Non-Melanoma Cutaneous Malignancies

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No Related Financial Disclosures
or
Conflicts of Interest

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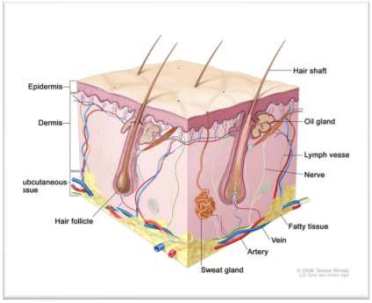
Overview

- Skin Cancer Epidemiology
- Squamous Cell Carcinoma (cSCC)
- Basal Cell Carcinoma (BCC)
- Merkel Cell Carcinoma (MCC)



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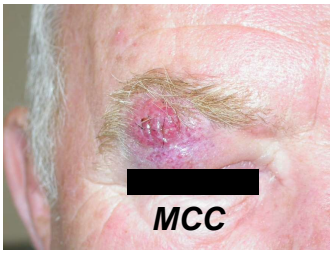
Non-Melanoma Skin Ca (NMSC)

> 80 different histologic types

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



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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)*

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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**

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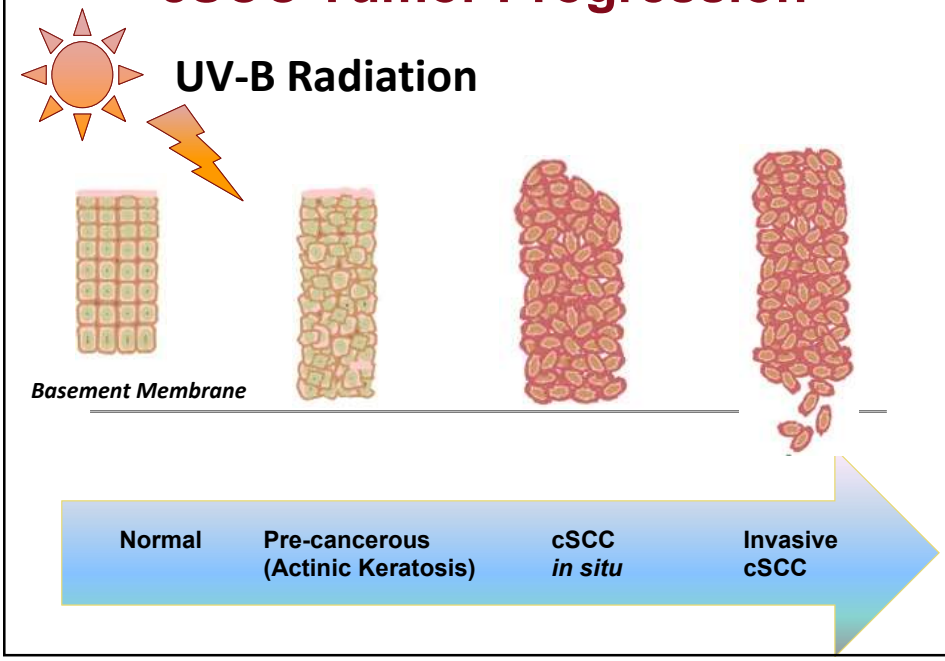
cSCC Tumor Progression



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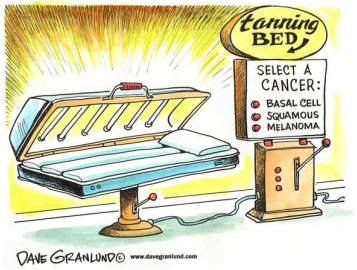
Tanning Booths

- 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.

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I. Management of Advanced Squamous Cell Carcinoma (SCC)

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cSCC Risk Stratification

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Squamous Cell Skin Cancer

STRATIFICATION TO DETERMINE TREATMENT OPTIONS AND FOLLOW-UP FOR LOCAL CSCC BASED ON RISK FACTORS FOR LOCAL RECURRENCE, METASTASES, OR DEATH FROM DISEASE

Risk Group[1]	Low Risk	High Risk	Very High Risk
Treatment options	See SCC-2	See SCC-3	See SCC-3
H&P			
Location/size[2]	Trunk, extremities ≤2 cm	Trunk, extremities >2 cm – ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital (any size)[5]	
Borders	Well-defined	Poorly defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammatory process	(-)	(+)	
Rapidly growing tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology (See SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poor differentiation
Histologic features: Acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarcomatous) subtypes	(-)	(+)	Desmoplastic SCC
Depth[3,4]: Thickness or level of invasion	≤6 mm and no invasion beyond subcutaneous fat		>6 mm or invasion beyond subcutaneous fat
Perineural involvement	(-)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(-)	(-)	(+)

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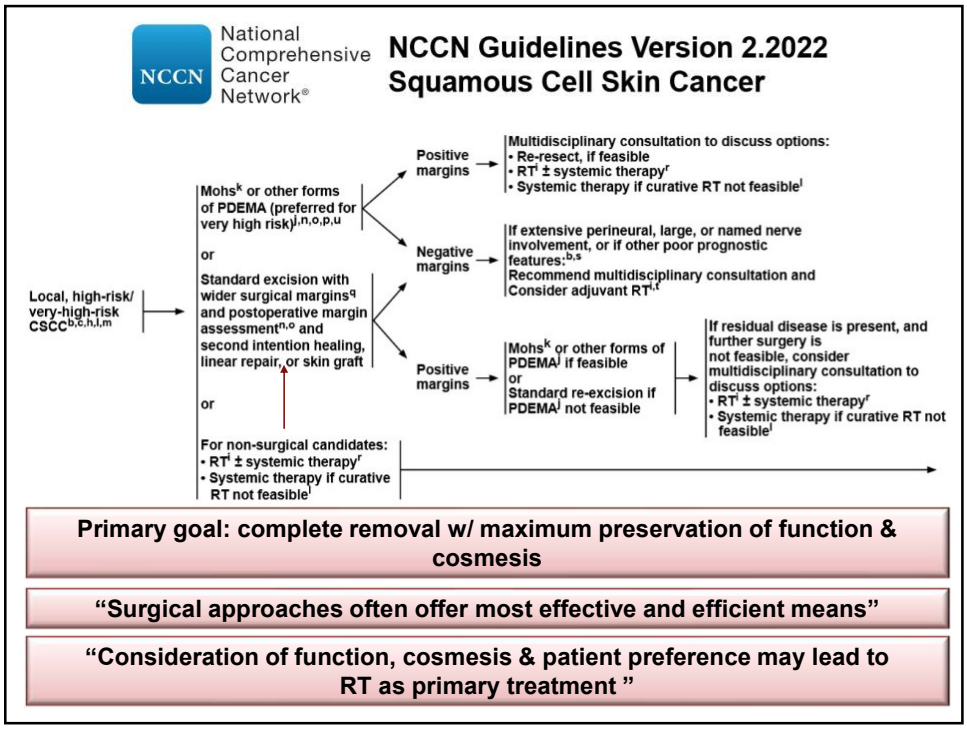

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Squamous Cell Carcinoma (SCC)

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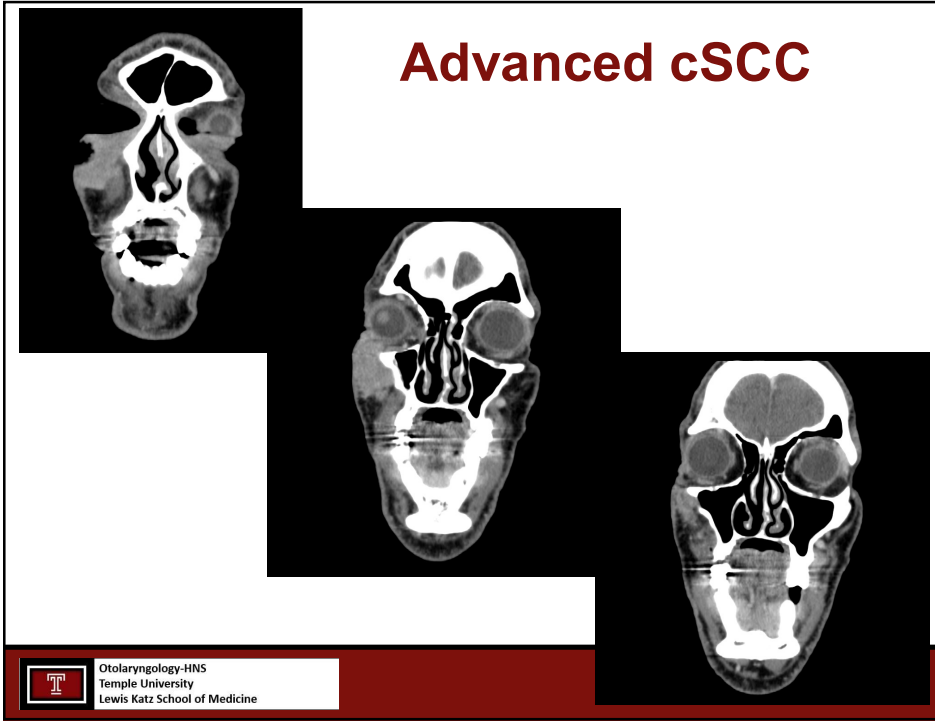
Advanced cSCC



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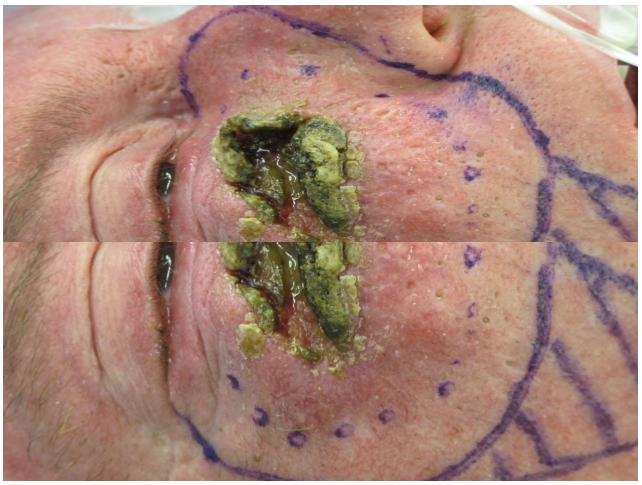
Surgical Management



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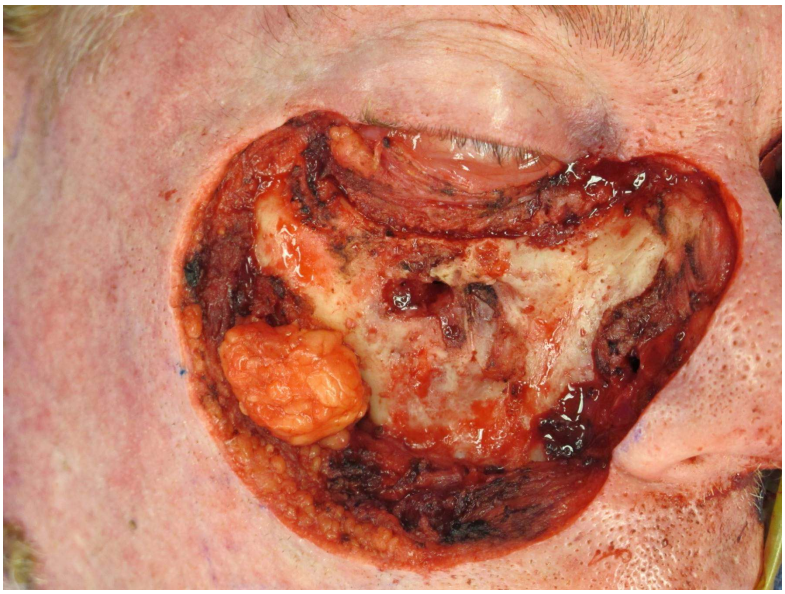

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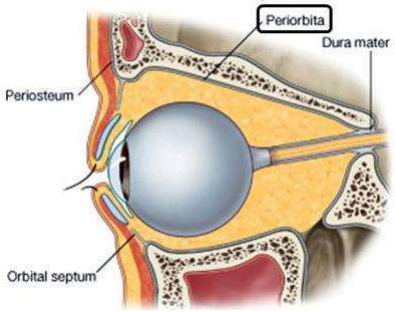
When do you Exenterate?

- 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



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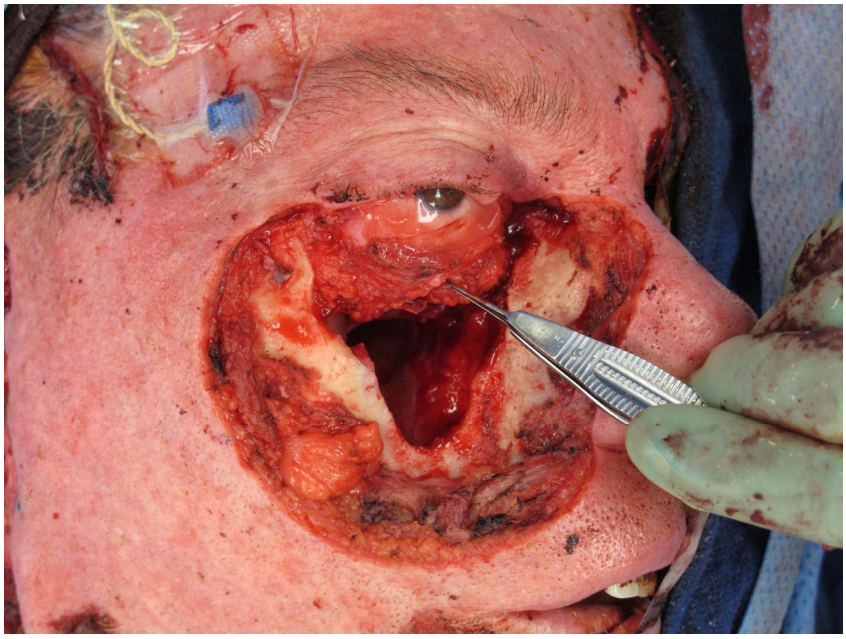

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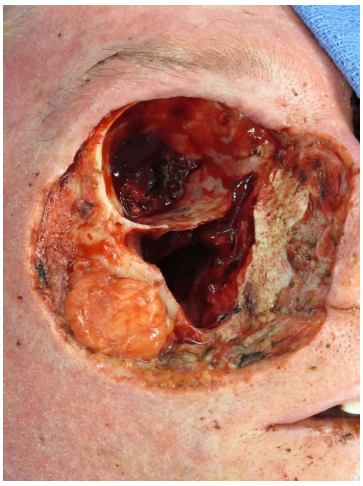
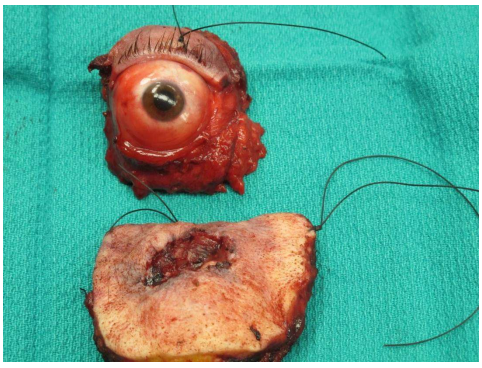
Orbital Exenteration





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ALT FF

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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

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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

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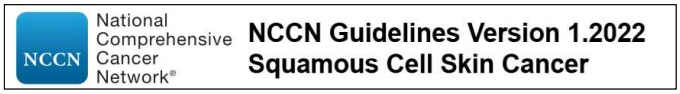
cSCC Surgical Margins



- WLE with 4-6mm margin for low risk cSCC (not HN)
- PDEMA (Peripheral & Deep en face Margin Assessment) preferred for high very risk cSCC
- NCCN unable to make definitive recommendations for WLE surgical margins in high risk patients due to "wide variability of clinical characteristics defining category".

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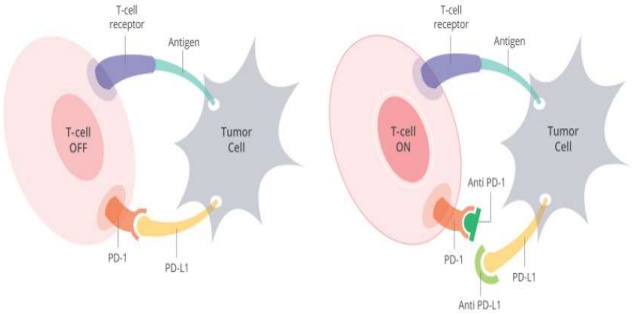
Checkpoint (PD-1) Inhibitors



Combat suppression of T cells

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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**

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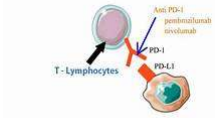

Pembrolizumab

- 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

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AHNS Position Statement on the Use of PD-1 inhibitors for Treating Advanced Cutaneous Squamous Cell Carcinoma (cSCC)

Goals

- Provide evidence based recommendations for utilization
- Identify knowledge gaps warranting further research

Methodology

- Literature review (PubMed, Cochrane, Google Scholar)
- Delphi Method (70% consensus)
- Multidisciplinary Review
  - Nancy Y. Lee MD, Rad Onc - MSKCC
  - Dan Zandberg MD, Med Onc - UPMC
- AHNS public review (n=147)

CUTANEOUS CANCER SECTION LEADERSHIP

Karen. Choi, MD	*Penn State Health*
Kevin Emerick, MD	*Mass Eye & Ear*
Brian Hughley, MD	*Univ of Florida*
Alice Lin, MD	*Kaiser Permanente*
Brian Moore, MD	*Ochsner Health*
Miriam O'Leary, MD	*Tufts Medical Center*
Thomas J. Ow, MD	*Montefiore Med. Center*
Cecelia Schmalbach, MD	*Temple University*
Steven Wang, MD	*Univ. Arizona*

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AHNS Position Statement on the Use of PD-1 inhibitors for Treating Advanced Cutaneous Squamous Cell Carcinoma (cSCC)

3A: Surgical resection with adjuvant radiation based on final pathology remains the standard of care for patients with resectable cSCC

3B. Primary radiation may be considered as definitive treatment for cSCC patients who are not eligible candidates for surgery

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AHNS Position Statement on the Use of PD-1 inhibitors for Treating Advanced Cutaneous Squamous Cell Carcinoma (cSCC)

3C: With rare exception, PD-1 inhibitor use outside of a clinical trial is not recommended for locally advanced cSCC in which curative intent surgery and/or radiation is likely to achieve meaningful disease free control

3D: With rare exception, PD-1 inhibitor use outside of a clinical trial is not recommended for regional metastasis in which curative intent surgery with adjuvant radiation based on final pathology is likely to achieve meaningful disease free control

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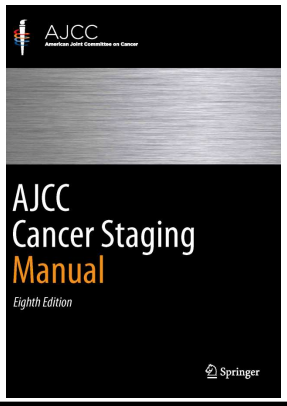
8th Ed AJCC Staging

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**



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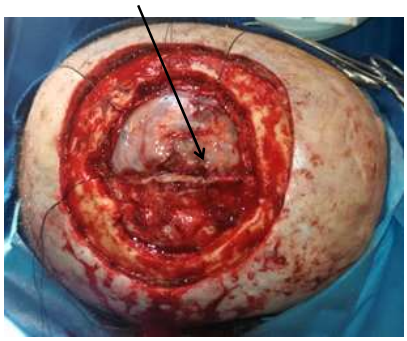
Organ Transplant: Risk Increases x 250

Sagittal Sinus Invasion



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8th Ed AJCC Staging

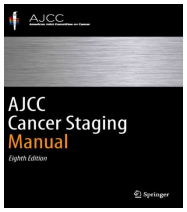
January 2018

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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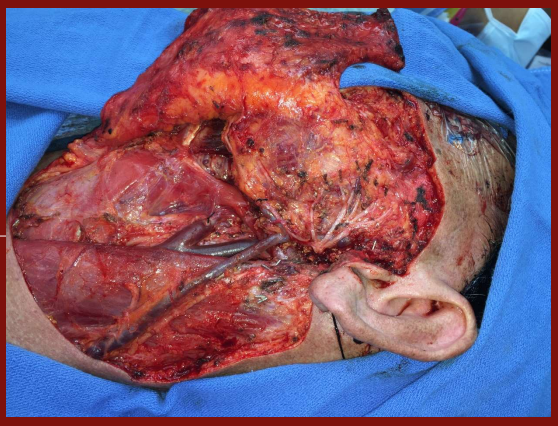

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http://otojournal.org
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Immunosuppression Impact on Head and Neck Cutaneous Squamous Cell Carcinoma: A Systematic Review with Meta-analysis

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

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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

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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%)**

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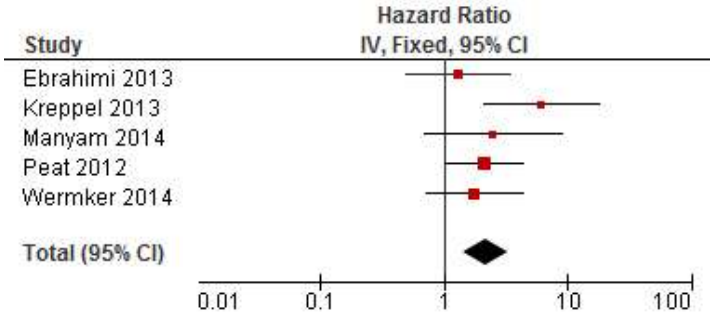
Results: Systematic Review

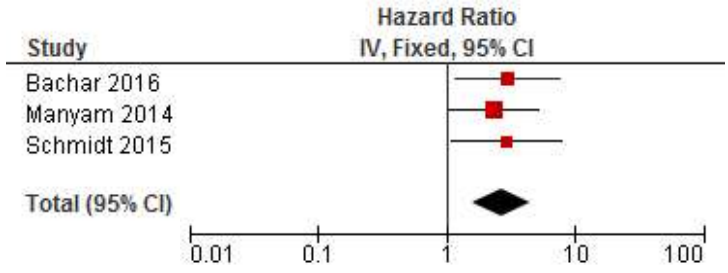
- Immunosuppressed cohort
  - n = 317 (11%)
- Etiology
  - Solid Organ (74; 23%)
  - Lymphoproliferative Disorders (70; 22%)
  - Chronic Immunosuppressive Tx (12; 4%)
  - Not specified (161; 51%)

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)

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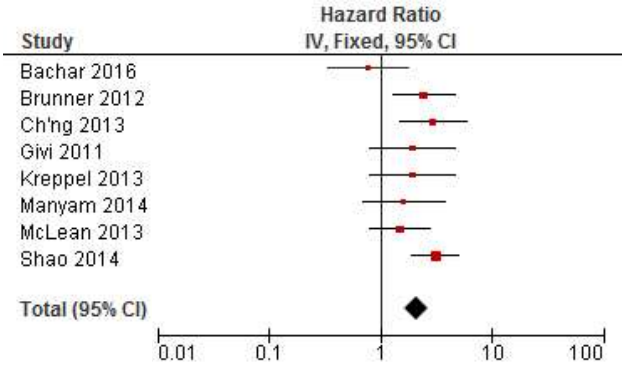
Meta-Analysis Results: Overall Survival (OS)



Immunosuppressed pts demonstrated worse OS
(Pooled HR: 2.09)

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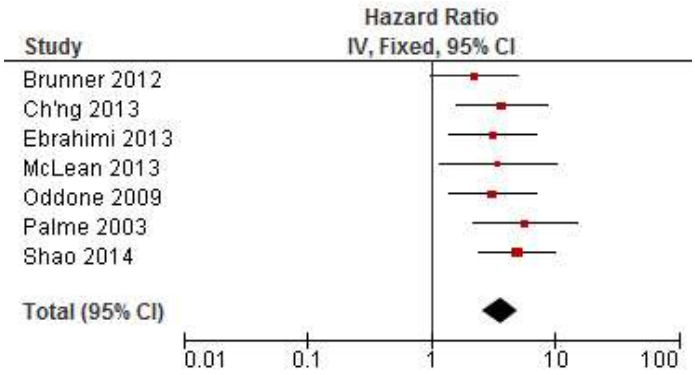
Meta-Analysis Results: Disease Specific Survival (DSS)



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

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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**

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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**

Regenstrief Institute

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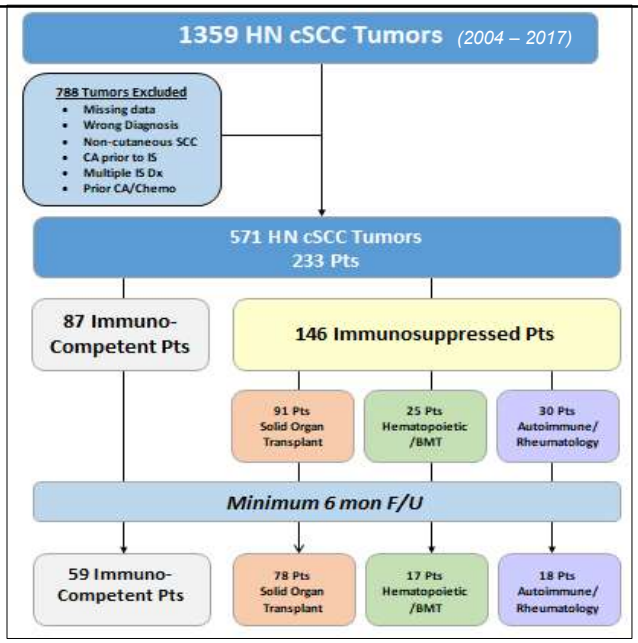

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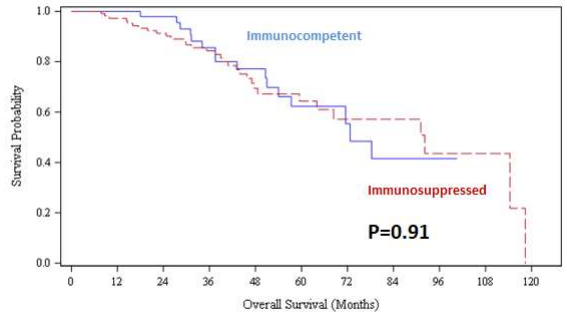
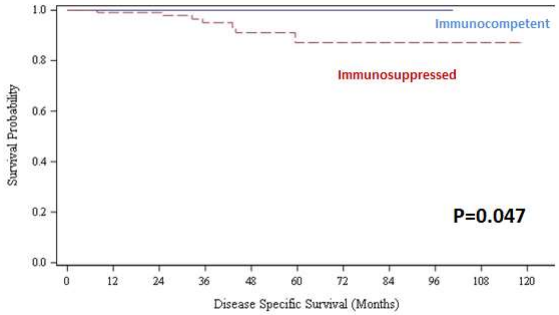


Overall Survival



Disease Specific Survival

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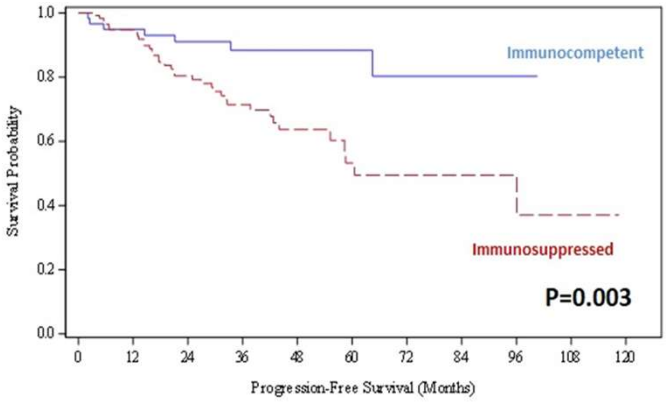
Progression Free Survival



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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.

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AHNS Position Statement on the Use of PD-1 inhibitors for Treating Advanced Cutaneous Squamous Cell Carcinoma (cSCC)

2G: Immunosuppression portends a poor prognosis with respect to tumor recurrence and survival; however, the degree of impact and associated implications to staging and treatment remains to be defined through further prospective trials

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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**

3G: FDA approval for PD-1 blockade in advanced cSCC is based on clinical trials performed in immunocompetent patients; the safety and efficacy in the immunosuppressed patient population to include organ transplant recipients remains to be determined by future clinical trials

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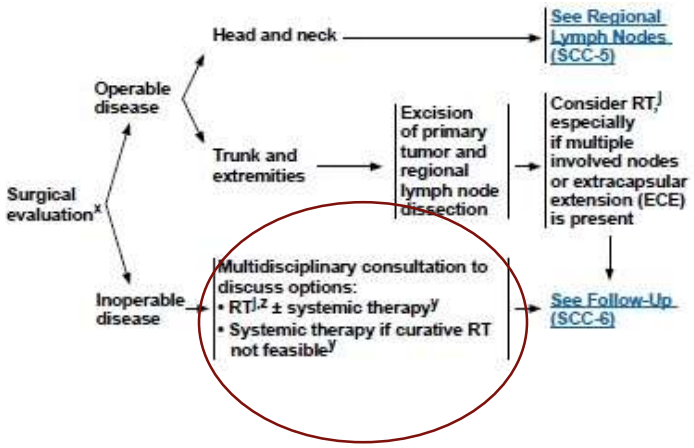
cSCC Adjuvant Systemic Therapy



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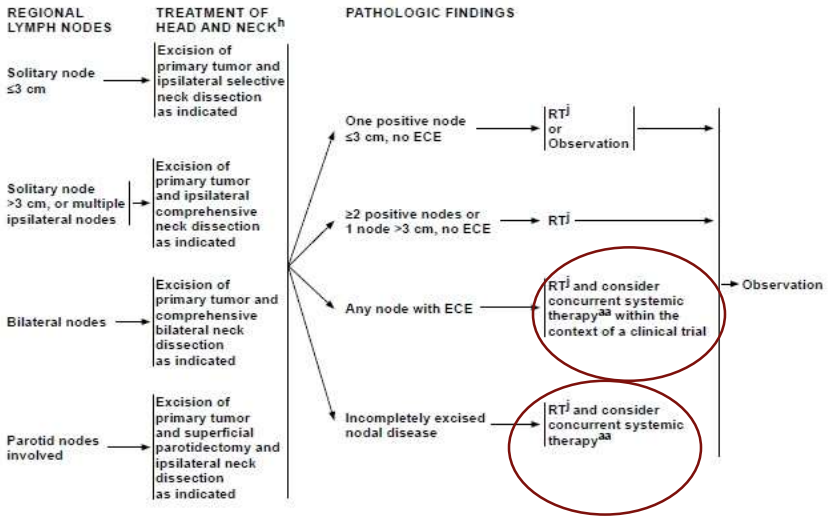
cSCC Adjuvant Systemic Therapy



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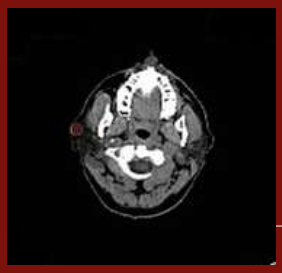

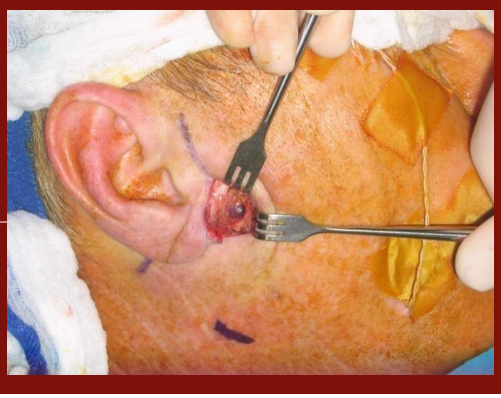

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http://otojournal.org
SAGE

Utility of Head and Neck Cutaneous Squamous Cell Carcinoma Sentinel Node Biopsy: A Systematic Review

Mostafa M. Ahmed, MD[1], Brian A. Moore, MD[2], and Cecelia E. Schmalbach, MD[3]

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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.

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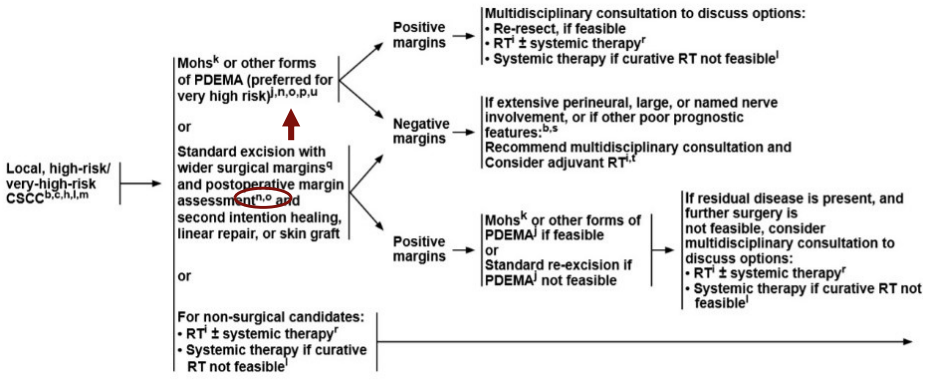
Squamous Cell Skin Cancer



0 – Discuss & consider SLNBx for very high-risk cSCC that are recurrent or have multiple risk factors and have normal nodal exam

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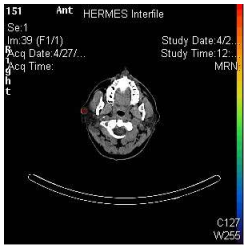
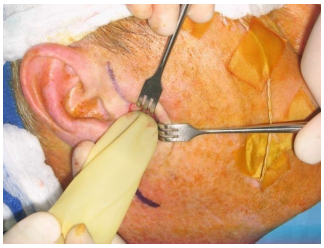
AHNS Position Statement on cSCC Sentinel Node Biopsy

2F: the most sensitive and specific means for identifying occult regional disease and is a helpful tool in tumor staging;

the impact on disease free survival and overall survival remains to be determined.





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II. Management of the Basal Cell Carcinoma (BCC)

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BCC Risk Stratification

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Basal Cell Skin Cancer

Risk Group	Low Risk	High Risk
Treatment Options	See BCC-2	See BCC-3
H&P		
Location/size	Trunk, extremities <2 cm	Trunk, extremities ≥2 cm
		Cheeks, forehead, scalp, neck, and pretibia (any size)
		Head, neck, hands, feet, pretibia, and anogenital (any size)[3]
Borders	Well-defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology (See BCC-A)		
Subtype	Nodular, superficial[2]	Aggressive growth pattern[4]
Perineural involvement	(-)	(+)

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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**

NCCN Guidelines 1.2018

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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

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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.

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Vismodegib: Side Effects (150 mg PO QD)

- Arthralgia
- Muscle Cramping

} **Hyponatremia**

- Alopecia
- Diarrhea
- Fatigue
- Dysguesia/loss appetite/weight loss
- Teratogen****

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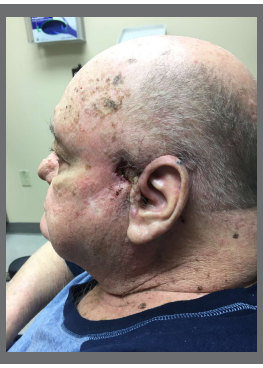

78 y.o. demented male presents with biopsy proven advanced BCC (present for > 3 yr)

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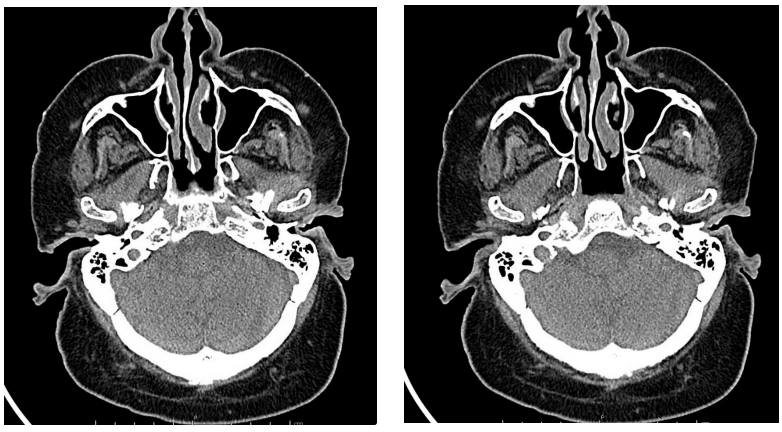
5 Months Vismodegib



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

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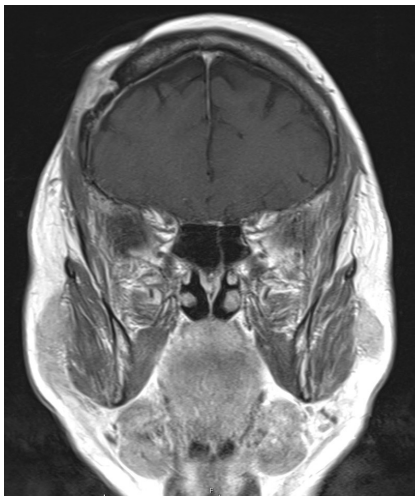
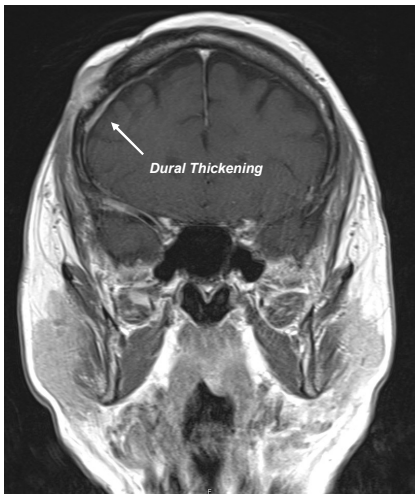
MRI with Gadolinium: BCC





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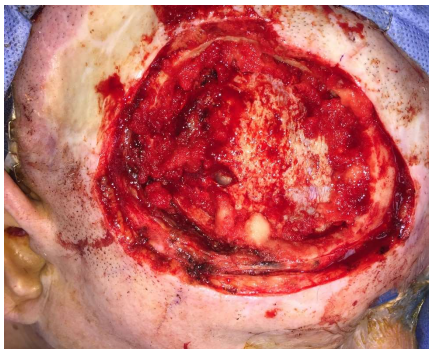
Cranial Erosion

Dural Involvement



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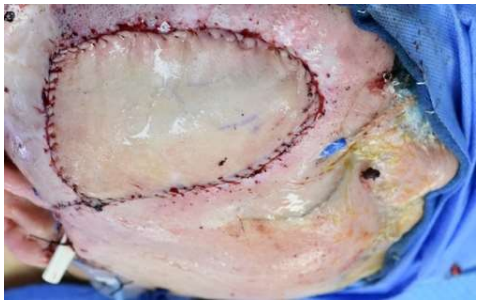
Dural Resection **Mesh & RFFF**



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3 weeks post-op

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9 weeks post-op

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HHg Inhibitor: Indications

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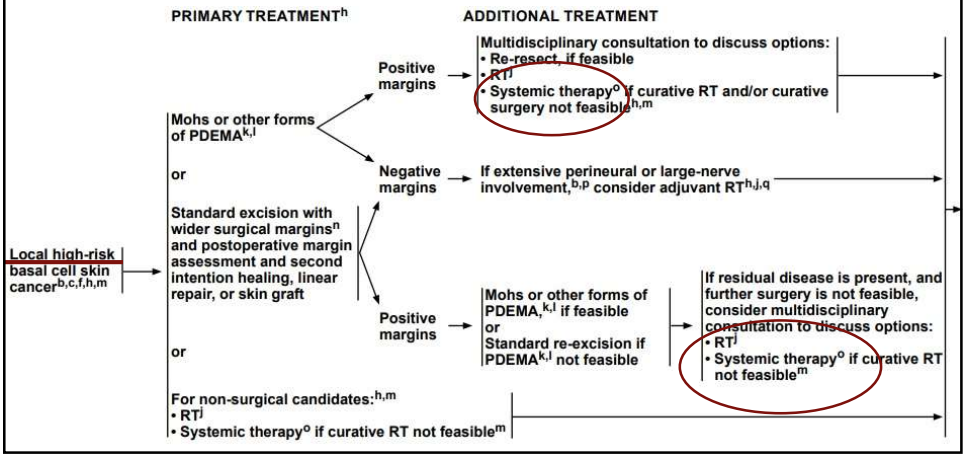

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HHg Inhibitor: Indications

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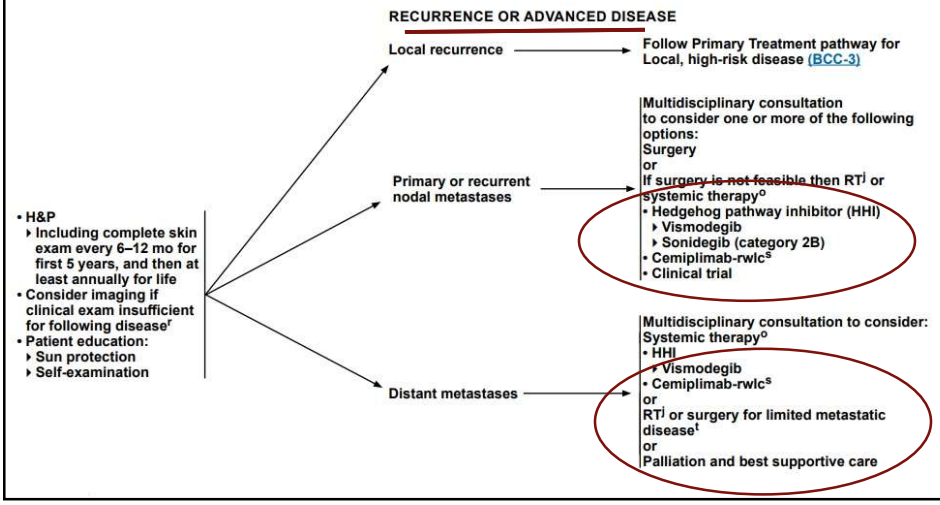
Basal Cell Skin Cancer



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FDA

Feb 9, 2021

The FDA has approved cemiplimab-rwlc (Libtayo) as the first immunotherapy for use in patients with advanced basal cell carcinoma (BCC) that has previously been treated with a hedgehog pathway inhibitor (HHI) or for whom a HHI is not appropriate.

Locally Advanced & Metastatic BCC

- **Progressed on HHI**
- **Failed to Respond to HHI over 9 month**
- **Intolerant to HHI**
- **Not a candidate for**
  - **HHI**
  - **Surgery**
  - **Radiation**

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FDA

Feb 9, 2021

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Locally Advanced BCC (n=84 pts)

- **Overall Response Rate = 29%**
  - **6% (n=5) Complete Response**
  - **23% (n=19) Partial Response**
- **79% achieved 6mon duration**

Metastatic BCC (n=28 pts)

- **Overall Response Rate = 21% (n=6)**
  - **All Partial response (no CR)**
- **79% achieved 6mon duration**

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BCC Systemic Therapy

- **Considered for locally advance & metastatic BCC**
- **NOT used where topical therapy, surgery, or XRT likely to be curative**
- **Multidisciplinary TB required**
- **HHI (*vismodegeb; sonidegib*) may be considered for diffuse BCC**
- ***Cemiplimab-rwlc* recommended for patient previously treated with HHI or in whom HHI not appropriate**

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III. Merkel Cell Carcinoma (MCC)

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

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Merkel Cell Carcinoma

<u>Differential Diagnosis</u>

Merkel Cell Carcinoma

Melanoma

Lymphoma

Neuroblastoma

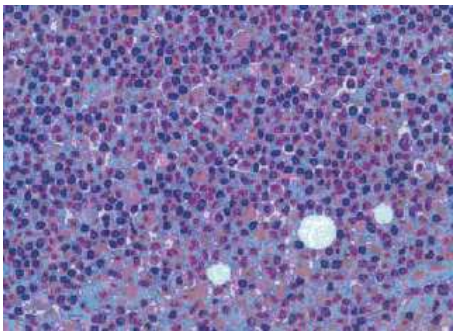
Carcinoid

Metastatic Small Cell Carcinoma of the Lung
Rhabdomyosarcoma

Extraskeletal Ewing's Sarcoma

Primitive Neuroectodermal Tumor (PNET)

Small Round Blue Cells



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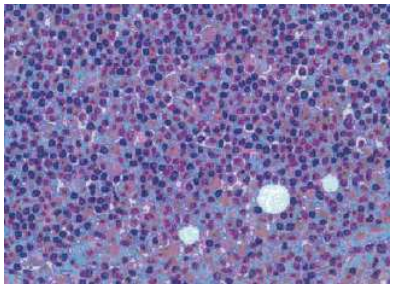
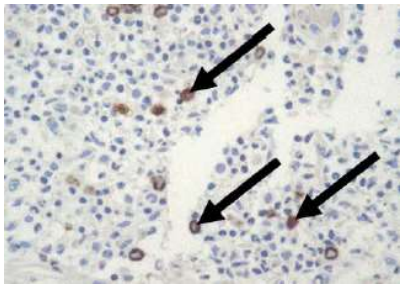
SLN Histologic Evaluation: MCC

H&E Staining

Small Round Blue Cells



CK-20 IHCS



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

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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**

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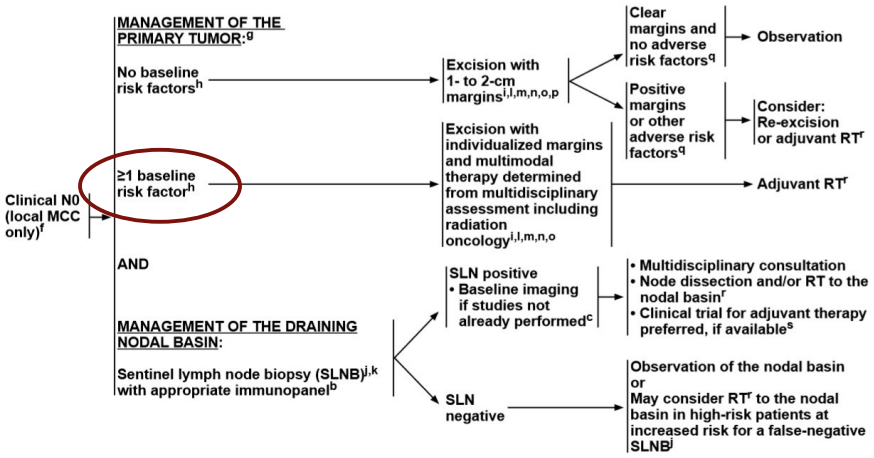
Merkel Cell Carcinoma



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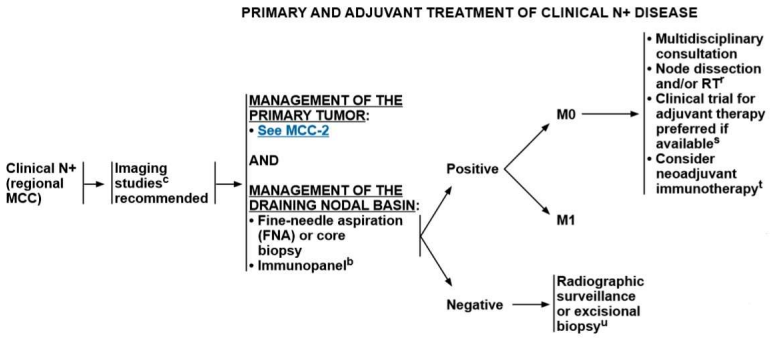
Merkel Cell Carcinoma



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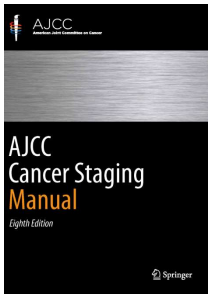
8th Ed. MCC Staging (2018)

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

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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**

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Key Pearls

Skin Cancer Epidemic

- Ultraviolet (UV) is a carcinogen

Basal Cell Carcinoma

- Systemic therapy for advanced disease

cSCC

- First line tx; surgery or radiation
- PD-1 inhibitors if first line fails
- Immunosuppressed population behaves differently
- Orbital exenteration for periorbital fat involvement

Merkel Cell Carcinoma

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