Treating Skin Cancer

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Boulder Community Health

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Skin Cancer

Update on Evidence and Radiation Treatment Indications for Basal Cell Carcinoma, Squamous Cell Carcinoma, and Melanoma

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Disclosures: None

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Dario Pasalic, MD

- Mayo Clinic School of Medicine
- Memorial Sloan-Kettering Cancer Center Transitional Year
- MD Anderson Cancer Center Residency

Patrick Richard, MD, MPH

- Tulane University School of Medicine
- Tulane University Public Health Masters
- University of Washington Residency
- Univ of Michigan Integrative Oncology Scholars Program

RMCC Boulder Scheduling
303-385-2068
303-385-2029

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Outline

Boulder Community Health

- Overview of skin cancer & treatment options
- Radiation therapy details
- Summary of data
- Radiation capabilities at Rocky Mountain Cancer Centers

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Outline

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- Overview of skin cancer & treatment options
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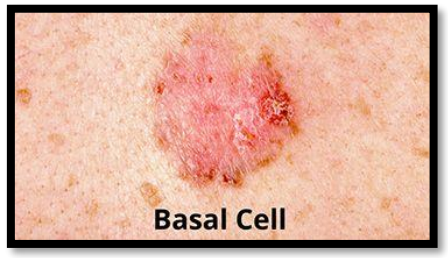
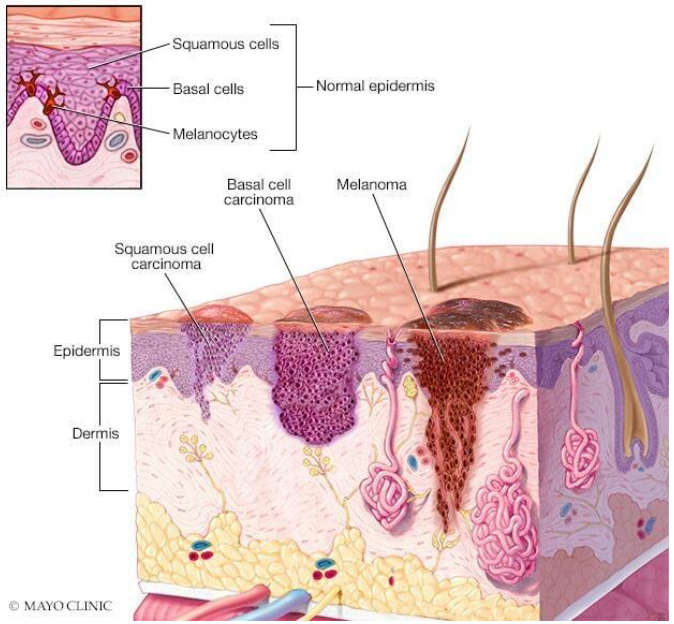
Overview of Skin Cancer

Boulder Community Health





Other indications: Merkel cell carcinoma, lymphoma, carcinoma in situ (Bowen's disease), erythroplasia, angiosarcoma, Kaposi's sarcoma, fibrosarcoma

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Mayo Clinic
Wikimedia Commons

Skin Cancer: Risk Factors

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- Cumulative ultraviolet (UV) light exposure
- Age
- Male > female (4:1)
- Immunosuppression (organ transplant, HIV)
- Syndromes (basal cell nevus syndrome, xeroderma pigmentosum, oculocutaneous albinism)

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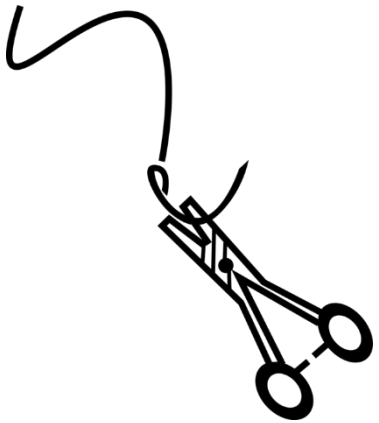
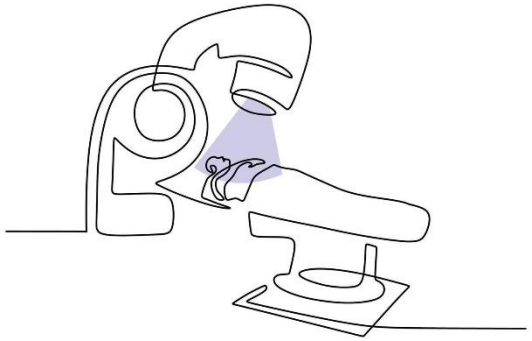
Skin Cancer: Treatment Options

Boulder Community Health

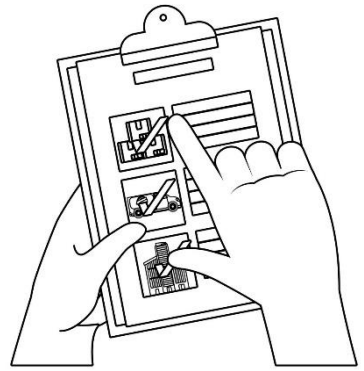


Surgery



Radiation Oncology

Systemic Therapy



Clinical Trial

Local & Regional Therapy

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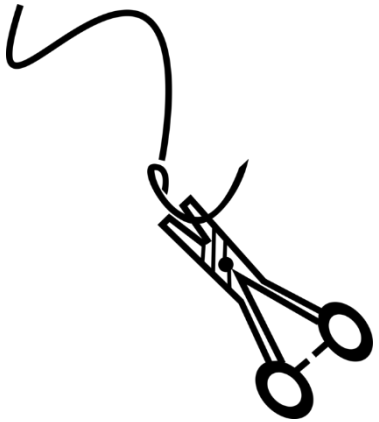
Skin Cancer: Treatment Options

Boulder Community Health



Surgery

Radiation Oncology

Systemic Therapy

Clinical Trial

Local & Regional Therapy

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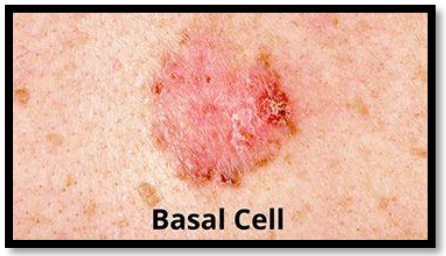
Skin Cancer: Treatment Options

Boulder Community Health

- **Surgery**
  - Mohs excision
  - Wide local excision
- **Surgery → Radiation**
- **Radiation**
- **Systemic Therapy → Radiation or Surgery**



- **Surgery**
  - Mohs excision
  - Wide local excision
- **Surgery → Radiation**
- **Radiation**
- **Systemic Therapy → Radiation or Surgery**
- **Topical chemotherapy**

- **Surgery**
  - Wide local excision
  - Mohs excision
  - +/- Radiation therapy
  - +/- Systemic therapy
  - +/- Chemotherapy

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Skin Cancer Treatment Options: Surgery

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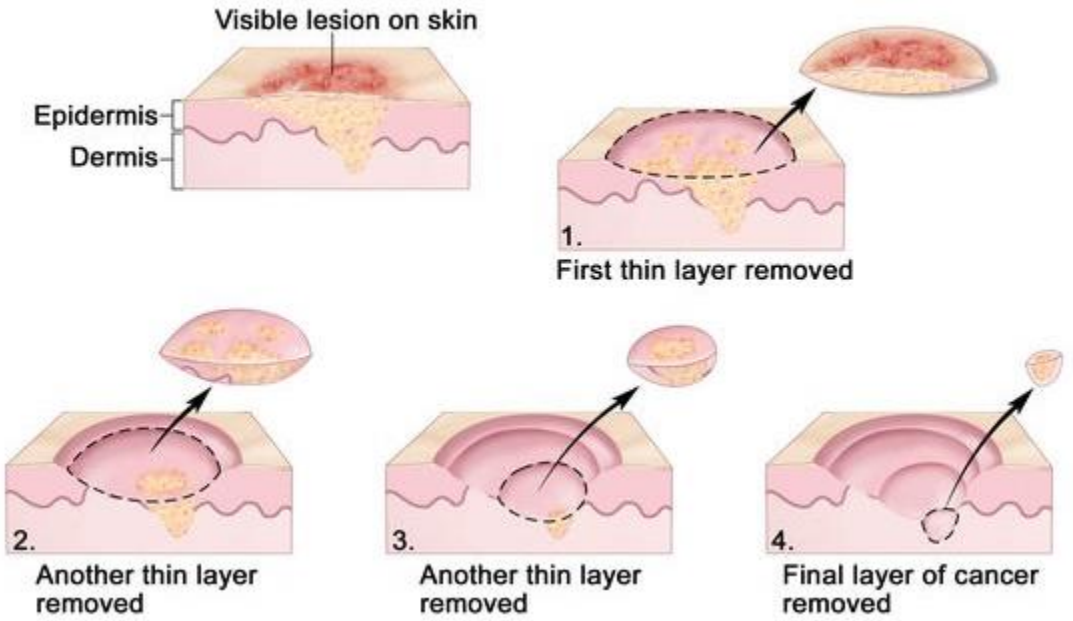
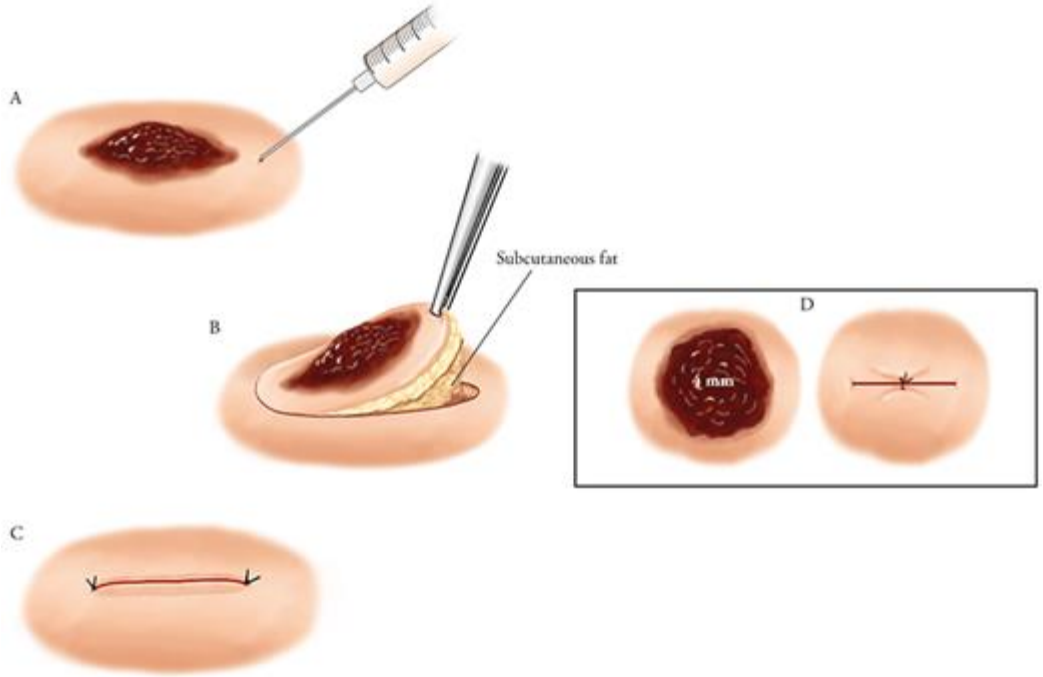
Mohs Surgery



Excisional Surgery



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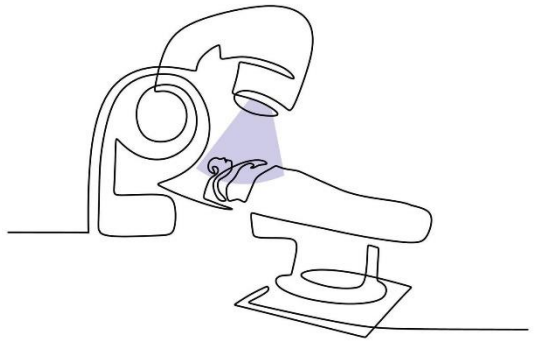
Morita et al., *Textbook of Complex General Surgical Oncology*
National Cancer Institute

Skin Cancer: Treatment Options

Boulder Community Health

Surgery



Radiation Oncology

Systemic Therapy

Clinical Trial

Local & Regional Therapy

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Skin Cancer Treatment Options: Radiation Therapy

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- **Definitive** radiation therapy (no surgery)
- **Post-operative** radiation
  - **High risk features** that increase chances of **local** (skin) or **regional** (lymph node) recurrence
  - Tumor diameter **≥2cm**, invasion **beyond subcutaneous fat**, **poorly differentiated**, **perineural** invasion, **location** (lips/ears/eyelid/nose/face)

Table 1 Comparison of Staging Systems for Basal Cell Carcinoma: the American Joint Committee on Cancer Staging Manual for Head and Neck Cancers, Eighth Edition (AJCC-8) vs. the Brigham and Women's Hospital Tumor Classification System (BWH).

	AJCC-8		BWH	
Staging	T1	Tumor < 2 cm in greatest diameter	T1	Tumor diameter < 2 cm or ≥ 2 cm with 0–1 risk factors[b]
	T2	Tumor ≥ 2 cm but < 4 cm in greatest diameter	T2	Tumor diameter ≥ 2 cm with 2–3 risk factors
	T3	Tumor ≥ 4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion[a]		
	T4a	Tumor with gross cortical bone and/or marrow invasion		
	T4b	Tumor with skull base invasion and/or skull base foramen involvement		
Sensitivity for the detection of metastasis or death	1.0		1.0	
Specificity for the detection of metastasis or death	0.80		0.92	
Positive predictive value	0.11		0.24	
Negative predictive value	1.0		1.0	

[a] Deep invasion defined as invasion beyond the subcutaneous tissue or > 6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 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.
[b] Risk factors include diameter ≥ 4 cm, head and neck location, and invasion beyond the subcutaneous tissue.
Source: Morgan et al.[3]

Figure 1. Overview of 4 Staging Systems for Cutaneous Squamous Cell Carcinoma

AJCC7[6a]		AJCC8[7]		BWH[9b]		Breuninger et al[8]	
T Stage	Risk Factors	T Stage	Risk Factors (Head and Neck Only)	T Stage	Risk Factors	Stage	Risk Factors
T1	Tumor diameter ≤2 cm with <2 high-risk factors	T1	Tumor diameter <2 cm	T1	No high-risk factors	Clinical tumor stage (cT)	Low risk: Tumor diameter ≤2 cm High risk: Tumor diameter >2 cm
T2	Tumor diameter >2 cm or tumor of any size with ≥2 high-risk factors	T2	Tumor diameter ≥2 cm and <4 cm in greatest dimension	T2a T2b	1 High-risk factor 2-3 High risk factors	Pathological tumor stage (pT)	No risk: Tumor thickness ≤2mm Low risk: Tumor thickness >2 mm and ≤6 mm High risk: Tumor thickness >6 mm
T3	Tumor with invasion of maxilla, mandibula, orbit, or temporal bone	T3	Tumor diameter ≥4 cm, or minor bone erosion, or perineural invasion, or deep invasion	T3	≥4 High-risk factors	Co-risk factors	Immunosuppression Desmoplastic type or poor differentiation Localization ear
T4	Tumor with invasion of skeleton, axial or appendicular, or perineural invasion of skull base	T4	Tumor with gross cortical bone/marrow invasion	T4	Not applicable		

AJCC indicates *American Joint Committee on Cancer Staging Manual*; BWH, Brigham and Women's Hospital.

[a]High-risk factors: tumor thickness >2 mm, Clark level IV/V, poor or undifferentiated, perineural invasion, localization at ear or lip.

[b]High-risk factors: Tumor diameter ≥2 cm, invasion beyond subcutaneous fat, poorly differentiated, and perineural invasion >0.1 mm.

Risk Group[a]	High Risk	Very High Risk
Treatment options	SCC-4	SCC-4 and SCC-5
H&P		
Location/size[b]	Trunk, extremities >2 cm – ≤4 cm	>4 cm (any location)
	Head, neck, hands, feet, pretibia, and anogenital (any size)[e]	
Clinical extent	Poorly defined	
Primary vs. recurrent	Recurrent	
Immunosuppression	(+)	
Site of prior RT or chronic inflammatory process	(+)	
Rapidly growing tumor	(+)	
Neurologic symptoms	(+)	
Pathology (SCC-A)		
Degree of differentiation		Poor differentiation
Histologic features: Acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarcomatous) subtypes	(+)	Desmoplastic SCC
Depth[c,d]: Thickness or level of invasion	2–6 mm depth	>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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Morgan et al., *J Am Acad Dermatol* (2021)
Roscher et al., *JAMA Oncol* (2018)
National Comprehensive Cancer Network Version 1.2024

Skin Cancer Treatment Options: Definitive Radiation

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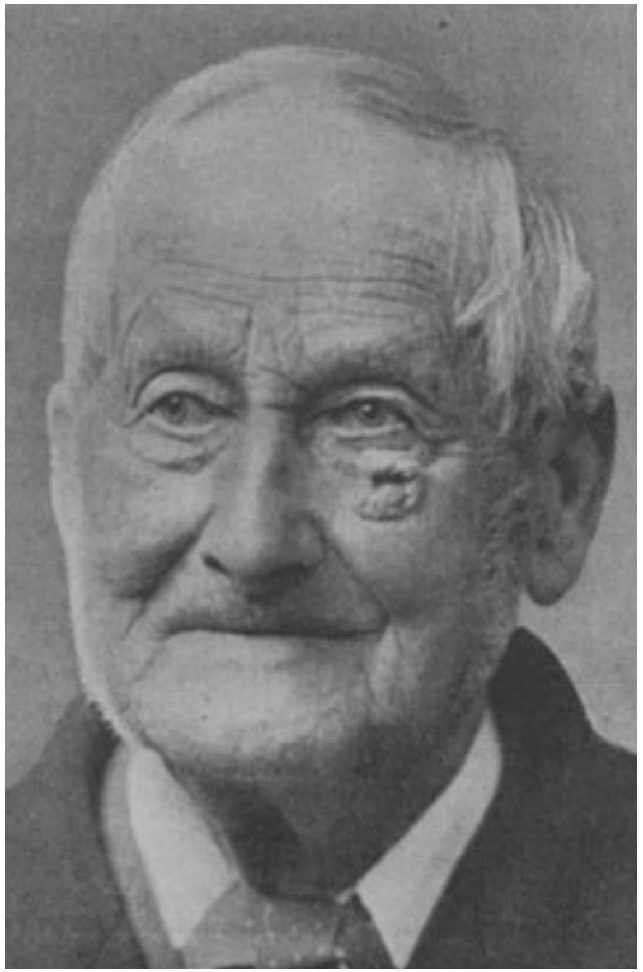

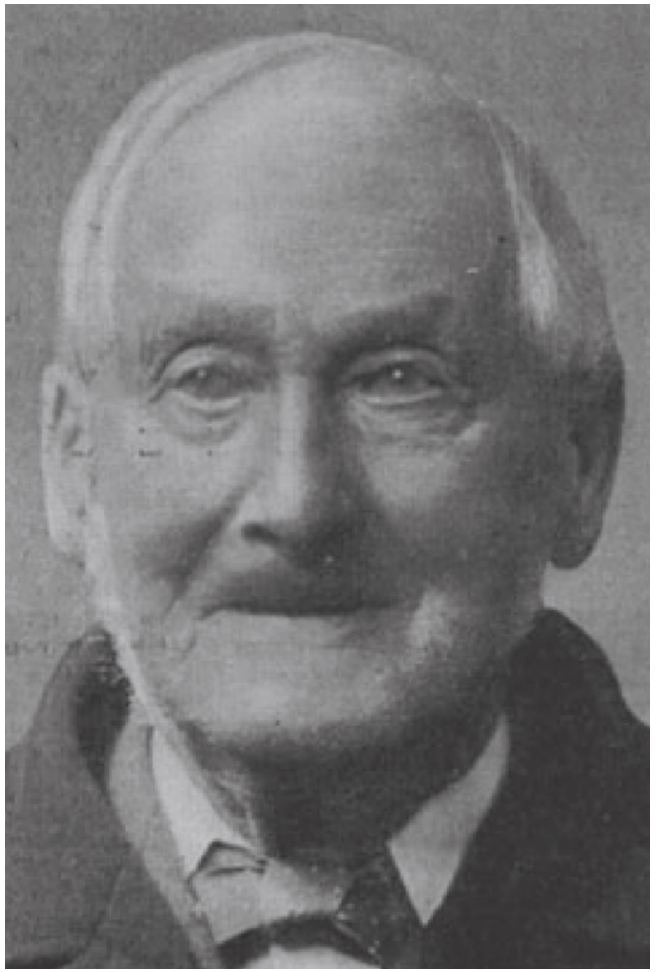

1902!

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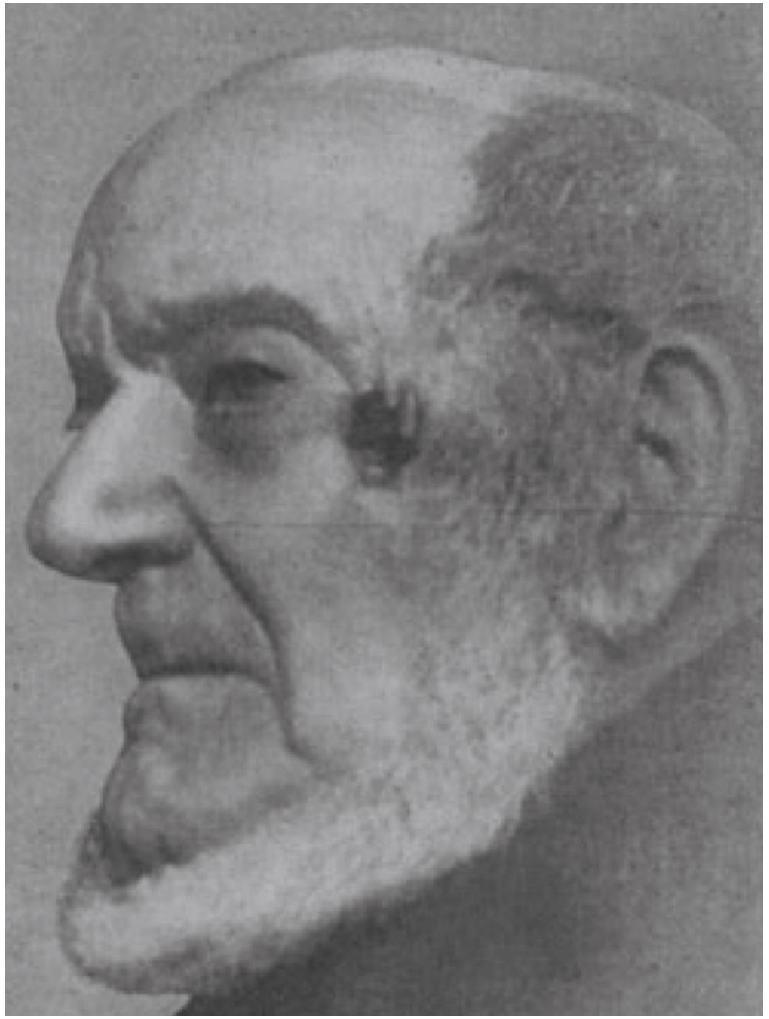
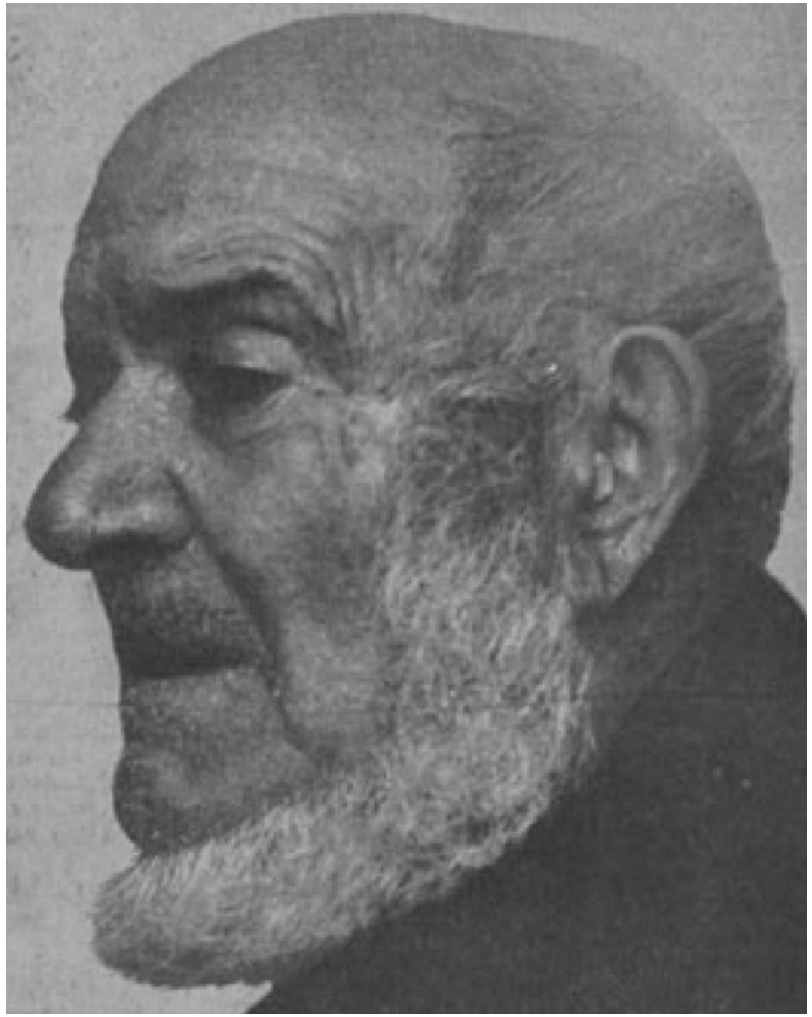
Cognetta Jr & Mendenhall, *Radiation Therapy for Skin Cancer* (2013)

Skin Cancer Treatment Options: Radiation

Boulder Community Health





1902!

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Cognetta Jr & Mendenhall, *Radiation Therapy for Skin Cancer* (2013)

Skin Cancer: Treatment Options Risks/Benefits

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	Surgery	Radiation
Time & Convenience	☑ One time procedure	☒ 5 – 35 daily sessions

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Skin Cancer: Treatment Options Risks/Benefits

Boulder Community Health

	Surgery	Radiation
Time & Convenience	☑ One time procedure	☒ 5 – 35 daily sessions
Tissue Preservation	☒ Cuts tissue out	☑ Spares tissue and often used in cosmetically sensitive areas (nose, ears, lips, etc.)

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Skin Cancer: Treatment Options Risks/Benefits

Boulder Community Health

	Surgery	Radiation
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Tissue Changes	= Scar tissue	= Hypopigmentation or spider marks

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Skin Cancer: Treatment Options Risks/Benefits

Boulder Community Health

	Surgery	Radiation
Time & Convenience	☑ One time procedure	☒ 5 – 35 daily sessions
Tissue Preservation	☒ Cuts tissue out	☑ Spares tissue and often used in cosmetically sensitive areas (nose, ears, lips, etc.)
Tissue Changes	= Scar tissue	= Hypopigmentation or spider marks
Blood Thinners	☒ Sometimes need to pause/stop	☑ No need to stop

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Skin Cancer: Treatment Options Risks/Benefits

Boulder Community Health

	Surgery	Radiation
Time & Convenience	☑ One time procedure	☒ 5 – 35 daily sessions
Tissue Preservation	☒ Cuts tissue out	☑ Spares tissue and often used in cosmetically sensitive areas (nose, ears, lips, etc.)
Tissue Changes	= Scar tissue	= Hypopigmentation or spider marks
Blood Thinners	☒ Sometimes need to pause/stop	☑ No need to stop
Pain	= Post-operative pain	= Irritation and soreness

Mohs surgery is the **gold standard** due to **time/convenience/outcomes**, but **radiation** is a **great option** for **sensitive areas** and patients who **cannot undergo surgery.**

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Skin Cancer: Treatment Options

Boulder Community Health

Systemic Therapy

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Skin Cancer Treatment Options: Immunotherapy

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- **Squamous cell carcinoma**
  - Anti-PD1 therapy (cemiplimab and/or pembrolizumab) for very high risk, recurrent, unresectable, locally advanced or metastatic disease
  - Chemotherapy
- **Basal cell carcinoma**
  - Hedgehog inhibitor (vismodegib or sonidegib) for locally advanced or metastatic disease
  - Anti-PD1 therapy in some specific circumstances
- **Melanoma**
  - BRAF/MEK inhibitor therapy
  - Anti-PD1 therapy
  - T-VEC injection
  - Interferon therapy

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Outline

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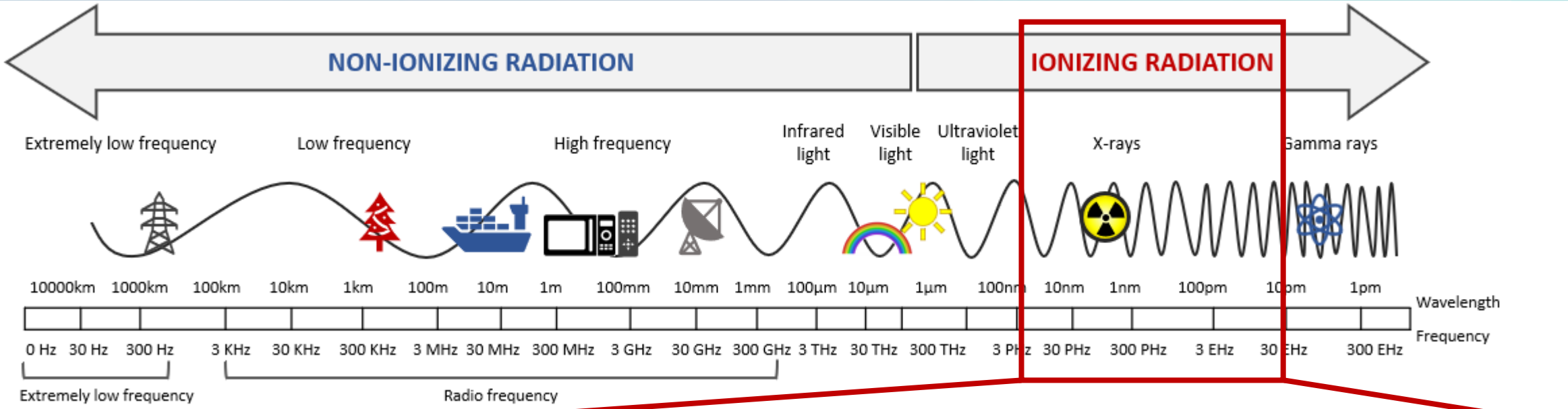
Radiation Therapy Spectrum

Boulder Community Health



Grenz Therapy

Soft X-Ray

Superficial X-Ray

Electronic Brachy

Orthovoltage

Megavoltage Linear Accelerator

University of Texas Rio Grande Valley
Glasser, *J Radiol Society North America* (1932)
Xstrahl
Xoft
Varian

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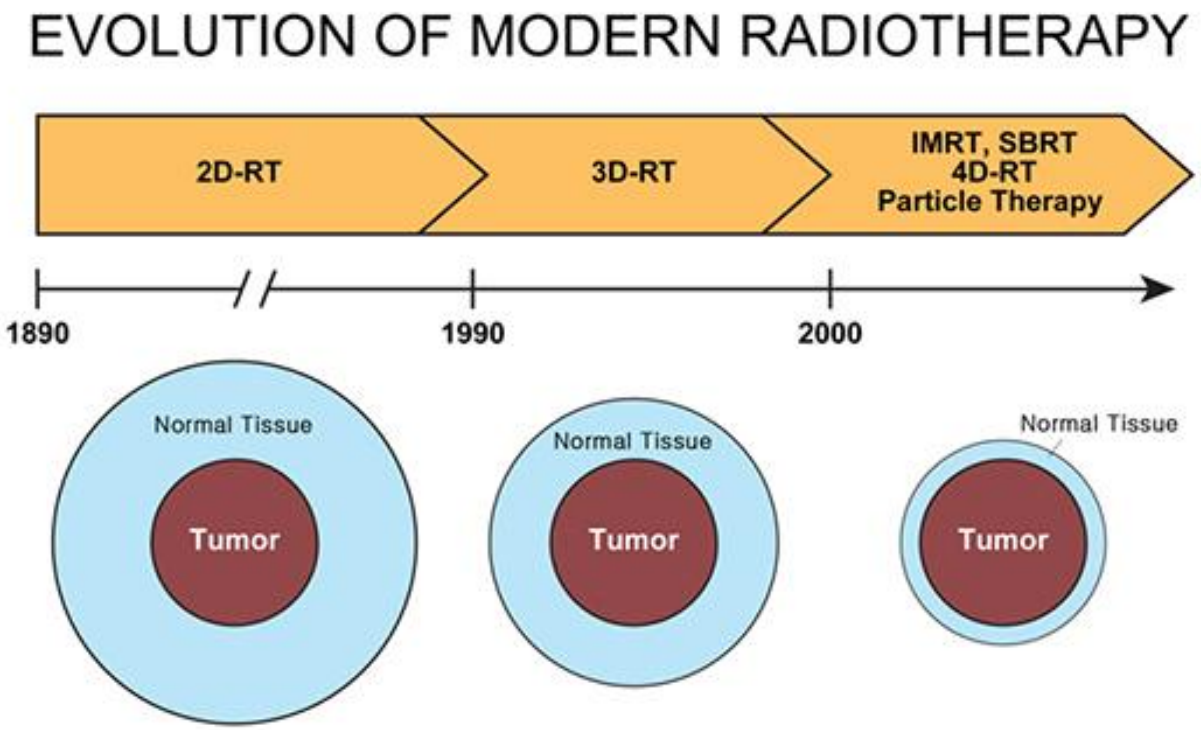
Treatment: Evolution & Goals of Radiation Therapy

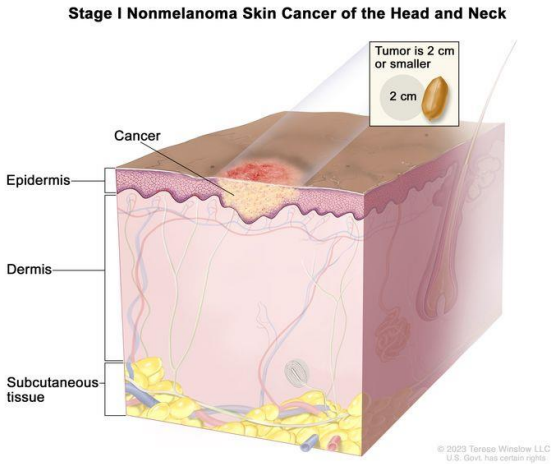


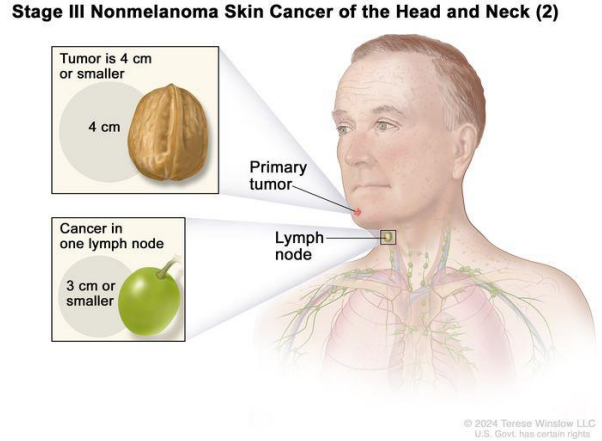
- **Design** radiation plan
  - Matches **individual** patient **anatomy**
  - **Minimize radiation** exposure to surrounding **normal tissue**
- **Delivery** radiation plan
  - **Timely**
  - Ensure **consistent daily setup**

Choi et al., *J Korean Med Sci* (2016)

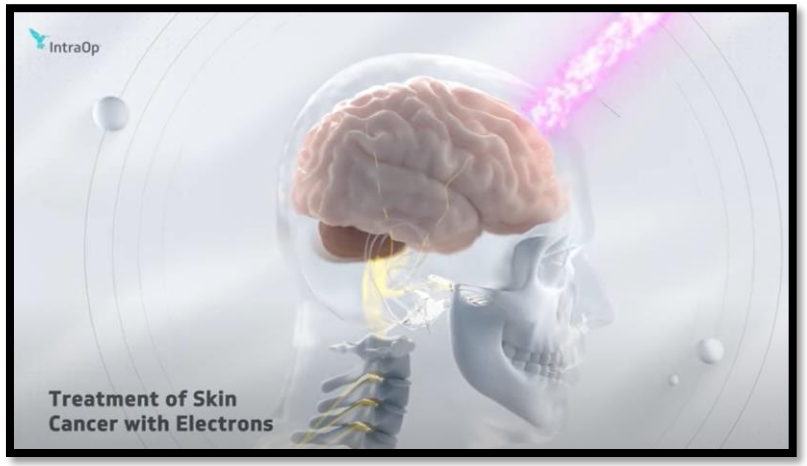
Types of External Beam Radiation Therapy

Boulder Community Health

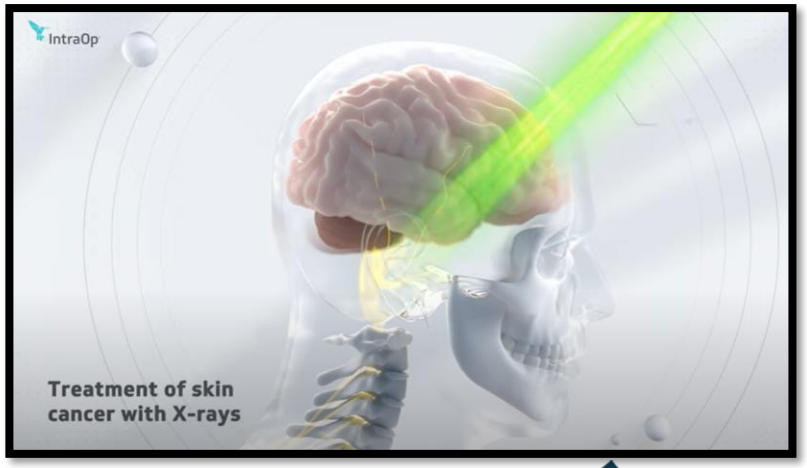




Electrons & Orthovoltage



Photons (X-Rays)



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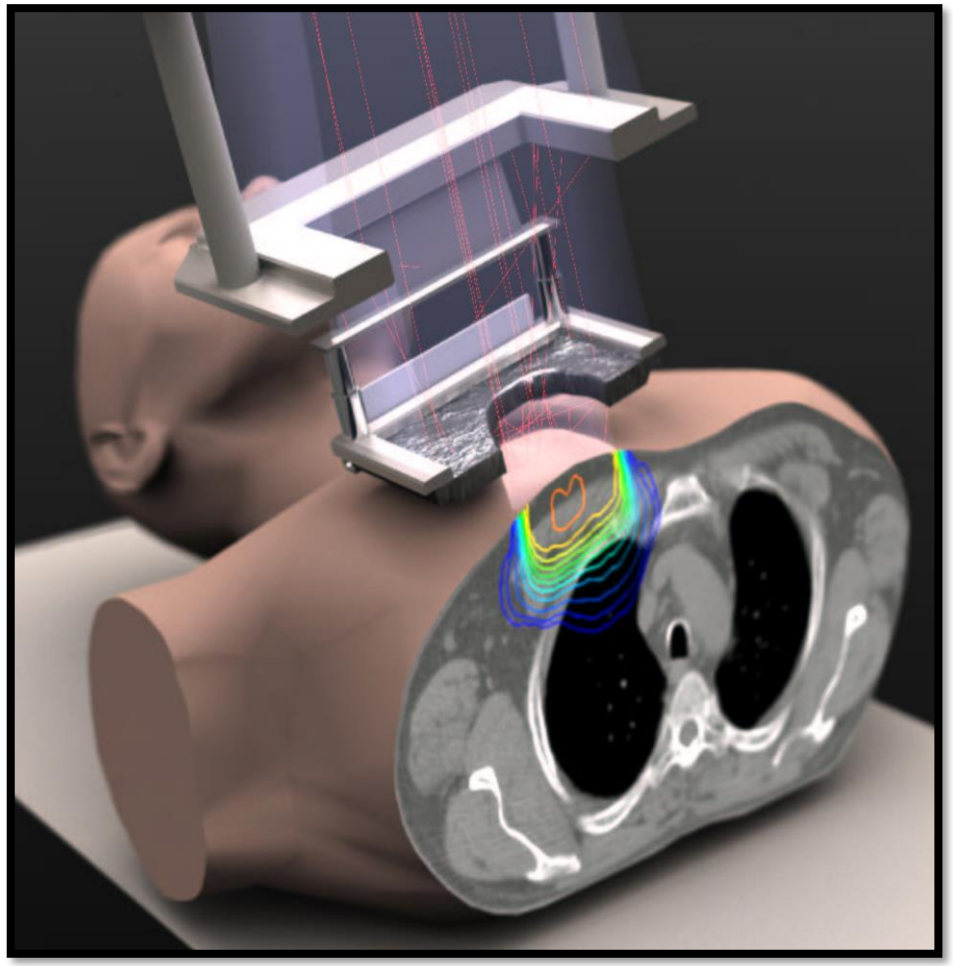
IntraOp
Varian
National Cancer Institute

Types of External Beam Radiation Therapy: Electrons

Boulder Community Health



2D Electron/Orthovoltage/Superficial Radiation Therapy

- Small dose daily (Mon-Fri) or twice weekly (Tu & Thu)
- 5 fractions to 35 fractions (2-7 week course)
- Treat superficial regions (skin!) and minimize radiation dose to deeper structures

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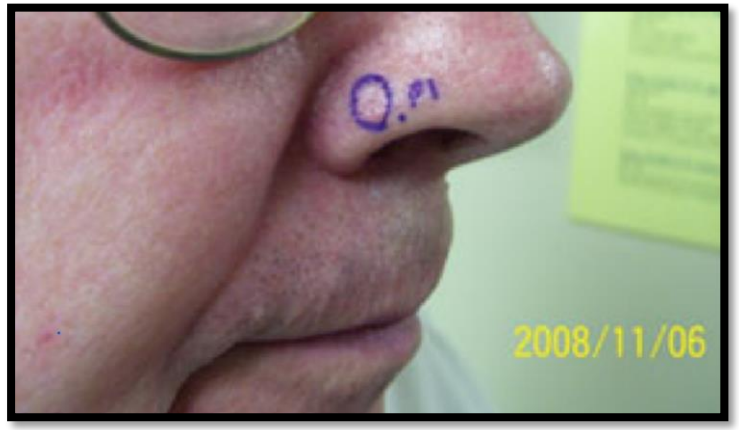
Rogers, *Ionizing Radiation Standards* (2002)

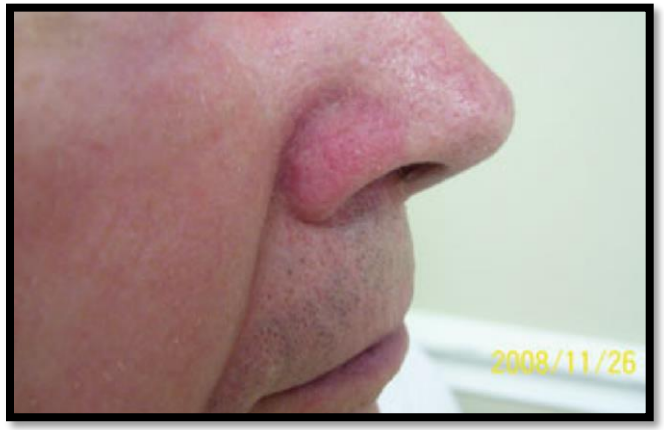
External Beam Radiation Therapy: Local Treatment

Boulder Community Health

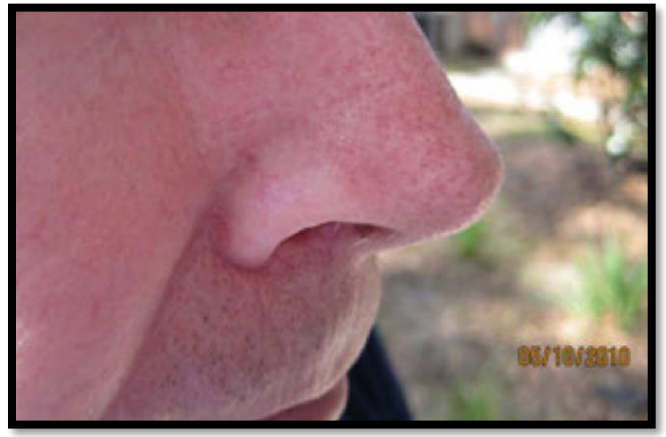
Pre-Treatment



Last Radiation Treatment
(Dermatitis)



~1 Year Post-Treatment
(Hypopigmentation)



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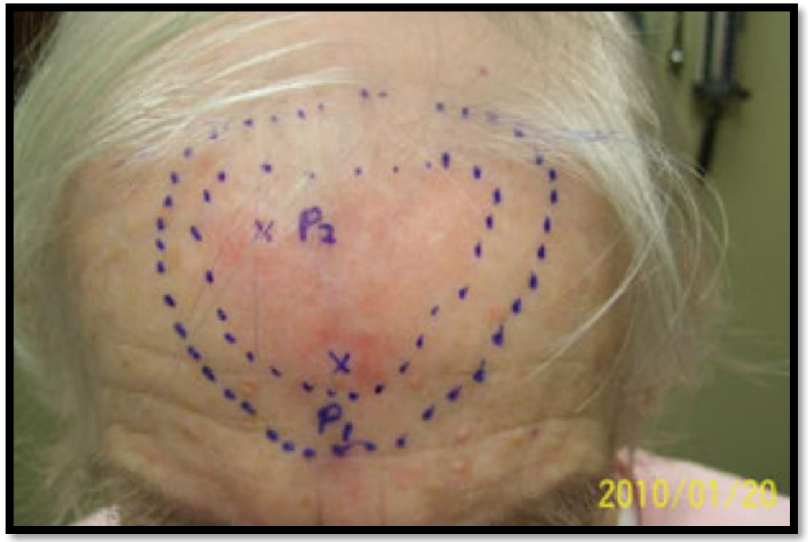
Cognetta Jr & Mendenhall, *Radiation Therapy for Skin Cancer* (2013)

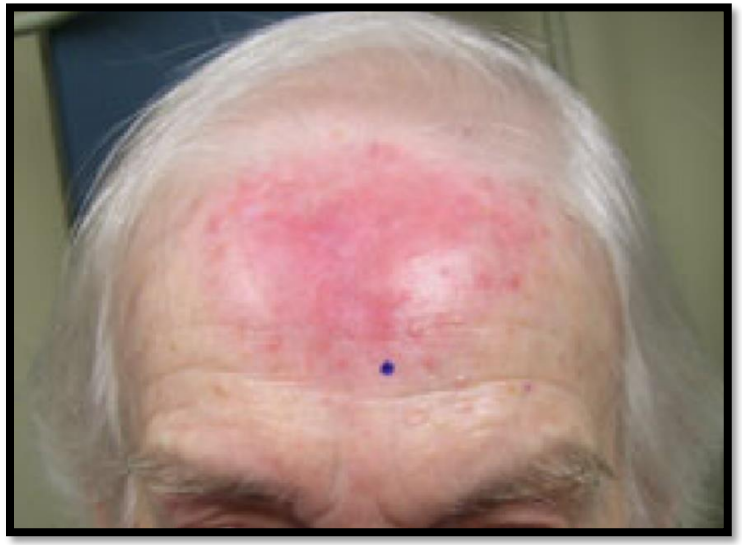
External Beam Radiation Therapy: Local Treatment

Boulder Community Health

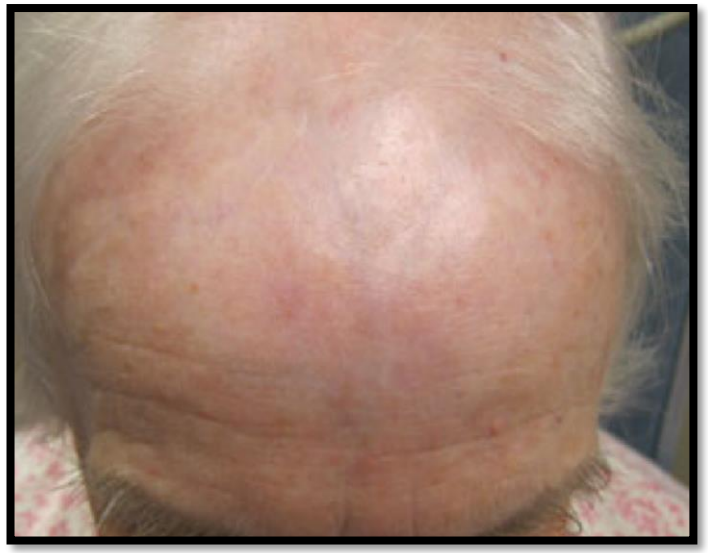
Pre-Treatment



Last Radiation Treatment
(Dermatitis)



~3 Months Post-Treatment
(Hypopigmentation)



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Cognetta Jr & Mendenhall, *Radiation Therapy for Skin Cancer* (2013)

Types of External Beam Radiation Therapy: Photons

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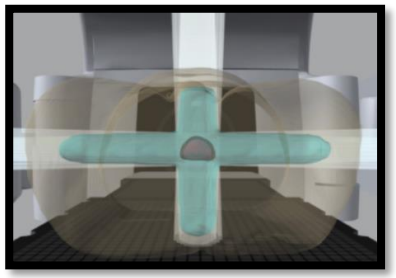

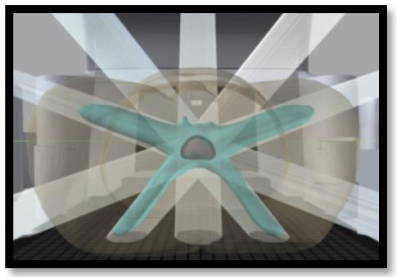

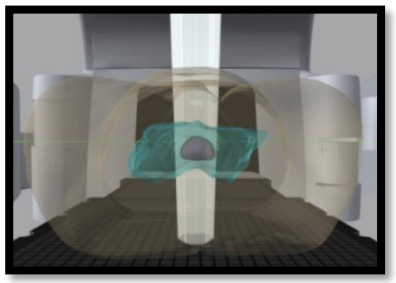

3D-conformal (**3D-CRT**)

↓

Intensity modulated (**IMRT**)

↓

Volumetric modulated arc therapy (**VMAT**)

Treat superficial (skin) + deeper regions (lymph nodes) in certain high-risk scenarios

Conventional EBRT
- Small dose daily (Mon-Fri)
- 6-9 week course

Hypo-fractionated EBRT
- Larger dose daily
- 4-6 week course

Ultra hypo-fractionated EBRT
- Stereotactic body radiation therapy

SBRT
- Larger dose per treatment
- 1-2 week course (1-5 total treatments)

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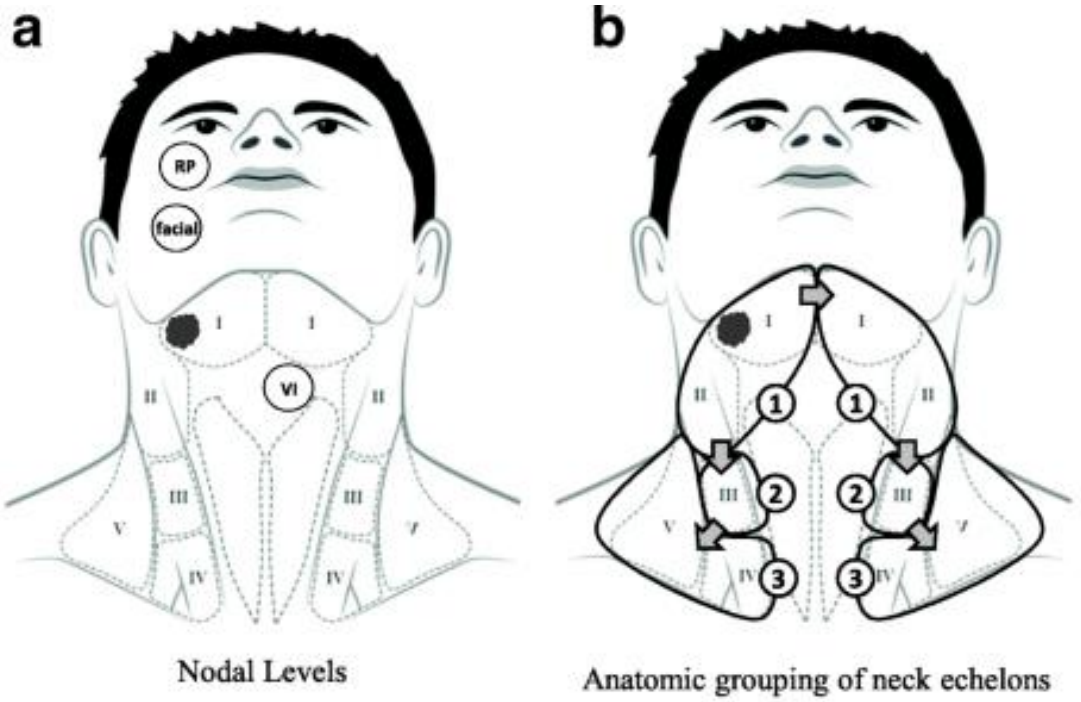
Leong et al., *J Med Radiat Sci* (2018)

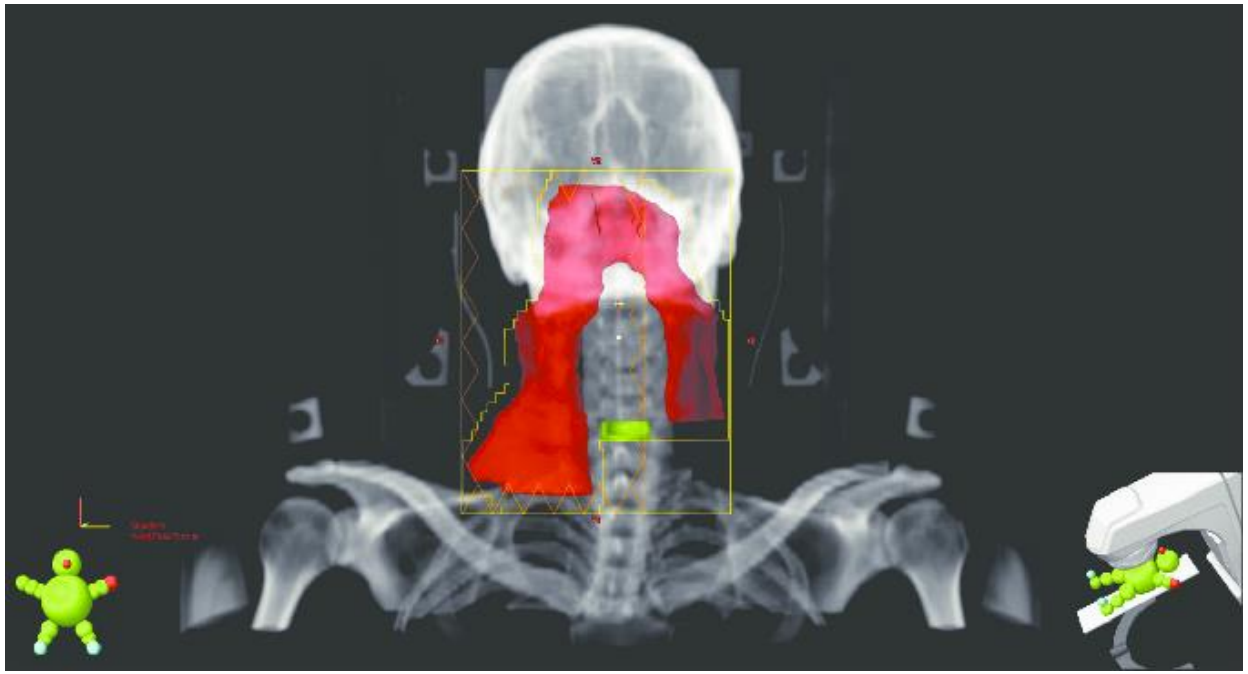
External Beam Radiation Therapy: Nodal Treatment

Boulder Community Health



Nodal Levels

Anatomic grouping of neck echelons



Hsieh et al., *Radiat Oncol* (2018)
Seol et al., *Radiat Oncol J* (2016)

ROCKY MOUNTAIN™ CANCER CENTERS

Outline

Boulder Community Health

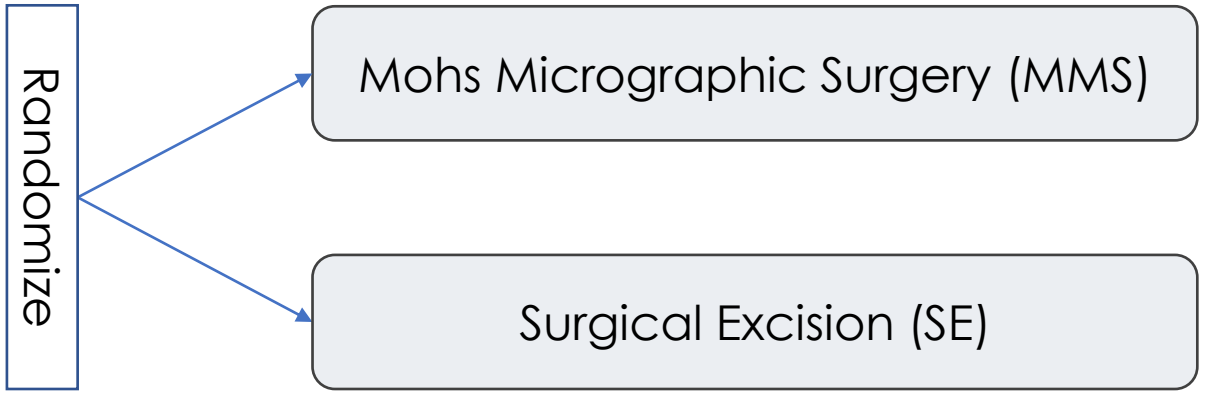
- Overview of skin cancer & treatment options
- Radiation therapy details
- Summary of data
- Radiation capabilities at Rocky Mountain Cancer Centers

ROCKY MOUNTAIN™ CANCER CENTERS

Summary of Data: Mohs vs Excision

Boulder Community Health

- 1999-2002
- Primary (67%) or recurrent (33%) basal cell carcinoma
- ≥1cm diameter
- Located in head/face area
- Multi-institution in Netherlands
- Primary endpoint: Recurrence by visual inspection and biopsy confirmation within 0.5cm around primary site



- Out of 397 primary lesions treated, 127 lesions (32%) in 113 patients were lost to follow-up; out of 202 recurrent lesions treated, 56 lesions (28%) in 52 patients
- In the 397 primary lesions, **no 5-year** difference in **recurrence** (2.5% MMS vs 4.1% SE, p=0.397); in 202 recurrent lesions, increased recurrence with SE (2.4% MMS vs 12.1% SE, p=0.015); **10-year recurrence** (3.9% MMS vs 13.5% SE p=0.023)
- No difference in **complication** rate with **primary** (12% MMS vs 14% SE, p=0.681), but **increased** rate of **complications** in **recurrent** setting (8% vs 19%, p=0.021)
- **No difference in cosmetic** aesthetic outcomes
- **Aggressive histological subtype** (morpheaform, micronodular, trabecular, infiltrative, or BCC with squamous differentiation) was significant risk factor for recurrence

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Smeets et al., *Lancet* (2004)
Mosterd et al., *Lancet Oncol* (2008)
Loo et al., *Eur J Cancer* (2010)

Summary of Data: Excision vs Radiation (BCC)

Boulder Community Health

Very limited phase III randomized trials comparing surgery and XRT in squamous cell and basal cell carcinoma

Surgical excision (SE)

External beam radiation (EBRT)

Brachytherapy (BT)

- French trial from **1982-1988**
- **347** patients with **small basal cell carcinoma** randomized between **wide surgical excision** and **XRT** (interstitial brachytherapy, superficial contact therapy or external beam)
- Majority of patients treated with brachytherapy; external beam used for larger tumors.
- **4-year recurrence** rates:
  0.7% surgery vs. **8.8% (brachytherapy)** vs. **6.6% (superficial)** vs. **5% (external beam)**
- Cosmesis: Similar right after treatments but trended to better results with surgery
  (**4-year good cosmesis: 87% surgery vs. 69% XRT**)

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Avril et al., *Br J Cancer* (1997)

Summary of Data: Mohs vs Excision vs Radiation

Boulder Community Health

With the lack of modern, high-quality randomized trials, we mainly have systematic reviews and meta-analyses of mostly prospective single arm trials and retrospective studies.

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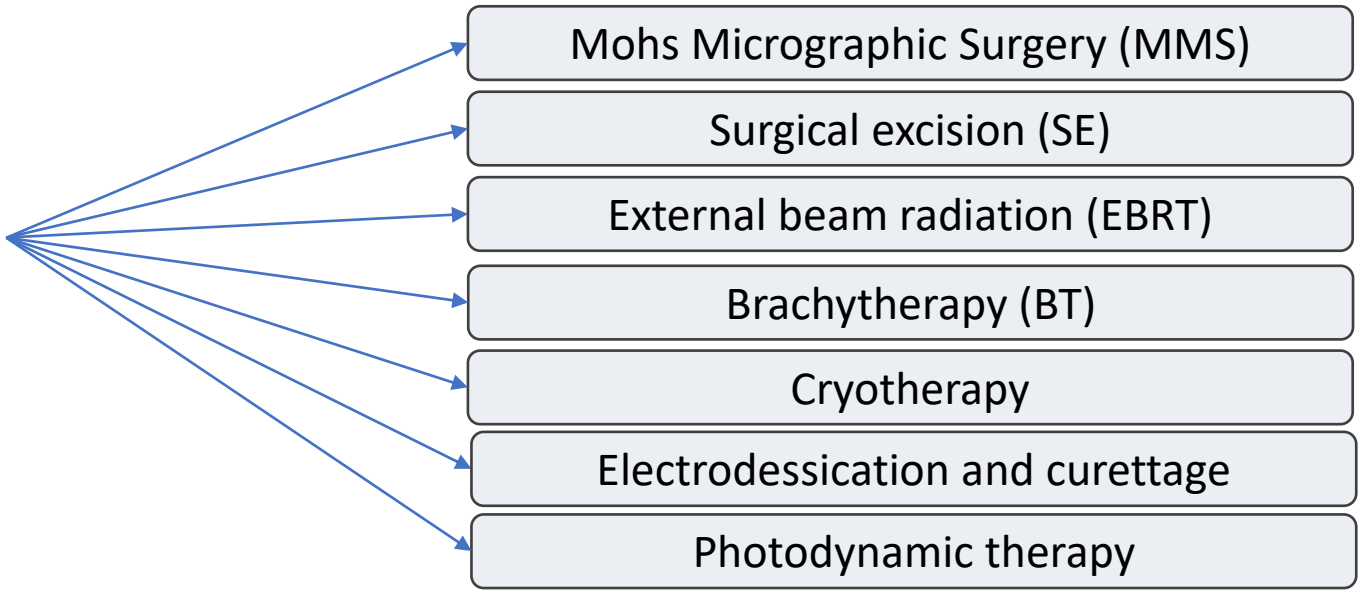
Lansbury et al., *BMJ* (2013)

Summary of Data: Surgery vs. Radiation (Basal Cell)

Boulder Community Health

- Systematic review and network meta-analysis for basal cell
- 45 trials included (with many different treatment types)
- 40 randomized controlled studies
- 5 non-randomized trials



- **Recurrence** rates
  - Wide excision 3.8%
  - Mohs 3.8%
  - External beam radiation 3.5%
  - Curettage and diathermy 6.9%

Equivalent

  - Cryotherapy 22.3%
  - Curettage & cryotherapy 19.9%
  - Topical chemo 14.1-18.8%
  - Photodynamic 16.6-18.8%

Not equivalent to above

- **Cosmesis** ("good or better")
  - Wide excision 77.8%
  - Cryotherapy 51.1%
  - Photodynamic 93-95%
  - **No difference between the other therapies** and/or **couldn't reach a conclusion**

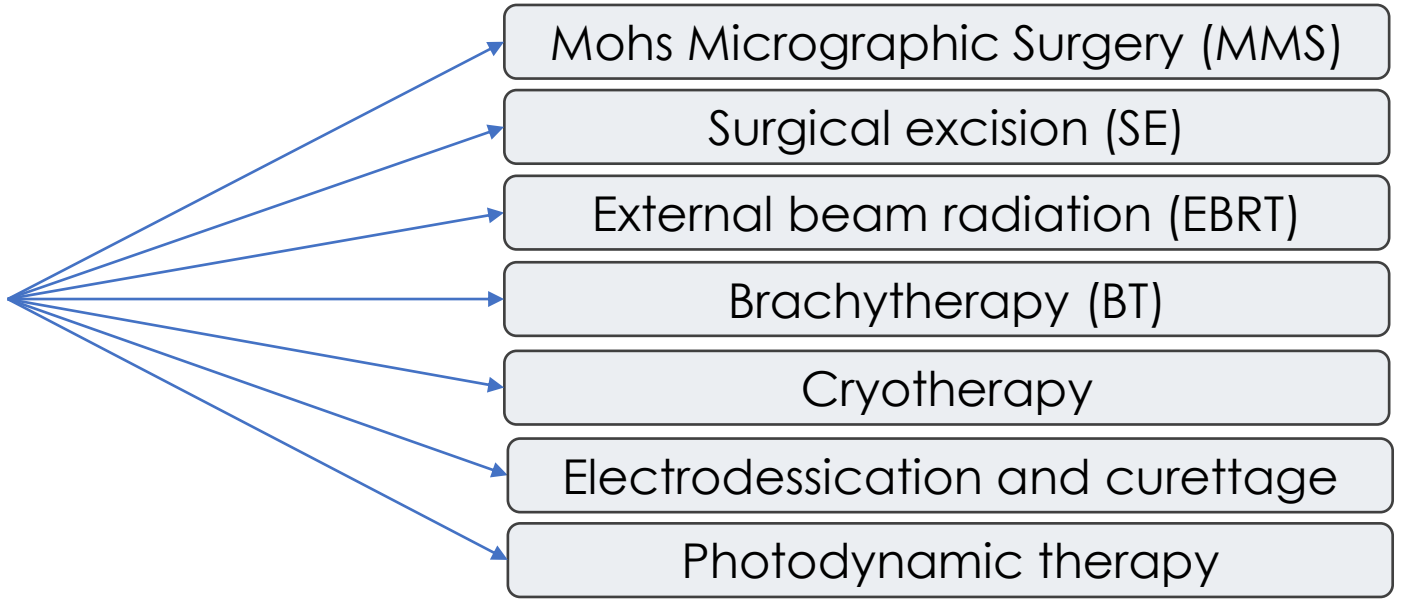
ROCKY MOUNTAIN™ CANCER CENTERS

Drucker et al., *Ann Intern Med* (2018)

Summary of Data: Mohs vs Excision vs Radiation (SCC)

Boulder Community Health

- Systematic review and pooled analysis of treatments for squamous cell carcinoma (SCC)
- 118 publications (with 7 different treatment types)
- 48% retrospective studies
- 36% prospective studies
- **54% of studies with possible selection bias**



- Estimates of **recurrences** were lowest with cryotherapy (0.8%) and E&D (1.7%) compared to Mohs (3%), surgical excision (5.4%) and external beam radiation (6.4%) – selection bias?
- Photodynamic therapy had the highest rate of recurrence (26.4%)
- Limited evidence for laser treatment and topical therapy

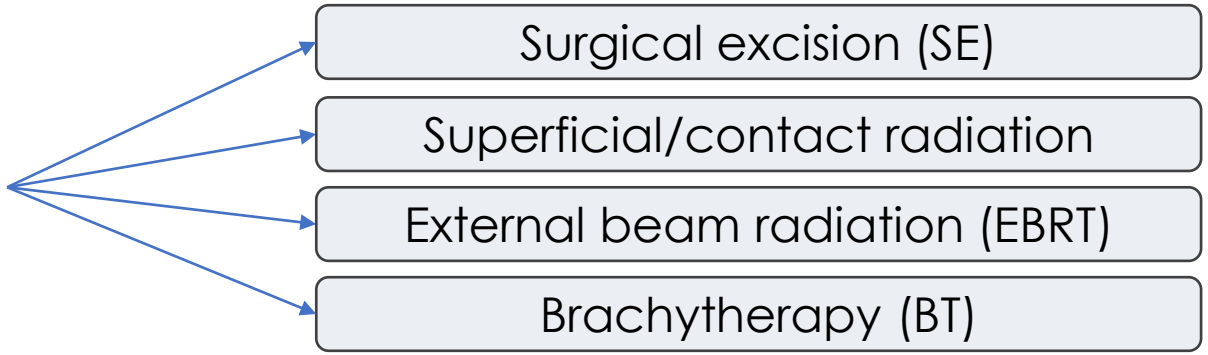
ROCKY MOUNTAIN™ CANCER CENTERS

Lansbury et al., *BMJ* (2013)

Summary of Data: Radiation (SCC)

Boulder Community Health

- Systematic review of primary, adjuvant, and salvage XRT for SCC
- 46 studies (4,141 tumors treated)
- Most studies retrospective (82%)
- 77% of studies were RT monotherapy
- Main indications for RT after surgery were PNI and positive margins



- Pooled/total **local control rates** of **87.3%** and **local recurrence rates** of **8.6%**
- **XRT as monotherapy**: local control of 87.2% and local recurrence rates 7.2%
- Low rates of nodal and distant mets (4.8% and 3.5%, respectively)
- **Larger tumors have higher recurrence rates** (1.7-8.3% T1 vs. 26-28% T4); **similar trend to surgical data**
- **Conclusion**: relatively low rates of local recurrence with RT alone and when used in combo with surgery
    - Data is very variable and no strong conclusions can be made.

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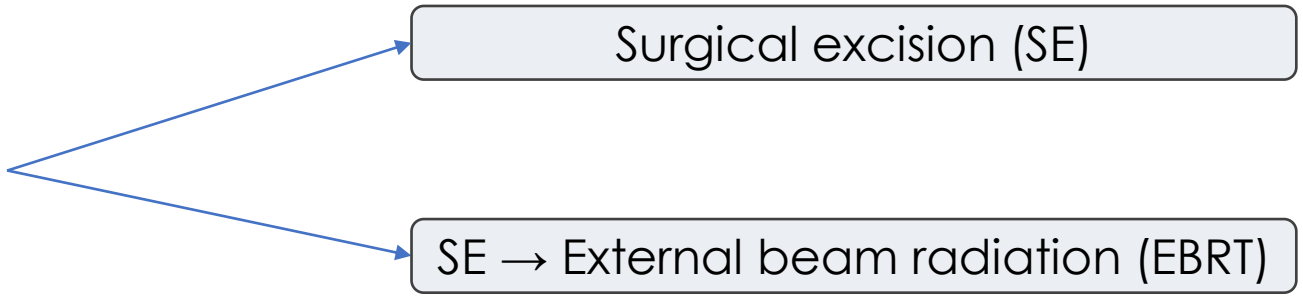
Krausz et al. Dermatologic Surgery 2021

Summary of Data: Adjuvant Radiation (Advanced SCC)

Boulder Community Health

- Retrospective analysis of adjuvant RT after surgery
- 349 patients included after surgery (2008-2016)
- Advanced SCC tumors treated at 2 institutions
- 54% received adjuvant RT



- More likely to receive adjuvant XRT
  - **Larger, grade 3, perineural invasion (PNI)** and **young immunosuppressed** patients
- **Adjuvant RT** was associated with **improved OS for entire cohort** (HR 0.59)
- Subset with **PNI**: XRT improved disease-free survival (HR 0.47) and OS (HR 0.36)
- **Regional/nodal disease**: XRT improved DFS and OS
- **Conclusion**: limited strength study but shows potential benefits of RT after surgery in high-risk cohort

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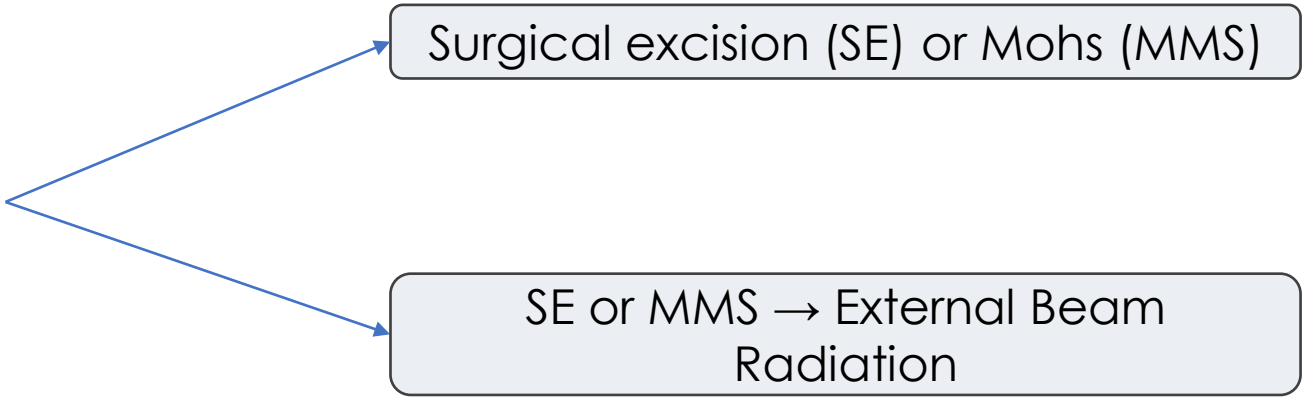
Harris et al., *Jama Otolaryngol Head Neck Surg* (2019)

Future Direction: Genomic Testing (SCC)

Boulder Community Health

- 40-gene expression profile testing (Decision DX SCC)
- Reclassifies "risk" not according to appearance of pathology but according to genes expressed
- 3 risk categories: Class 1→ Class 2B predictive of risk of recurrence and nodal/distant metastases
- May help us determine who needs adjuvant therapy (i.e. XRT after primary surgery)
- n=920 patients in this study
- 40-gene test run on tumor specimens from surgery



- 96 patients developed a local recurrence (all received primary surgery)
  - 54 patients developed metastases and **98%** of those had **nodal metastases** (65% distant)
  - This would suggest a **potential linear sequence from local recurrence → nodal → distant**.
  - Median time from local to distant was ~3 months.
- 40 GEP results (matched XRT vs. non-XRT patients)
  - For class 2B: **50% reduction in recurrence with XRT**
  - **5-yr metastasis rates reduced with XRT** for **class 2B** (46.2% median difference)
  - XRT reduces the time to metastatic events (2-year peak rate without XRT vs. 5-fold longer time with XRT)

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Arron et al., *Int J Radiat Oncol Biol Phys* (2024)

Summary of Data

Boulder Community Health

- **Radiation** seems to be **on par with surgical excision/Mohs** in terms of local recurrence and cosmetic results for both BCC and SCC.
- Can **safely and effectively be used to prevent recurrence** in high-risk cases after surgical excision/Mohs (adjuvant/salvage).
- Future role of **gene expression testing** to help determine who is high risk after surgery to guide RT use.

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Lansbury et al., *BMJ* (2013)

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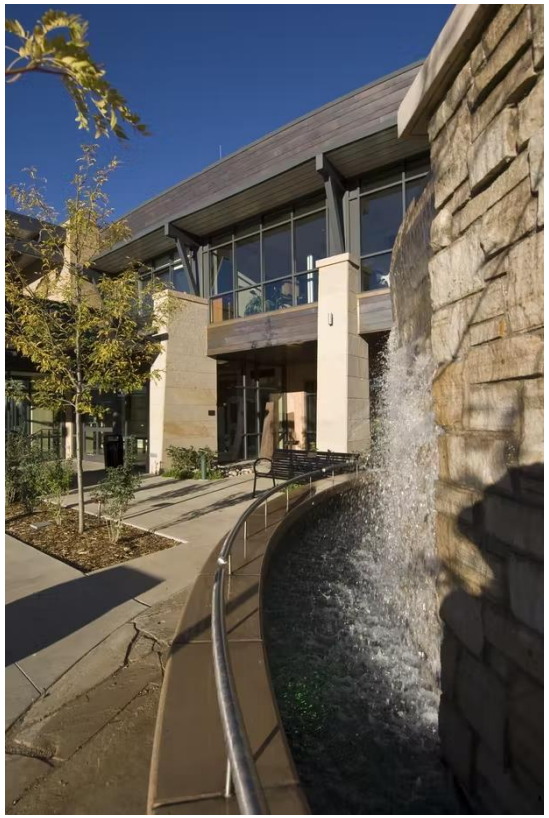
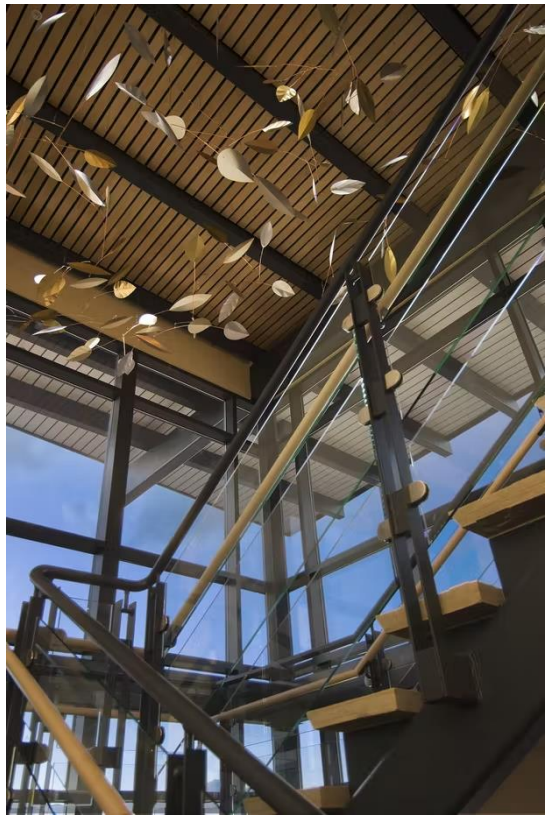
ROCKY MOUNTAIN™ CANCER CENTERS

Rocky Mountain Cancer Centers in Boulder

Boulder Community Health





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Archinect

Radiation Oncology Capabilities in Boulder

Boulder Community Health

Varian TrueBeam Edge

Electron Therapy

- Superficial
- 5 fractions to 35 fractions (2-7 week course)

Photon Therapy

- Superficial + deeper (lymph nodes)
- 5 fractions to 35 fractions

Varian Clinac iX

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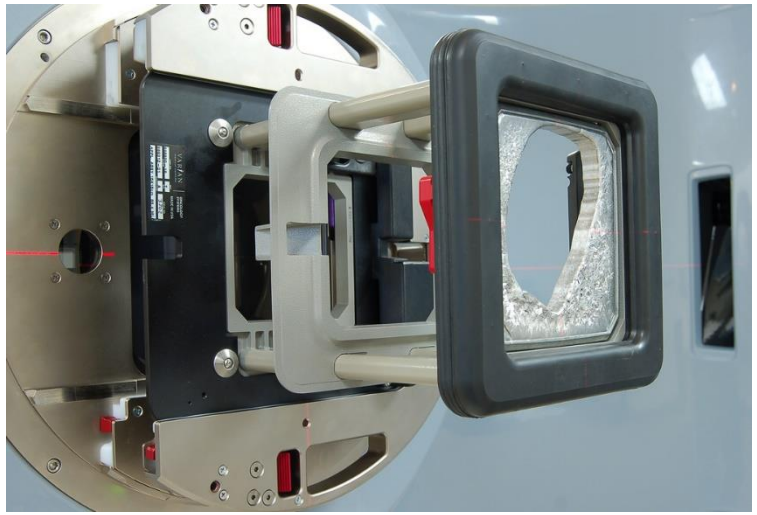
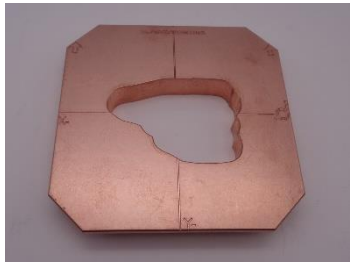
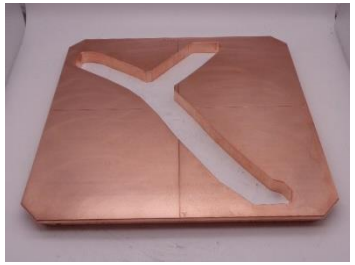
Radiation Oncology Capabilities in Boulder

Boulder Community Health

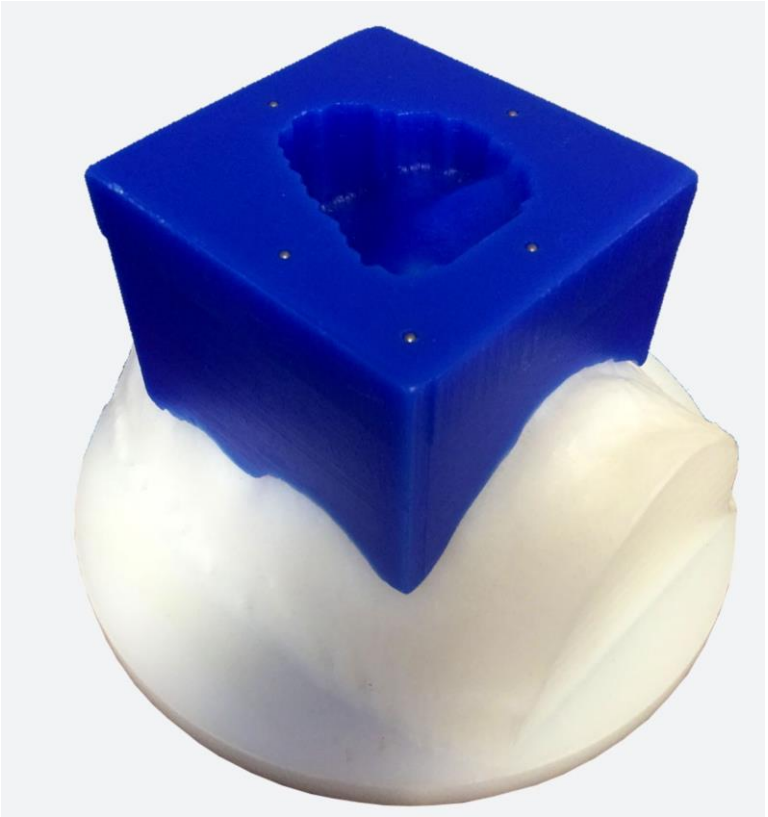
Custom Electron Cutouts



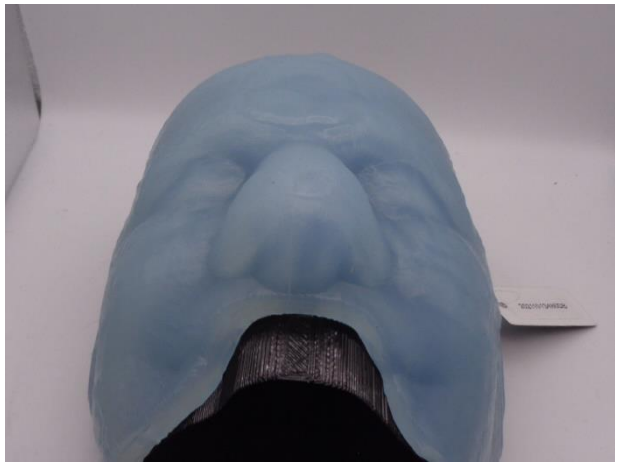


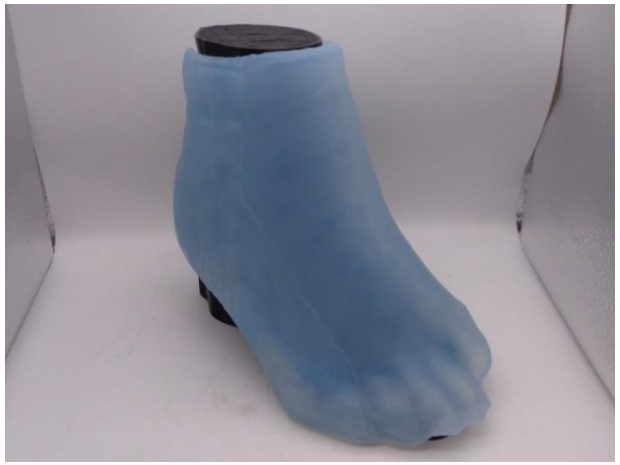


Custom Electron Compensators



Custom Bolus





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Van Ngo, *Electron Applicators*
Dot Decimal

Radiation Decisions

Boulder Community Health

- Definitive or post-operative?
- Treat or not?
- Treat the primary site only?
- Treat the lymph nodes prophylactically?
- Dose and fractionation?
- Electrons or photons?
- Custom electron cutout?
- Custom compensator?
- Custom bolus?

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Dermatology Radiation Education & Utilization

Boulder Community Health

- Survey of **dermatology resident education**
  - 79 out of 80 (**99%**) "SRT [superficial radiation therapy] **equipment was not available for dermatology residents to treat skin cancer** or that they did not know if it was available"
  - 52 of 80 (**65%**) "**no didactic or practical exposure to SRT**"
  - 61 of 80 (**76%**) "**did not feel prepared to discuss…radiotherapy** with patients as an option to treat their skin cancer"

- Additional post-graduate learning usually a **limited clinical training or certification session**

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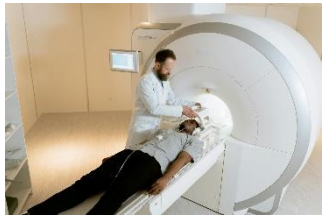
Cognetta Jr et al., *Dermatol Clin* (2016)

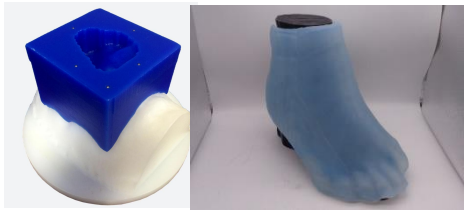
Radiation Oncology vs Dermatology Workflow

Boulder Community Health

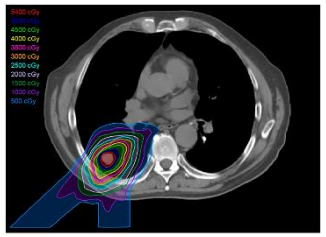
Physician Eval



CT Scan 3D Planning



Bolus Compensator Cutout



Dosimetrist Radiation Plan

Physicist Quality Assurance

Treatment Delivery

Physician Eval

CT Scan 3D Planning

Bolus Compensator Cutout

Dosimetrist Radiation Plan

Physicist Quality Assurance

Treatment Delivery

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Thank you for your time!

Boulder Community Health