Highlights of RT as a Component of Multidisciplinary Skin Cancer Management

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Learning Objectives

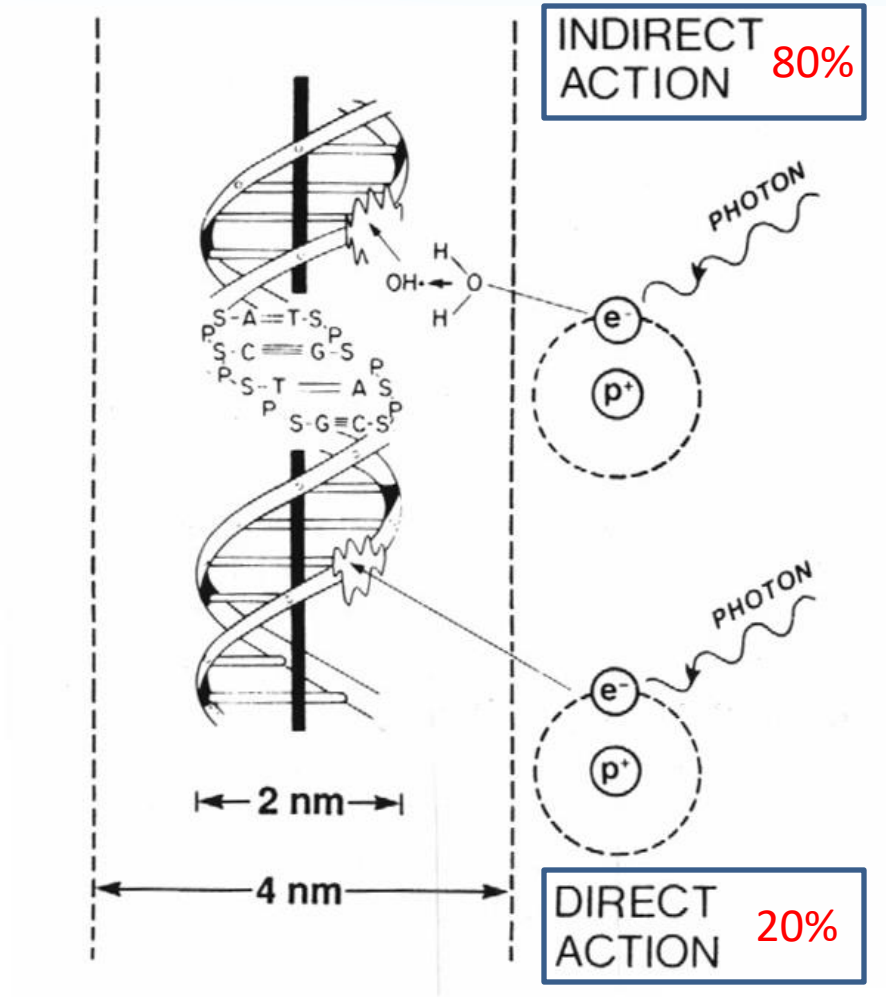
- Understand basic principles of radiation therapy and the modalities used to deliver it for skin cancer
- Discuss indications for definitive and adjuvant radiation therapy in the management of keratinocyte skin cancer
- Importance of multi-disciplinary relationships
  - Rad oncs need to start seeing derm as partners, not competitors
  - Not all rad oncs are up to date with treatment techniques

Background Information

Terminology

- RT is used to treat cancer in the following ways:
  - **Definitive RT** is used instead of surgery as the primary curative treatment modality for the primary tumor and/or regional lymph nodes
  - **Adjuvant RT** is used after definitive surgery in patients at high risk of recurrence of their primary tumor and/or regional lymph nodes
  - **Neoadjuvant RT** is used before definitive surgery to downstage and enable a complete surgical resection
  - **Palliative RT** is used in metastatic patients for symptom relief
- Each of these forms of radiation may be applicable to patients with skin cancer

How Does Radiation Work?



X-rays interact with **water**

↓

radiolysis

↓

free radicals

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bind to and damages **DNA**

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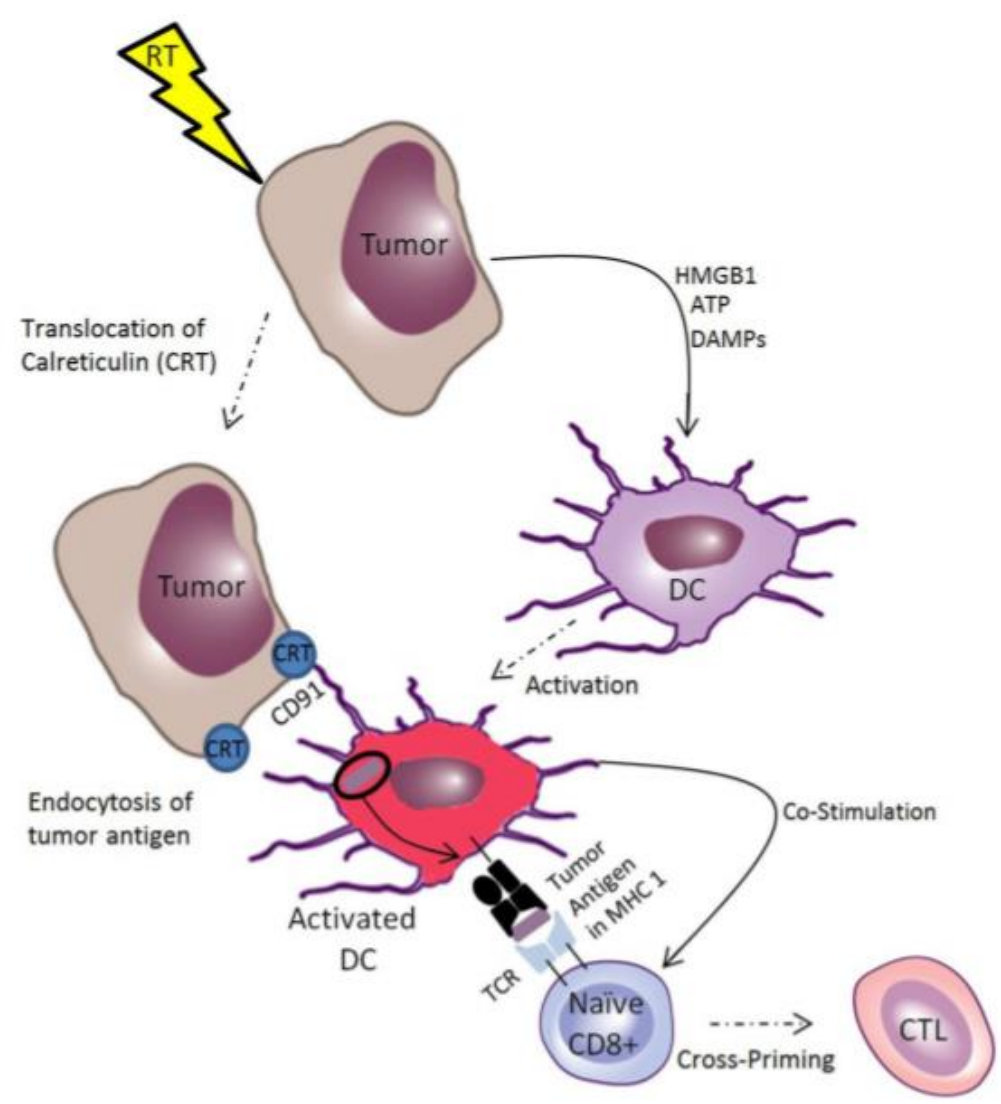
mitotic catastrophe

↓

cell death

Cancer cells are more susceptible to RT due to impaired DNA repair pathways

Radiation May Also Help Promote an Immune Response



Relevant to advanced melanoma and SCC, which are commonly treated with immune checkpoint inhibitors

Radiation Dosing

- **Gray (Gy)** is the unit of RT dose
  - 1 Gy = 100 centiGray (cGy)
  - The dose from 1 cGy roughly equals 1 CT scan

- Dose prescription depends on:
  - Goal of treatment (curative > palliative)
  - Amount of disease (gross > microscopic)
  - RT sensitivity of tumor (melanoma > SqCC or BCC)
  - RT sensitivity of surrounding normal tissue

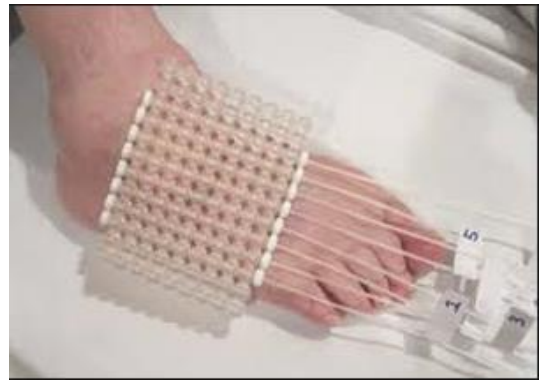
Understanding your RO's Tools

Superficial or Orthovoltage Units
deliver low energy X-rays

Linear Accelerators
deliver electrons or high energy X-rays

Methods of Radiation Delivery For Skin Cancer

Brachytherapy uses a radioactive source to deliver gamma rays

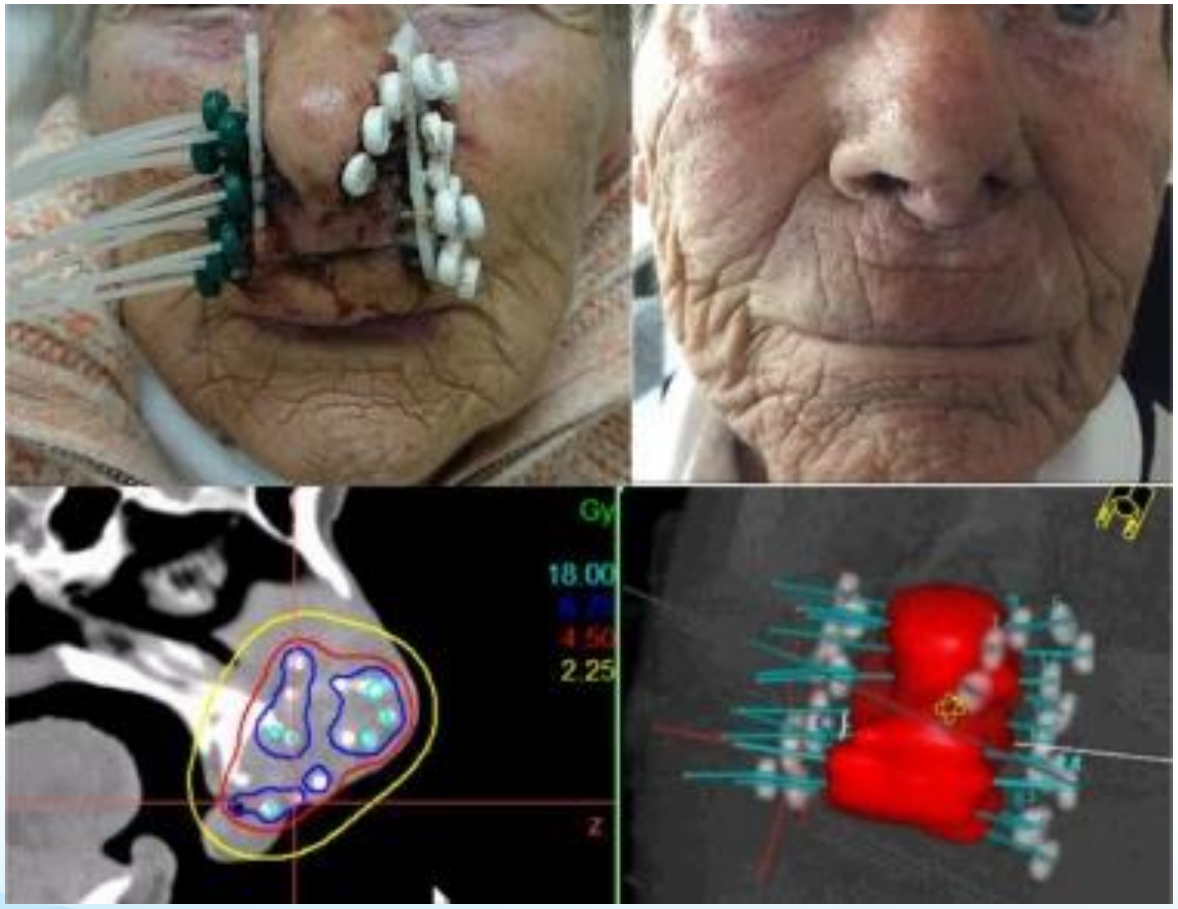


Potential Indications to Use Brachytherapy

- When protracted daily fractionation is inconvenient for the patient
- When the tumor has a more convex/irregular surface contour
- Per institutional expertise

Examples of Brachytherapy

- Interstitial brachytherapy may be useful for periorofacial tumors



Interstitial brachytherapy to treat a SCC of the columella

Examples of Brachytherapy

- Surface applicators may be useful for small, superficial tumors on a flat surface

Valencia applicator

Leipzig applicators

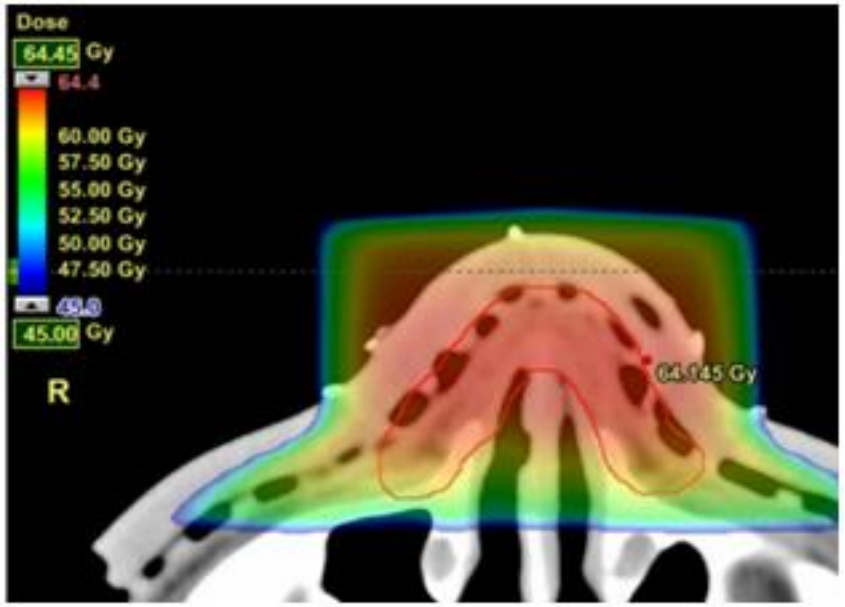
Examples of Brachytherapy

- Surface molds may be useful for superficial tumors ≤4mm thickness on curved surfaces like the shin or hand

VMAT

- Not your grandmother's radiation
- Major advances in hardware, software, imaging
- SIB, dose painting

VMAT


Dose
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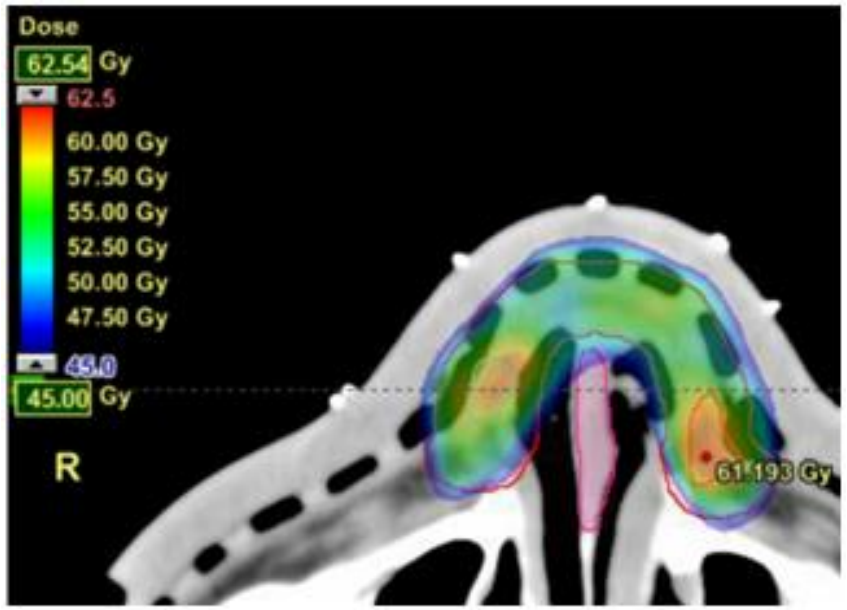
Dose
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52.50 Gy
50.00 Gy
47.50 Gy
45.0
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R
61.193 Gy

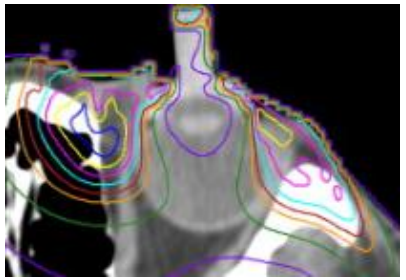
RT Long Term Cosmetic Outcomes are Often Very Good with Modern Techniques

However, like any cancer treatment modality, radiation can cause long term toxicity too. Much less with modern techniques

Special Scenarios: The Eye

- Areas outside of the tumor volume to shield/spare:
  - Lacrimal gland, to avoid xeropthalmia and keratoconjunctivitis
  - Lacrimal duct to avoid stricture and epiphora
  - The uninvolved eyelid to avoid ectropia or epilation of the eyelashes

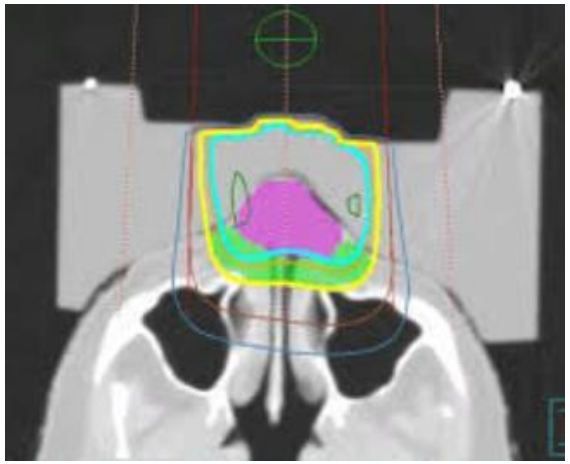
- A tungsten eye shield can protect the superficial structures of the eye and lens
  - Topical anesthetic facilitates shield placement
  - Antibiotic ointment after removal
  - Alternatively, can rotate the lens and cornea out of the beam by having the patient stare away from the beam during Tx



- Brachytherapy can offer unique dosimetric advantages when treating periorbital, perioral, and nasal cutaneous targets
- The above complications often can be treated with minor surgical procedures

Special Scenarios

- Nose
  - Sloping surface → may use tissue equivalent material on outside to ensure a flat surface and homogeneous dose
  - Lead strips coated with either wax or dental acrylic placed directly in the nose to shield the nasal septum and canal
  - Brachytherapy can also be used to treat these tumors instead of external beam radiotherapy



- Mouth
  - Similar shields are placed under the lip to protect the gingiva and oral mucosa.
  - Brachytherapy can also be used to treat these tumors instead of external beam radiotherapy

Cutaneous SCC Management

Surgery remains first choice

- Where does radiation fit in?
  - A few scenarios I want to highlight:
    - SRT in the primary setting/derm office
      - Another tool for derms, many patients may do better functionally with SRT.
    - VMAT/Wide field radiation therapy
    - Adjuvant radiation in very high risk patients
      - In close collaboration with head and neck surgery team, medical oncology

SRT

- Another tool for dermatologists?
  - ASTRO should support this modality more
  - Select patients when surgery would have poor cosmesis
    - "organ preservation" leads to better cosmesis and function
      - Ears, nose, eyelids, lips, underlying nerves

SRT Data

- LC: 93-100% at 2-5 years
  - A retrospective analysis on 1715 histologically confirmed primary cutaneous BCC and SCC treated with SRT between 2000 and 2010.
  - 712 BCC (631 nodular and 81 superficial), 994 were SCC (861 SCC in situ and 133 invasive SCC), and 9 features of both BCC and SCC
  - Cumulative recurrence rates of all tumors at 2 and 5 years were 1.9% (1%-2.7%) and 5.0% (3.2%-6.7%), respectively;
    - BCC were 2% (0.8%-3.3%) and 4.2% (1.9%-6.4%),
    - SCC were 1.8% (0.8%-2.8%) and 5.8% (2.9%-8.7%),
    - Male patients and greater than 2 cm increased recurrence.
  - Energy: Approximately 3500, Fractions 5 - 8
  - Conclusion: SRT viable nonsurgical option for BCC and SCC

Cognetta et al., J Am Acad Dermatol. 2012 Dec;67(6):1235-41

Closing the gap?

Image-guided superficial radiation therapy has superior 2-year recurrence probability to Mohs micrographic surgery

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ABSTRACT

Introduction: Non-melanoma skin cancers (NMSCs) are the most common cancers in the USA, and their incidence is rising. Mohs micrographic surgery (MMS) is commonly performed to excise NMSCs. MMS replaced superficial radiotherapy (SRT) as a first line treatment, given its superior efficacy. Image-guided superficial radiation therapy (IGSRT) was invented to improve the precision of SRT. This study investigates how the 2-year recurrence probability of IGSRT-treated NMSCs compares to that of MMS-treated lesions.

Methods: This retrospective cohort study compared the 2-year recurrence probability of early stage NMSCs (squamous and basal cell carcinomas (SCCs and BCCs)) treated by IGSRT (2,286 lesions) to data on NMSCs treated by MMS (5,391 lesions) via one sample proportion tests. Medical Subject Headings were used to search PubMed for reports of 2-year recurrence probability rates of NMSCs treated by MMS. Seventeen studies were screened; 14 studies were excluded for lack of 2-year time to event analysis, or irrelevant patient population (non-BCC/SCC study, advanced disease), leaving 3 studies for comparison.

Results: IGSRT-treated NMSCs have a statistically significantly improved 2-year recurrence probability than those treated by MMS, $P < 0.001$ for pooled data.

Conclusion: The 2-year recurrence probability IGSRT-treated NMSCs is superior to MMS-treated and supports IGSRT as an effective treatment option for individuals with early stage NMSCs.

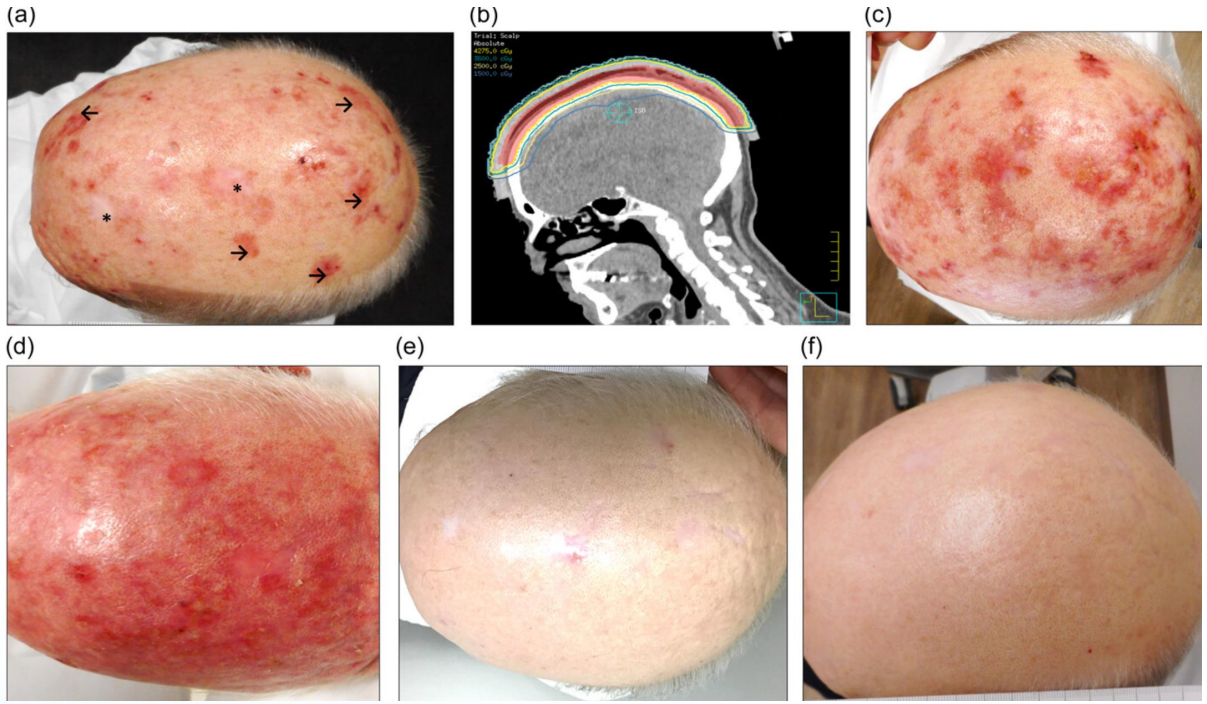
McClure EM, Sedor G, Jin Y, Kattan MW. Image-guided superficial radiation therapy has superior 2-year recurrence probability to Mohs micrographic surgery. Clin Transl Radiat Oncol. 2023 Sep 17;43:100678. doi: 10.1016/j.ctro.2023.100678. PMID: 37781716; PMCID: PMC10539860.

Factors That May Favor Definitive RT Over Surgery

- Older patients (less risk of late side effects)
- Medically inoperable or debilitated patient
- Larger (>5mm) central face tumor
  - especially eyelids, tip/ala of the nose, lips
- Larger (>5mm) eyelid tumors where negative margins are not possible
- Larger tumor of the ear, forehead, scalp, legs
- Upper lip tumors

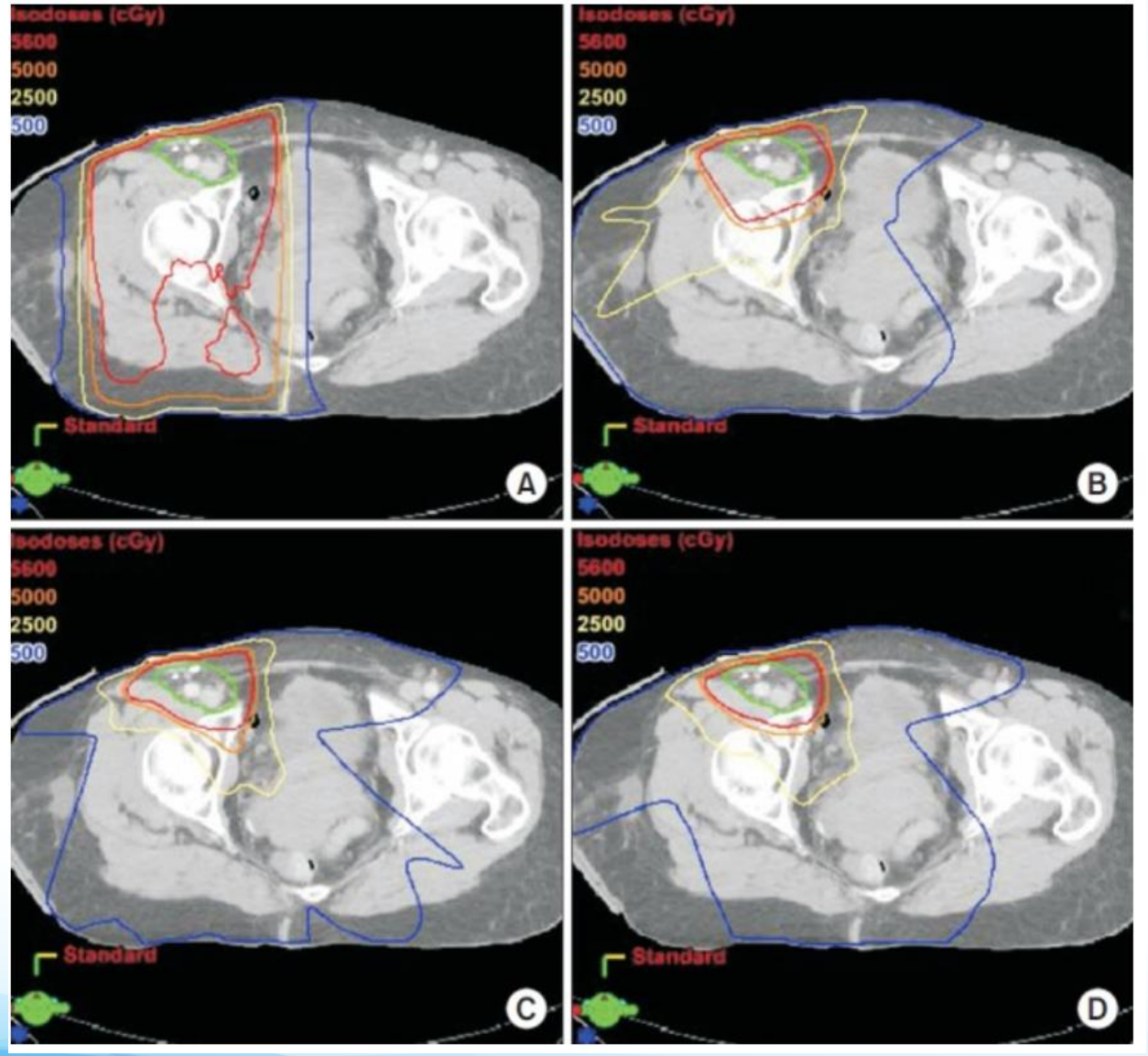
VMAT

- Allowing better outcomes with less side effects
  - Target coverage
  - Avoid OARs



RT Techniques

AP/PA



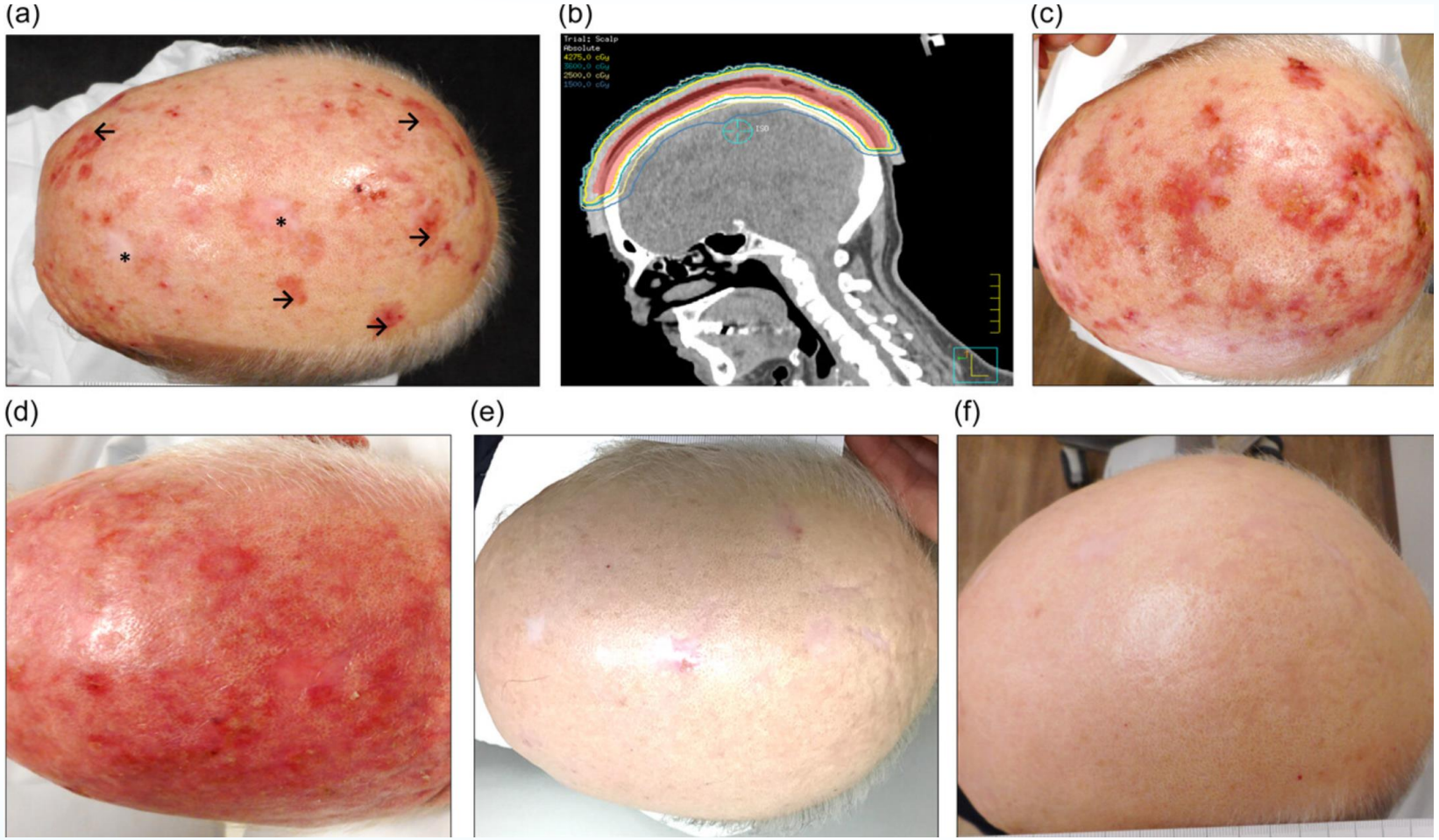
IMRT

3-D CRT

VMAT

Recent advancements in radiation techniques provide better sparing of normal structures.

A new option: Wide field Radiation for extensive skin field cancerization



Spelman L, Potter AE, Baker C, Shumack S, Sinclair R, Christie D, et al. Efficacy and safety analysis: 24-month outcomes from a prospective cohort of 106 fields treated with widefield radiation therapy for extensive skin field cancerization, with or without keratinocyte cancers. *JEADV Clin Pract*. 2024; 3: 487–497. https://doi.org/10.1002/jvc2.312

24 month data Spelman et al., 2024

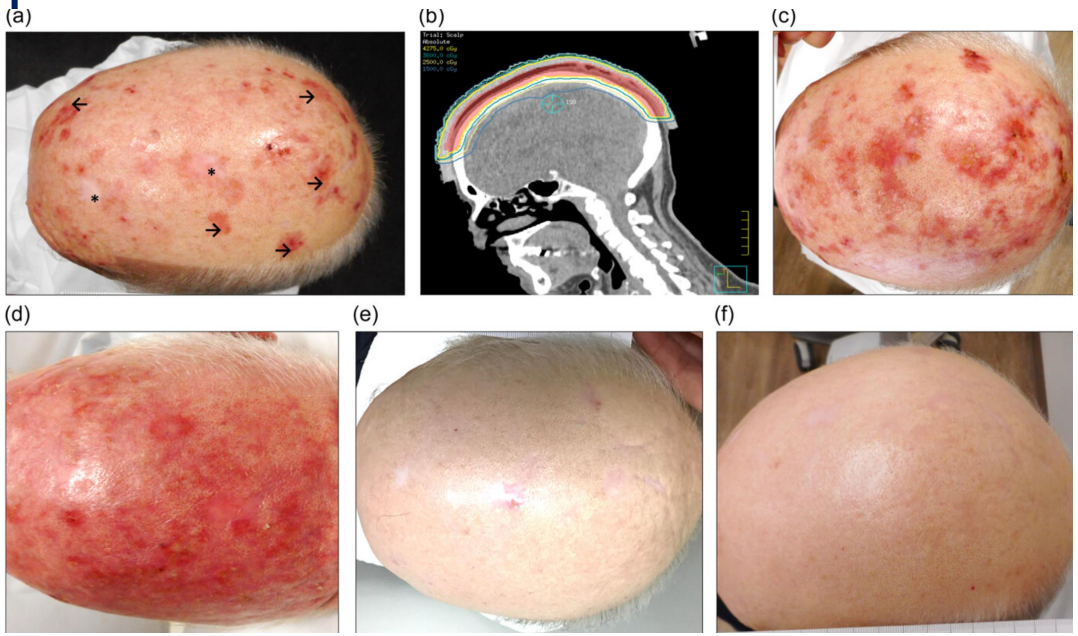
- Heavy pretreated, advanced patients
- 194 patients in prospective cohort
- RT: VMAT SIB 55Gy/45Gy custom bolus
- 92% Grade 1-2 acute effects; 6% G3 effects (resolved after RT)
- MC long term effects: alopecia
- Good/Excellent cosmesis 98% at 2 years
- Low rates of fibrosis; recurrent disease treatable

24 month data Spelman et al., 2024

- Significant QOL improvements compared to pre-tx
  - Pt can get back to their lives
- >95% clearance rate (>90% field clearance)
  - Invasive SCC: CR was maintained in patients at 24 months; 100%
- 10% new KC infield (BCC and BCC)
  - Heavy dz burden
  - Recurrence/persistant invasive dz was BCCs (lower dose received).

A new option: Wide field Radiation: extensive skin field cancerization

- Very highly selected patients
  - Importance of multi-d discussion
  - Limited other options
  - Not mainstream in rad onc



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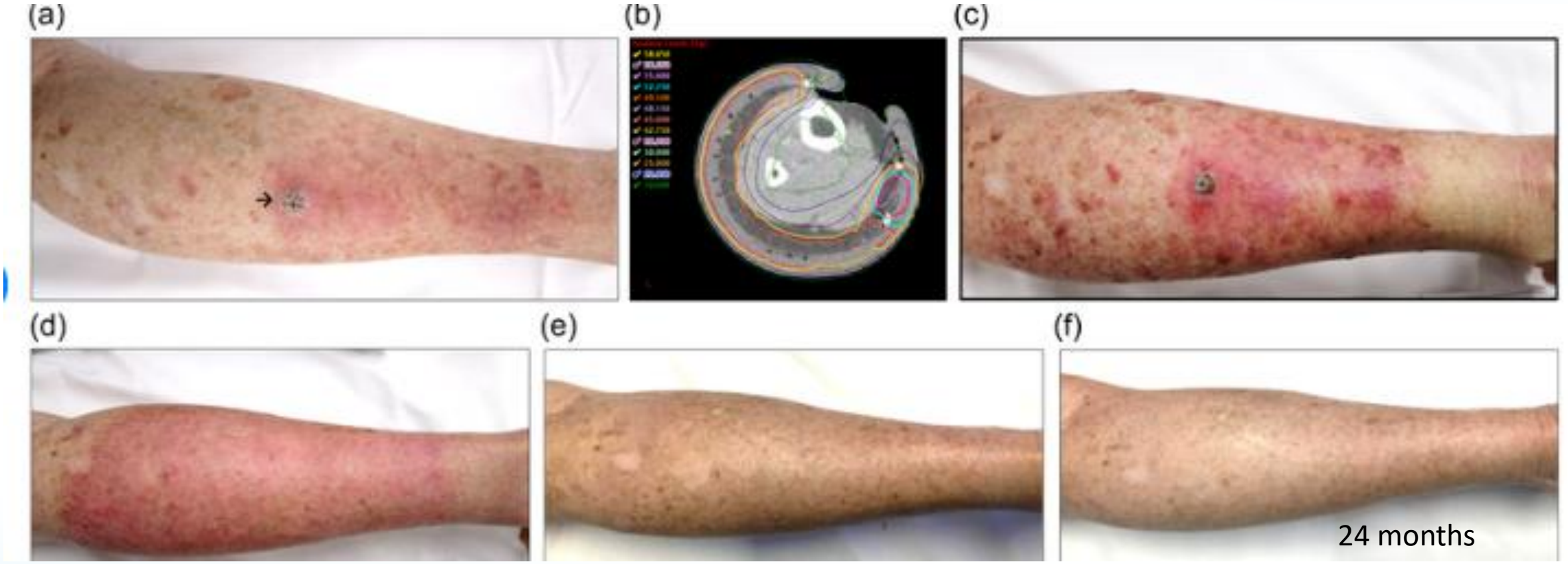
Wide field Radiation



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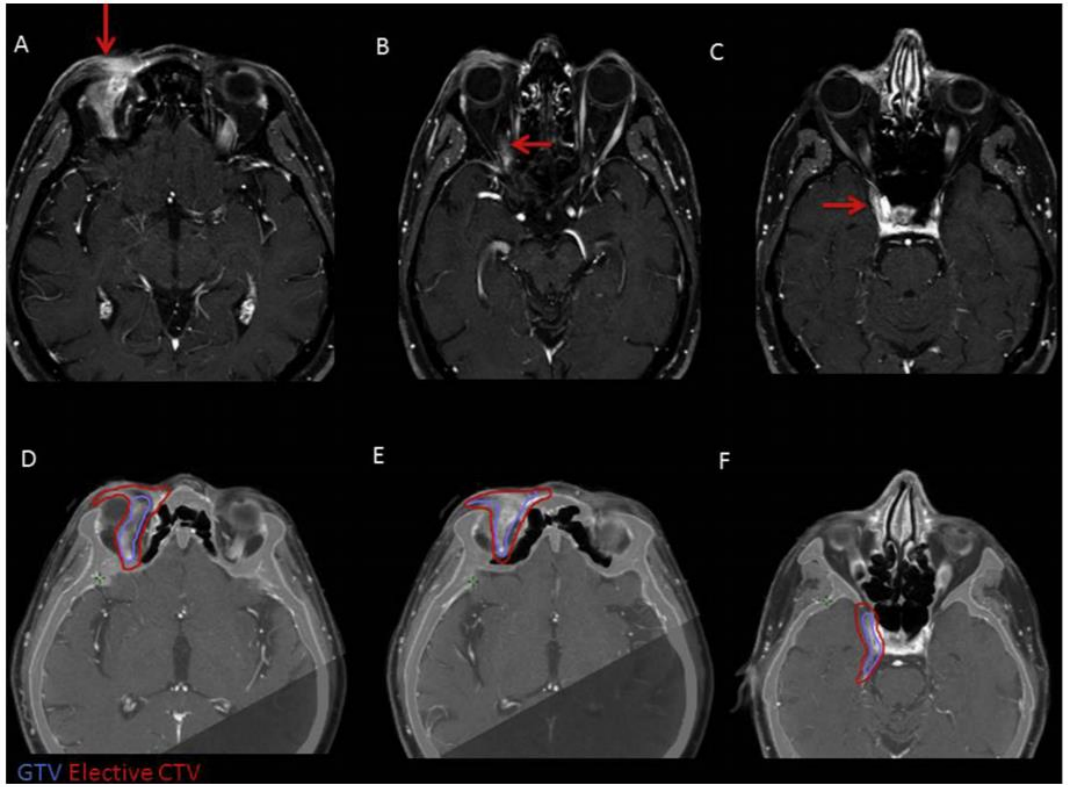
Very high-risk patients

- Similar to head and neck patients
  - Gross PNI
  - Node positive
  - Base of skull
- Head and neck surgery
  - Adjuvant radiation usually indicated
    - Direct convo with surgery team and rad oncs
  - Immunotherapy?

Addressing Perineural Invasion in Adjuvant RT

- For clinical PNI or involvement of a named nerve of the H and N, cover nerve at risk to the base of skull



Right supraorbital SCC with tumor spread along the frontal branch of V1 to the superior orbital fissure (red arrow) is covered into the cavernous sinus in this case.

- For microscopic PNI, may not need to cover as much

Learning Objectives

- Understand basic principles of radiation therapy and the modalities used to deliver it for skin cancer
- Discuss indications for definitive and adjuvant radiation therapy in the management of keratinocyte skin cancer
- Importance of multi-disciplinary relationships
  - Patient centered partners, not competitors
  - Get to know a rad onc
    - **Need to see across the board improved communication/relationships
  - Not all rad oncs are up to date with skin treatment techniques
    - May see big differences in outcomes

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Additional Information

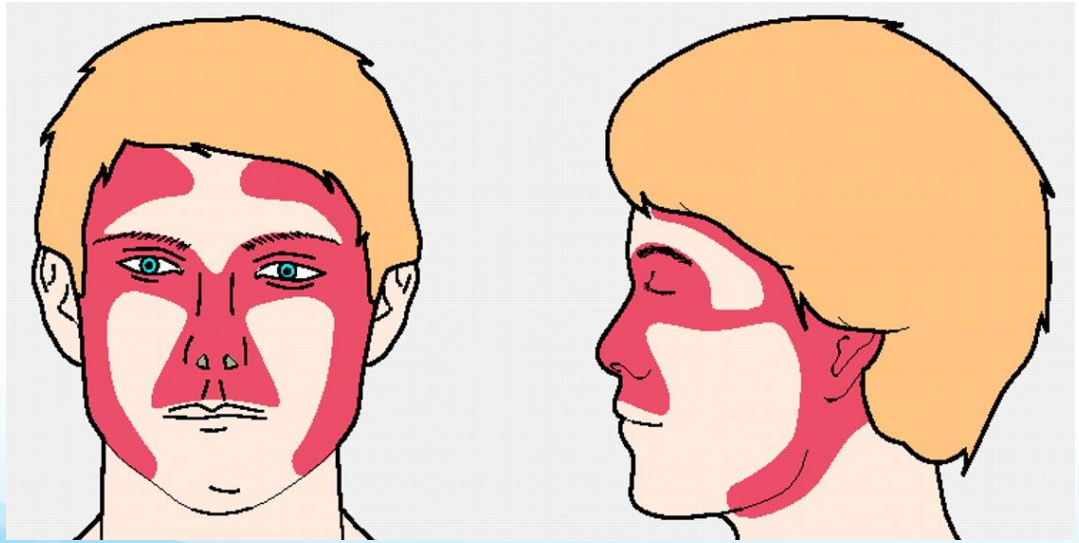
Risk Stratification Based on Tumor Location

- Areas L (low), M (medium), and H (high) correlate with recurrence risk after definitive treatment

Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

Area M = cheeks, forehead, scalp, and neck.

Area L = trunk and extremities.



Area H includes the mid-face where the embryonic fusion planes lie (easier for a tumor to penetrate)

NCCN High Risk Features for any Keratinocyte Skin Cancer

- Location/size:
  - Area L ≥ 20mm
  - Area M ≥ 10mm
  - Area H (any size)
- Poorly defined borders
- Recurrent tumor (vs. primary)
- Immunosuppression
- Site of Prior RT
- Perineural involvement

Additional High-Risk Features for Recurrence for SCC

- Site of chronic inflammatory process
- Rapid tumor growth
- Neurologic symptoms
- Poorly differentiated
- Adenoid (acantholytic), adenosquamous(showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes
- Depth of invasion $\geq$ 6mm or into SubQ fat
- Lymphatic or vascular involvement

Management of Keratinocyte Skin Cancers

- Surgery is often most effective and efficient
  - However, consideration of function, cosmesis and patient preference may lead to choosing RT.
  - Shared decision-making between patient and providers is optimal

- Cosmetic benefits of RT are most significant for tumors on or around the lips, nose, ears and eyelids.

Comparing Outcomes of Treatment Modalities

Summary of Reported Studies	Low Risk Tumors Local Control	High Risk Tumors Local Control
Surgical Excision with Post-Operative Margin Assessment	90-95%	83-88%
Mohs Micrographic Surgery	99%	90-94%
Radiation Therapy	90-96%	80-88%

Results of Treatment

- Randomized evidence comparing RT to surgery for BCC of the face favors surgery in terms of both cosmesis and local control (Avril *et al* 1997, Petit *et al* 2000)
  - However, nuances in patient selection may favor RT in some cases

- A more recent matched-pair cohort analysis of 369 patients (Patel *et al* 2017) treated with electron brachytherapy vs. Mohs showed 3Y-LC rates of 99-100% in both groups

- Meta analysis (Drucker et al. 2018) of 40 RCTs show surgical treatments and external-beam radiation have low recurrence rates for the treatment of low-risk BCC
- Locally advanced tumors (i.e. those involving cartilage, bone, nerve and/or muscle) have lower cure rates (50-80%)

Special Scenarios

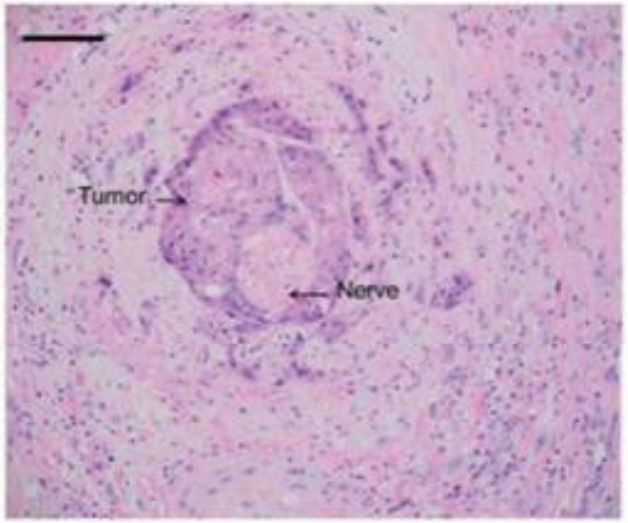
- Ear
  - A shield can be used behind the ear to treat auricle lesions
  - To minimize the irregular shape, may try to flatten the ear or put water in the concha and external auditory canal

- Elderly Patients
  - Brachytherapy may be preferred if patient has limited mobility, and positioning for daily external beam RT may be challenging

Adjuvant RT for Squamous Cell Carcinoma

Indications for Adjuvant RT to Tumor Bed for SCC

- Close or positive margins than cannot be cleared surgically
- Clinically or radiographically apparent perineural invasion (PNI)
- Recurrent SCC s/p prior margin-negative resection
- pT3-4 (>4cm, PNI, deep invasion >6mm or beyond subQ fat, or invasion of bone, skull base, or foramen)
- Desmoplastic or infiltrative tumors in chronically immunosuppressed patient



Squamous cell carcinoma with perineural invasion

Management of Positive Lymph Nodes

- If operable → regional LND
  - Adjuvant RT for multiple involved LNs or extranodal extension
- If inoperable → definitive RT
  - Minimal evidence for concurrent chemotherapy
- Regional nodes are generally not treated electively in node-negative patients with high-risk primary tumors
  - May consider elective nodal RT if already treating tumor bed, and target volume overlaps much of draining lymphatics

Potential Late Toxicity from Definitive RT

- Radiation necrosis of the skin
  - Can occur months to years after RT
  - Due to poor vascularity and atrophy, and usually precipitated by trauma
  - 3% incidence using < 4 Gy/fraction
- Chondronecrosis or osteonecrosis
  - Currently very uncommon using modern techniques and equipment, even if tumor involves cartilage or bone
- RT-induced malignancy (in treated field)
  - Typically occur 5+ years after RT
  - May behave more aggressively

Take-Home Points

- Though surgery is the mainstay of treatment for most cutaneous malignancies, RT has an integral role in the definitive and adjuvant management for a variety of patients and tumor types.

- The expected cosmetic benefits of definitive RT for keratinocyte carcinomas is likely to be most significant for larger tumors on or around the lips, nose, ears and eyelids.

- Multidisciplinary consultations and shared decision-making are appropriate for patients with keratinocyte carcinomas of borderline operability, or when surgery would render a relatively poor cosmetic outcome.

- Post-op RT for cutaneous SCC is recommended for T3-4 stage, gross PNI, close or positive margins, and recurrence after a prior margin-negative resection.