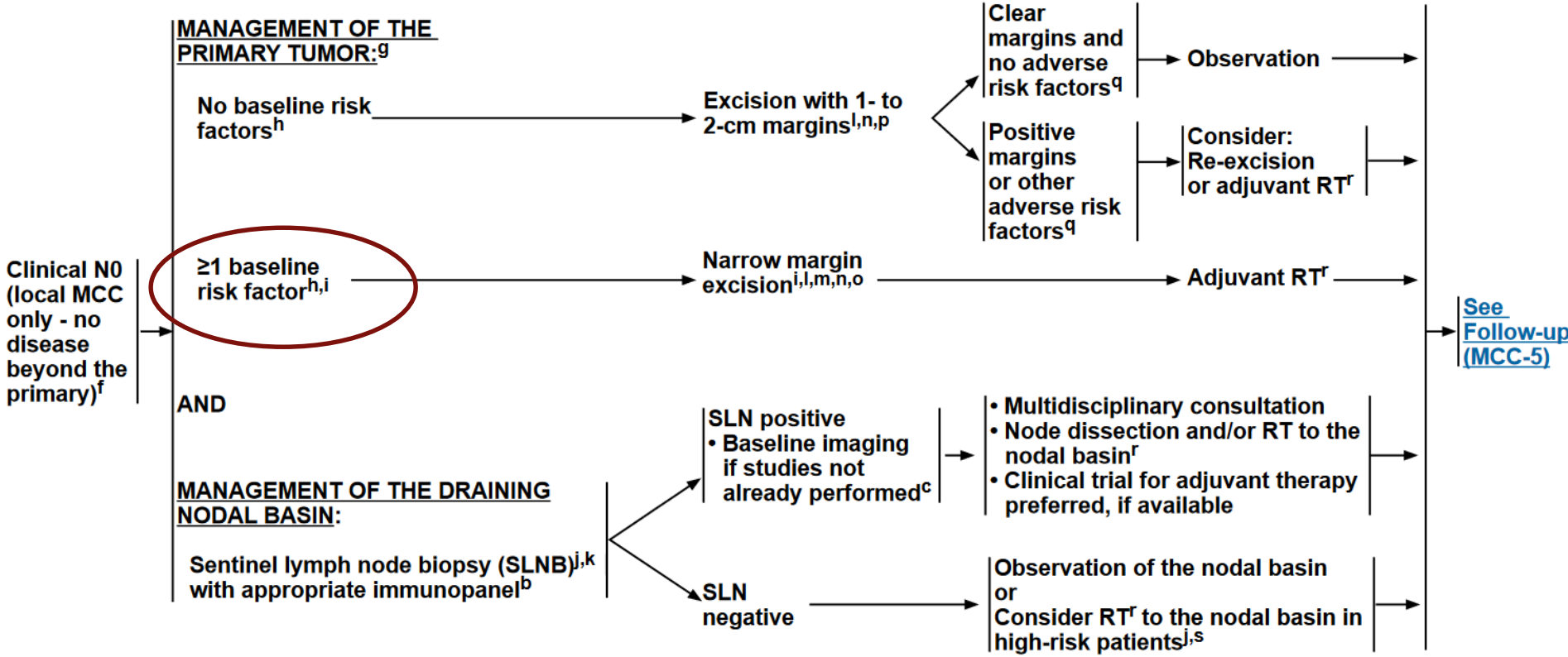
Reliability of SLNB for Regional Staging of H&N MCC

Schmalbach CE, Lowe L, Teknos TN, Johnson TM, Bradford CR. Archives Otolarygol 2005; 131:610

- **10 patients (1995 – 2003)**
- **Median F/U: 34.5 months**
- **SLN identified in 100% Pts (mean: 2.4)**
- **2 of 10 pts (20%) had a + SLN**
  - **Both negative on H&E**
  - **Occult metastasis only identified with CK-20**
- **1 of 8 (12%) – SLN patients recurred regional**
  - **Rate of false omission = 12%**
- **SLN technique safe and reliable for MCC**

MERKEL CELL CARCINOMA 1.2020

PRIMARY AND ADJUVANT TREATMENT OF CLINICAL N0 DISEASE



National Comprehensive Cancer Network®

MERKEL CELL CARCINOMA 1.2020

Clinically N-Zero

- ***Narrow Margin Excision***
- **SLNBx**

Considered the most sensitive staging technique

Clinically N-Positive

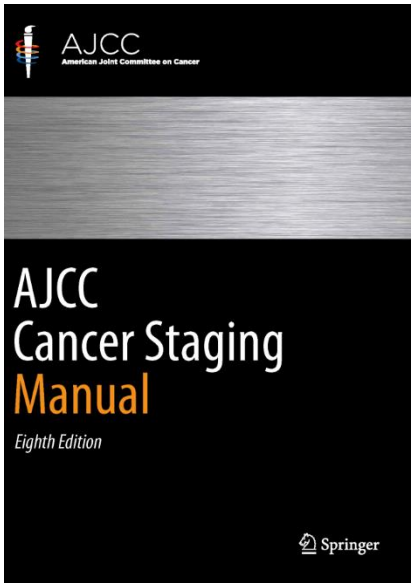
WLE

- ***Therapeutic Neck Dissection and/or radiation therapy***
- ***To consider Chemotherapy***

Distant Metastasis

- ***Supportive Care***
- ***T/C Surgery, Radiation, and/or Chemotherapy***

8th Ed. MCC Staging (2018)



Primary Tumor Stage Features

Tx Tumor cannot be assessed

T0 No evidence of primary tumor

Tis *In situ* primary tumor

T1 2 cm in maximum dimension

T2 > 2 cm but ≤ 5cm in maximum dimension

T3 > 5cm in maximum dimension

T4 Tumor invades extracutaneous structures

Fascia; Muscle; Cartilage; Bone

MCC Staging

Regional Lymph Nodes

Nx	Nodes cannot be assessed
cN0	No regional lymph nodes on clinical or radiographic exam
pN0	No regional lymph node metastases on pathologic exam
N1a	Micrometastasis (SLNB)
N1b	Macrometastasis
N2	*In transit* metastasis without LN metastasis
N3	*In transit* metastasis with LN metastasis

Distant Metastases

M0	No distant metastasis
M1a	Metastasis to skin, subcutaneous tissues, or distant LN
M1b	Metastasis to lung
M2b	Metastasis to all other visceral sites

Key Pearls

Skin Cancer Epidemic

- Ultraviolet (UV) is a carcinogen

Basal Cell Carcinoma

- Hedgehog Inhibitors for advanced disease

cSCC

- Formal staging disbanded
- Immunosuppressed population behaves differently
- Orbital exenteration for periorbital fat involvement
- SLNB promising but investigational

Merkel Cell Carcinoma

- Elderly; Poor Prognosis
- Small round blue cells (CK-20+; TTF-1 negative)
- SLNB standard of care