Module 1 - Identifying High-Risk Cutaneous Squamous Cell Carcinoma (cSCC)

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The Purpose of Risk Stratification

Prior to surgery

- To identify patients who require radiologic staging
- To identify patients who require multidisciplinary care
- To inform decision-making regarding neoadjuvant therapy
- To inform primary treatment

Following surgery

- To identify patients who may benefit from adjuvant therapy
- To identify patients who may benefit from surveillance imaging

Throughout the treatment process:

To aid physicians in counseling patients about their tumor and prognosis

Resources Available to Risk Stratify cSCC

NCCN National Comprehensive Cancer Network®

riSCC riSCC Calculator

ACS AJCC
American Joint Committee on Cancer
American College of Surgeons

Erasmus MC Cancer Institute

Brigham and Women's Hospital
Founding Member, Mass General Brigham

Case Example

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

- Patient presents for surgical consultation for a biopsy-proven squamous cell carcinoma on the scalp

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

What information about **the patient** is useful for risk stratification and decision-making?

- Age
- Sex
- Immune status
- Overall health and comorbidities

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

Patient factors

- Male
- 75 years old
- Myasthenia gravis; on azathioprine for over a decade

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

What information about **the tumor history and presentation** is useful for risk stratification and decision-making?

- Preoperative size
- Whether tumor is rapidly growing
- History of previous tumor treated in this area (primary vs recurrent tumor)
- History of radiation or chronic inflammation at the site
- Whether the site is symptomatic
- Whether the lesion appears fixed on exam

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

Tumor history and presentation

- Preoperative size: 5 cm
- Rapidly growing
- Primary tumor
- No history of radiation or chronic inflammation at the site
- Lesion is tender
- Lesion appears fixed

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

What information about **the tumor pathology** is useful for risk stratification and decision-making?

- Histologic differentiation
- Depth of invasion
- Perineural invasion
- Lymphovascular invasion

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp

Tumor pathology

- Moderate differentiation
- Invading at least dermis—biopsy captured only dermis
- No perineural invasion observed on biopsy
- No lymphovascular invasion observed on biopsy

Image courtesy of Nina Ran, MD, MPH, MSTR

NCCN Risk Stratification: Very High Risk

STRATIFICATION TO DETERMINE TREATMENT OPTIONS FOR LOCAL cSCC BASED ON RISK FACTORS FOR LOCAL RECURRENCE, METASTASES, OR DEATH

Risk group	Low risk	High risk	Very high risk
Treatment options	SCC-4	SCC-5	SCC-5 and SCC-6
H&P			
Location/diameter (cm)	Trunk, extremities <2 cm	Trunk, extremities 2 cm to ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital area (any size)	
Clinical borders	Wel -defined	Poorly defined	
Primary vs recurrent	Primary	Recurrent	
Immunosuppression	(–)	(+)	
Site of prior RT or chronic inflammation	(–)	(+)	
Rapid growth tumor	(–)	(+)	
Neurologic symptoms	(–)	(+)	
Pathology (SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poorly differentiated
Histologic subtype	(–)	(+)	(+)
Depth: Thickness or level of invasion	<2 mm thick and no invasion beyond subcutaneous fat	2 to 6 mm depth 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	(–)	(–)	(+)

NCCN Recommendations for Very High Risk

VERY-HIGH-RISK cSCC

Very-high-risk cSCC with significant risk of extensive local recurrence, nodal, or in-transit metastasis

TREATMENT PLANNING

- Multidisciplinary consultation at center with specialized expertise to discuss options
- Radiologic staging
  - MRI with and without contrast or CT with contrast and/or ultrasound
  - Abnormal lymph nodes identified by imaging studies (SCC-8)

or

- Consider SLNB in cases that are recurrent or with multiple high-risk features

and

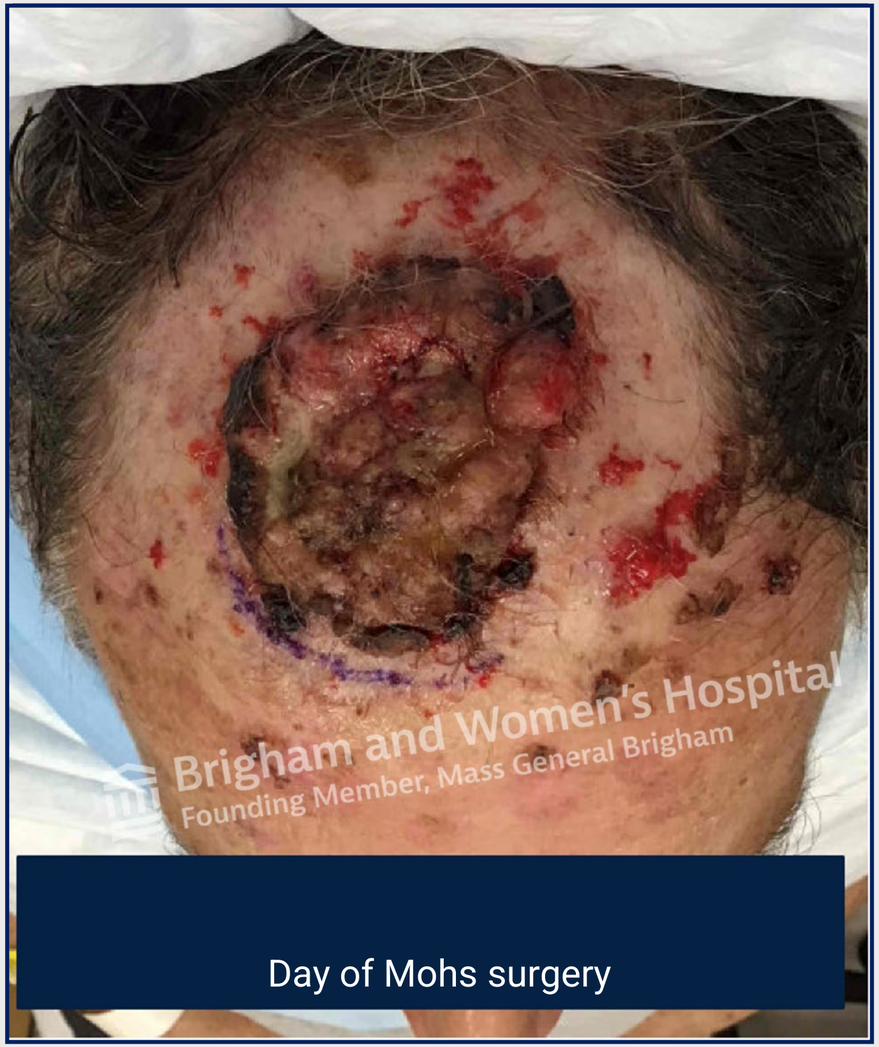
- Consider neoadjuvant therapy with cemiplimab-rwic if
  - Nonreactive nonkeratoacanthomatous rapid growth tumors
  - In-transit metastasis
  - Borderline resectable
  - Surgery alone may not be curative or may result in significant functional limitation

Pause for discussion on

Consideration of imaging
Consideration of MDC
Consideration of neoadjuvant cemiplimab

CT = computed tomography; MRI = magnetic resonance imaging; SLNB = sentinel lymph node biopsy.

Case 1 Continuation: Biopsy-Proven cSCC on the Right Parietal Scalp



Patient presents for surgical consultation for a biopsy-proven squamous cell carcinoma on the scalp

↓

Head CT negative for bone invasion

Neck CT negative for lymph node metastasis

↓

Multidisciplinary tumor board:

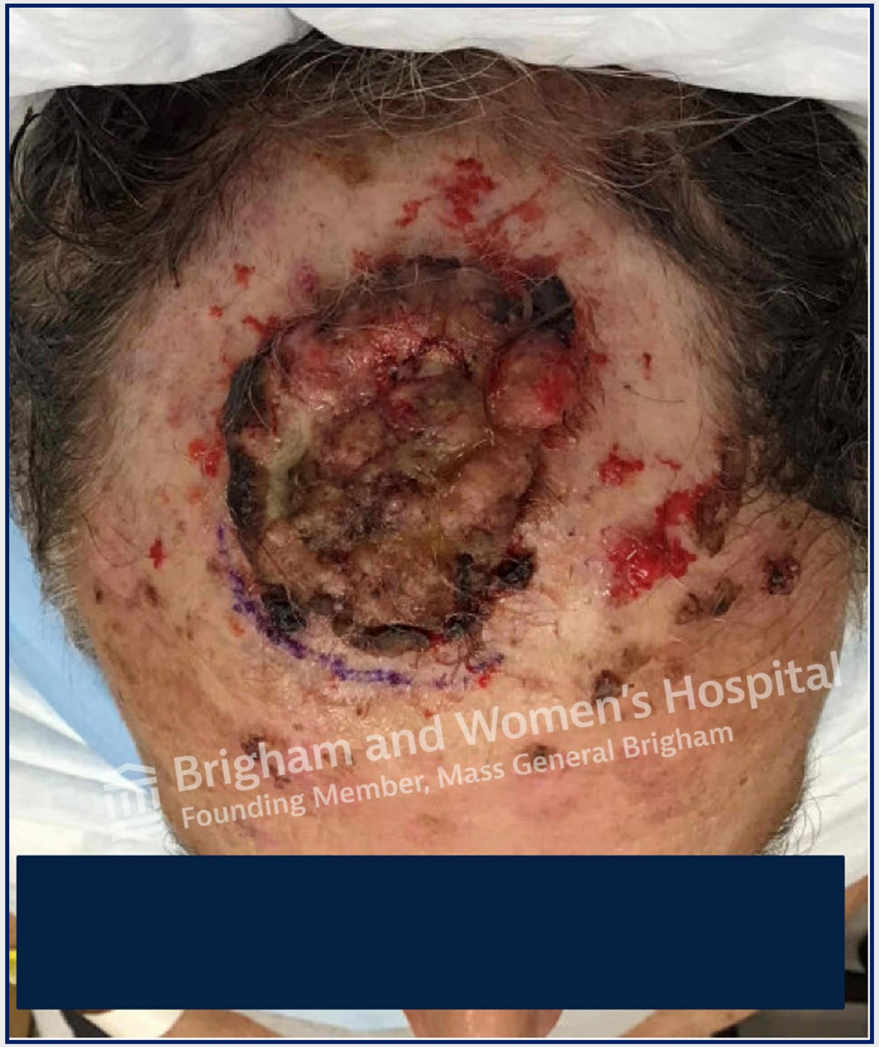
Not a good candidate for neoadjuvant cemiplimab and for general anesthesia; upfront surgery recommended

↓

Underwent Mohs surgery

Image courtesy of Nina Ran, MD, MPH, MSTR

Case 1: Biopsy-Proven cSCC on the Right Parietal Scalp



- Male
- 75 years old
- Myasthenia gravis; on azathioprine for over a decade

- Preoperative diameter: 5 cm
- Moderate differentiation
- Invasion to galea
- No perineural invasion on biopsy or Mohs debulk
- No lymphovascular invasion on biopsy or Mohs debulk

AJCC8 = 8th edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*; BWH = Brigham and Women's Hospital staging system.

Image courtesy of Nina Ran, MD, MPH, MSTR

AJCC 8th Edition T Staging: T3

4.1 Definition of Primary Tumor (T)

✓	*T Category*	*T Criteria*
	TX	Primary tumor cannot be assessed
	Tis	Carcinoma *in situ*
	T1	Tumor smaller than or equal to 2 cm in greatest dimension
	T2	Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
→	T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
	T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
	T4a	Tumor with gross cortical bone/marrow invasion
	T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or > 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

Brigham and Women's Hospital Staging: T2b

Table 3. Alternative T staging system

Alternative T staging system	Definition	Patients in study cohort, number (%)
T0	In situ SCC	Not included
T1	0 risk factors	134 (52)
T2a	1 risk factor	67 (26)
→ **T2b**	2–3 risk factors	49 (19)
T3	4 risk factors or bone invasion	6 (2)

Risk factors

- **Tumor diameter 2 cm or greater**
- Poorly differentiated histology
- Perineural invasion
- **Tumor invasion beyond subcutaneous fat**
  - Bone invasion automatically upstages to T3

Jambusaria-Pahlajani A, et al. *JAMA Dermatol*. 2013;149(4):402-410.

Staging Systems

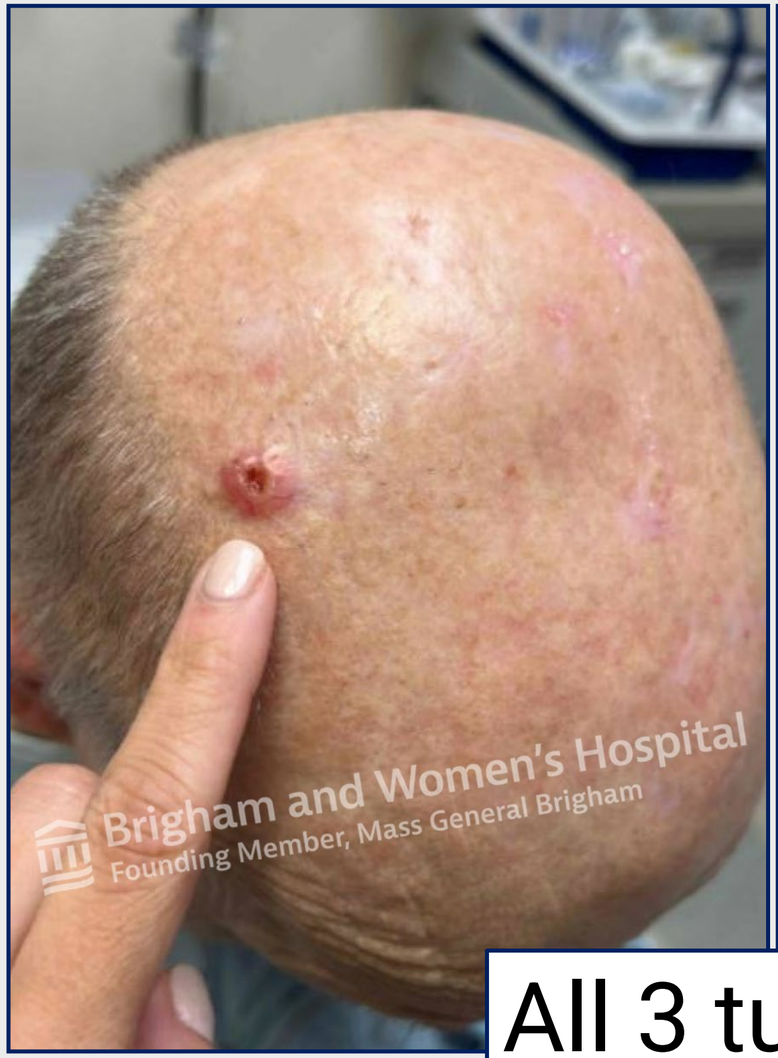
Discussion on the benefits/drawbacks of staging system

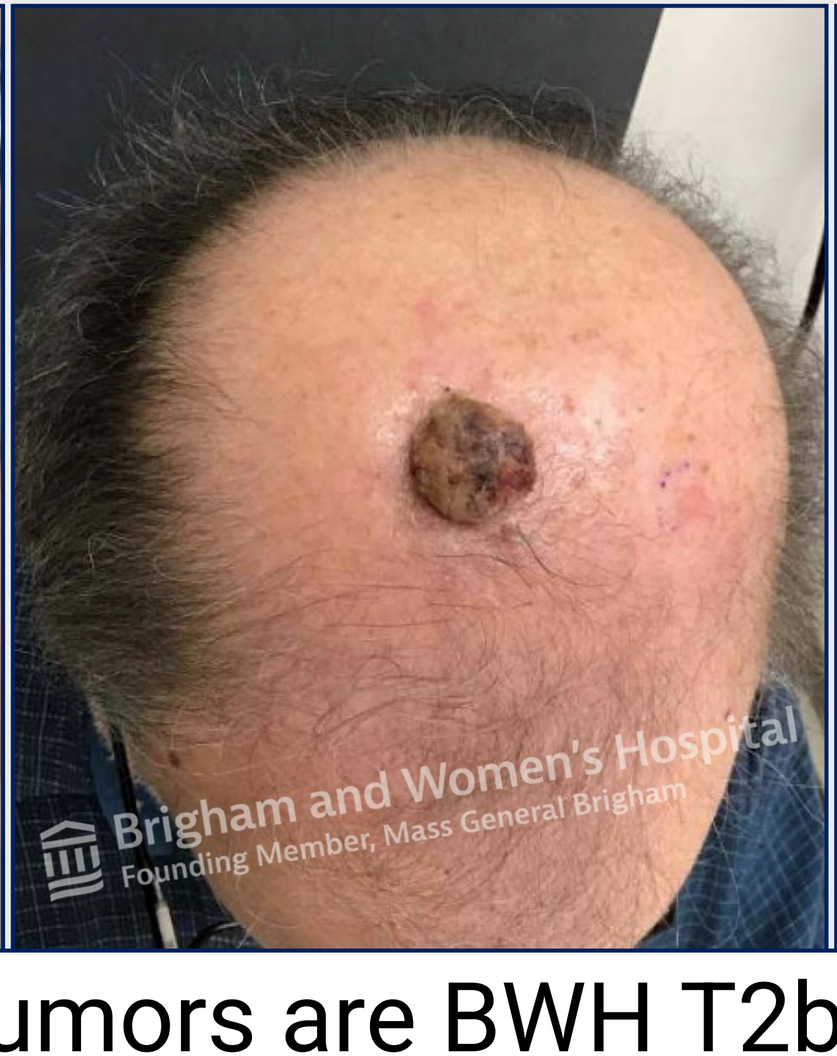
Benefits including

- Unified language to discuss risk
- Advantageous for study recruitment

Drawbacks including

- Tumors with the same stage can have different risks
- Predictions of risk are not precise
- AJCC8 for head/neck tumors only
- Do not include patient-associated factors (age, sex, immune status)





All 3 tumors are BWH T2b and are assigned the same risk.

Images courtesy of Nina Ran, MD, MPH, MSTR

Tumor-Specific Risk Prediction Modeling: Erasmus

Prediction of metastatic risk in patients with cutaneous squamous cell carcinoma (cSCC)

Erasmus MC Cancer Institute

This web-based calculator has been developed by the Skin Cancer Research Group of the Department of Dermatology at the Erasmus MC Cancer Institute in Rotterdam, and validated in an external cohort of cSCC patients, as described in Rentroia-Pacheco et al (2023) .

This model has only been developed and validated in cSCC and not in mucosal or genital SCC.

Patient characteristics

Age, in years

75

Age, in years. Patients should be adults (18 years or older)

Sex

Male

Number of prior cSCCs

2

Tumor location

Scalp or neck

Tumor characteristics

Tumor diameter, in cm

5

Macroscopic tumor diameter, as measured by a pathologist, in centimeters. Decimals are allowed e.g. 2.2

Tissue involvement

Beyond subcutaneous fat

Deepest layer of tissue involvement

Differentiation Grade

Good/moderate

Differentiation grade according to the adjusted Broder classification system: good/moderate differentiation 0-75% undifferentiated cells, poor/undifferentiated >75% undifferentiated cells.

Perineural or lymphovascular invasion

Absent

Presence of perineural invasion (>=0.1mm) or lymphovascular invasion of any size

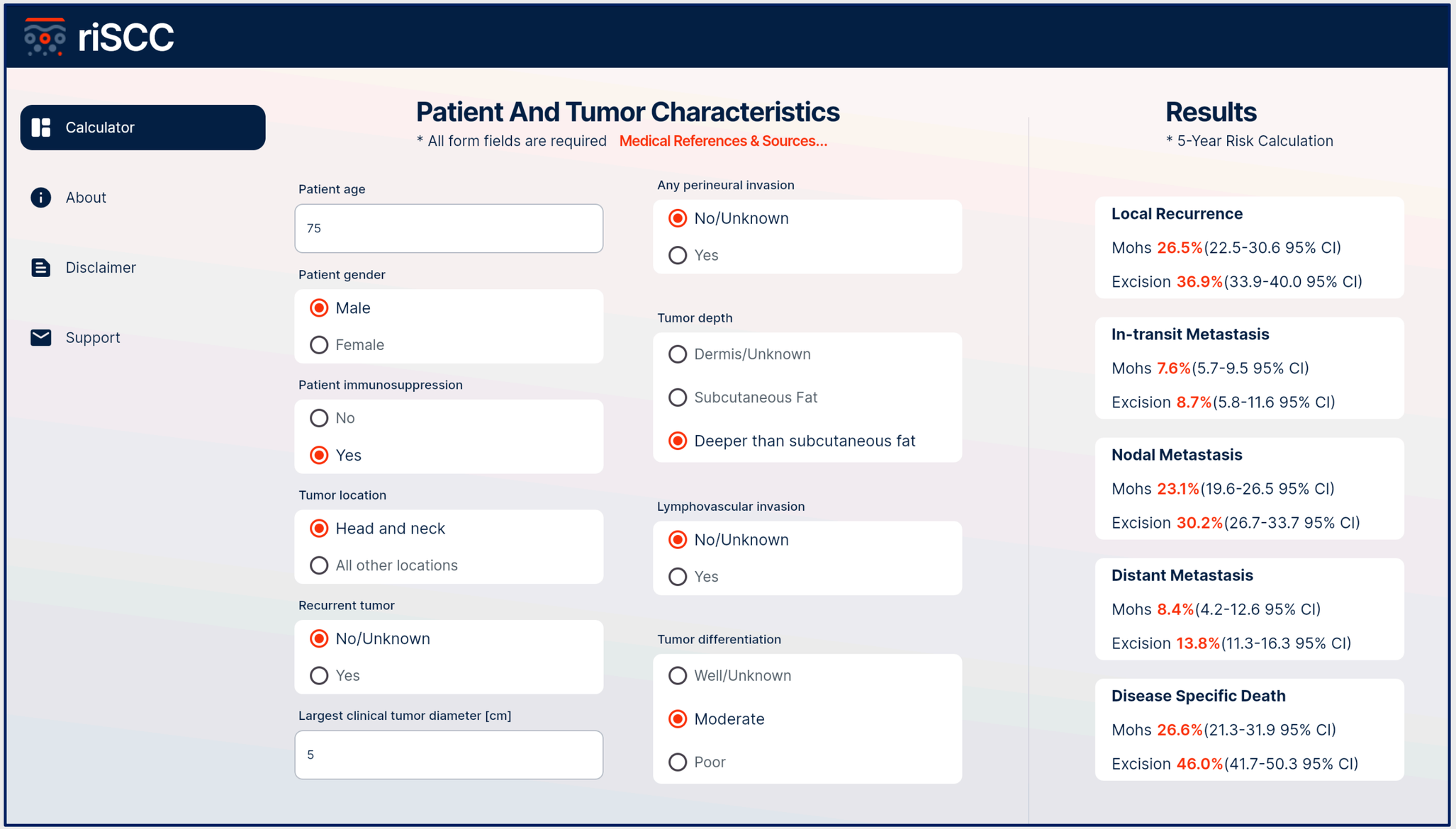
Predict

A patient with these characteristics has a probability of :

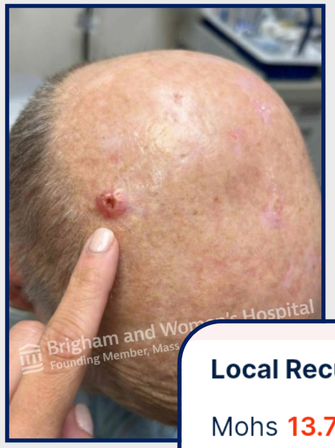
- **7.8** % of developing a metastasis within 1 year
- **14** % of developing a metastasis within 3 years
- **15.6** % of developing a metastasis within 5 years

DISCLAIMER: Currently, this calculator can only be used for research purposes. It cannot be used as a medical device. Erasmus MC has no liability for any medical decision taken based on the information provided by the calculator.

Tumor-Specific Risk Prediction Modeling: riSCC



Images courtesy of Nina Ran, MD, MPH, MSTR



Local Recurrence

Mohs **13.7%**(10.7-16.8 95% CI)

Excision **19.8%**(18.2-21.5 95% CI)

In-transit Metastasis

Mohs **3.1%**(2.3-3.8 95% CI)

Excision **3.6%**(2.4-4.7 95% CI)

Nodal Metastasis

Mohs **15.2%**(12.9-17.5 95% CI)

Excision **20.3%**(18.1-22.5 95% CI)

Distant Metastasis

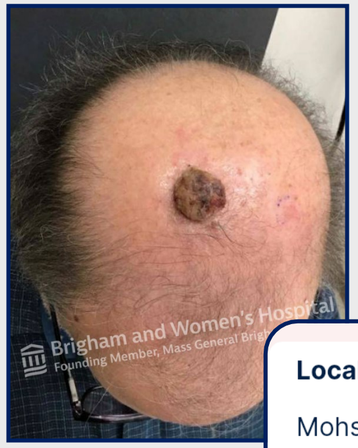
Mohs **5.0%**(2.8-7.1 95% CI)

Excision **8.3%**(7.0-9.6 95% CI)

Disease Specific Death

Mohs **8.6%**(5.0-12.1 95% CI)

Excision **16.3%**(14.8-17.9 95% CI)



Local Recurrence

Mohs **8.8%**(6.3-11.3 95% CI)

Excision **12.9%**(11.6-14.1 95% CI)

In-transit Metastasis

Mohs **0.8%**(0.5-1.0 95% CI)

Excision **0.9%**(0.5-1.2 95% CI)

Nodal Metastasis

Mohs **8.6%**(7.0-10.1 95% CI)

Excision **11.6%**(10.0-13.1 95% CI)

Distant Metastasis

Mohs **1.1%**(0.5-1.7 95% CI)

Excision **1.9%**(1.5-2.2 95% CI)

Disease Specific Death

Mohs **7.2%**(4.0-10.5 95% CI)

Excision **13.9%**(12.6-15.2 95% CI)

Local Recurrence

Mohs **26.5%**(22.5-30.6 95% CI)

Excision **36.9%**(33.9-40.0 95% CI)

In-transit Metastasis

Mohs **7.6%**(5.7-9.5 95% CI)

Excision **8.7%**(5.8-11.6 95% CI)

Nodal Metastasis

Mohs **23.1%**(19.6-26.5 95% CI)

Excision **30.2%**(26.7-33.7 95% CI)

Distant Metastasis

Mohs **8.4%**(4.2-12.6 95% CI)

Excision **13.8%**(11.3-16.3 95% CI)

Disease Specific Death

Mohs **26.6%**(21.3-31.9 95% CI)

Excision **46.0%**(41.7-50.3 95% CI)

Images courtesy of Nina Ran, MD, MPH, MSTR