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Non-surgical management of advanced skin cancers

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Non-surgical management of advanced skin cancers

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24th Mar 2022

Disclosure

- None

Learning objectives

After participating in this e-ESO activity, the learner should be able to:

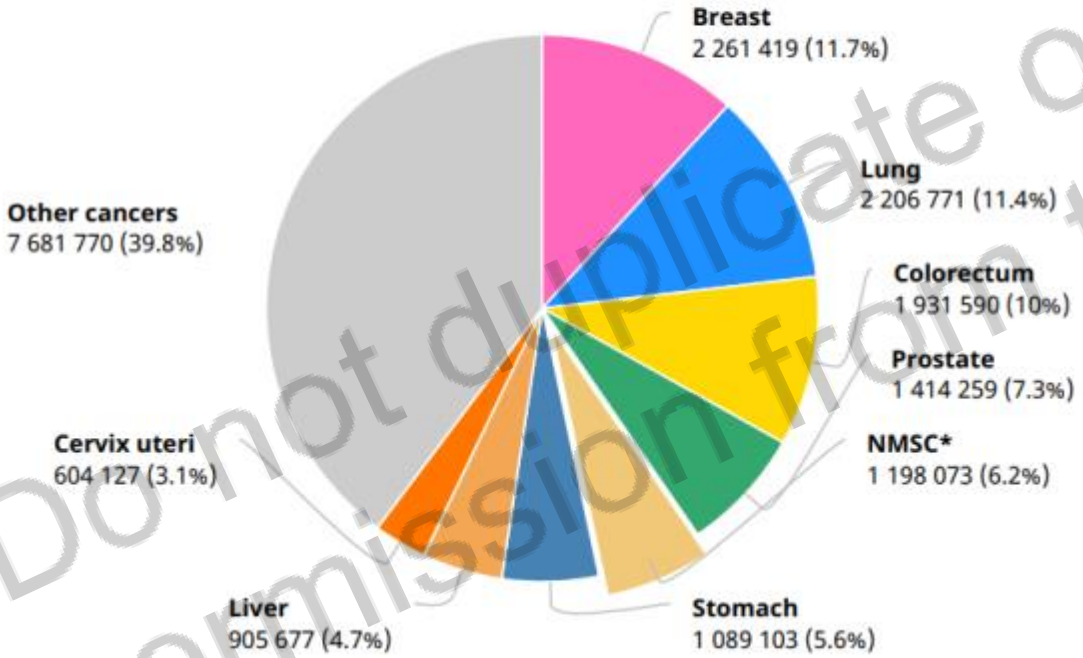
1. Describe the concept of high / very high risk and advanced skin cancer.
2. Understand the role of radiotherapy and systemic treatments in advanced skin cancer
3. Create management plans for patients with advanced skin cancer

Introduction

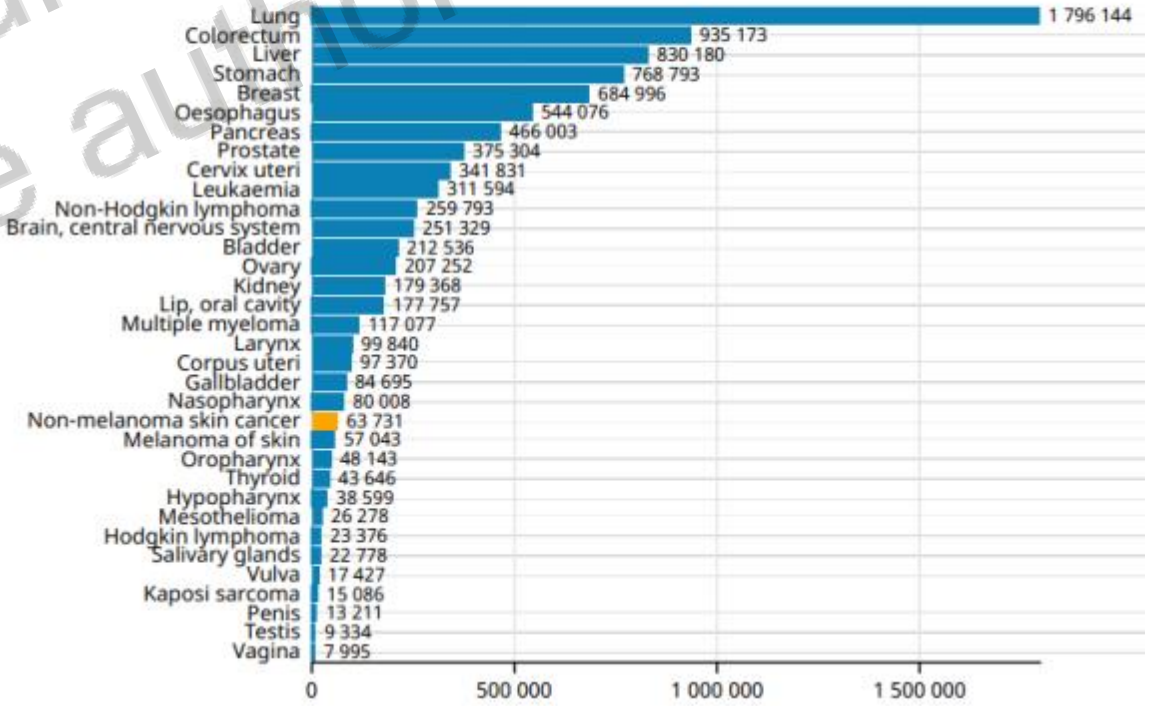
Non-melanoma skin cancer

Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



Number of deaths in 2020, both sexes, all ages



https://gco.iarc.fr/today/data/factsheets/cancers/17-Non-melanoma-skin-cancer-fact-sheet.pdf, assessed 14.03.22

Introduction

- Non-melanoma skin cancers are regarded as the most common malignancy in adults
- Diverse group but **BCC** (rodent ulcer) **and cSCC** (both called keratinocyte cancers KC) accounts for the majority (95%) of NMSC cases. MCC (skin neuroendocrine tumour) tends to be highly aggressive. Rare skin cancers - limited literature.
- Substantial economic burden
- The incidence 18-20 x higher than malignant melanoma
- The incidence is increasing: BCC by 145% and cSCC by 263% from 2000 to 2010 in US
- Multifactorial reasons: UV exposure, aging population, increased awareness
- Local control is the key. BCC rarely metastasise, cSCC risk of nodal or distant metastases
- Majority of KC successfully cured by dermatology and surgical treatments
- Local treatment and local recurrence of significant risk to cosmesis and

Risk factors in BCC and cSCC

TABLE 29-1
Risk Factors for BCC Recurrence

Characteristic	Low Risk	High Risk
Primary vs. recurrent	Primary	Recurrent
Borders	Well defined	Poorly defined
Immunosuppression	No	Yes
Location: Eyelids, ears, nose, lips, genitals, hands, feet Cheeks, forehead, scalp, neck Trunk, extremities	Size <20 mm Size <10 mm Size <6 mm	Size ≥20 mm Size ≥10 mm Size ≥6 mm
Pathology	Nodular, superficial	Aggressive growth pattern
Perineural involvement	No	Yes
Site of previous radiation treatment	No	Yes

BCC:
https://static1.squarespace.com/static/55b9b764e4b015d421de3aee/t/55c2946ee4b0d9038d7b9c6f/1438815342223/Chapter+29+MCGH322-c29_p353-369.pdf

SCC:
https://www.uptodate.com/contents/recognition-and-management-of-high-risk-aggressive-cutaneous-squamous-cell-carcinoma

Factors associated with increased risk for local recurrence and metastasis of cutaneous squamous cell carcinoma

Tumor factors	Rate of recurrence (percent)	Rate of metastasis (percent)
Location		
Lip	2.3 to 22.2	3 to 20
Ear	5.3 to 18.7	8.8 to 11.6
Anogenital	14 to 15	15 to 74
Chronic wound or scar	N/A	26.2 to 37.9
Irradiated skin	N/A	20 to 26
Size		
≥2 cm	15.2	5.8 to 42.5
Depth		
>4 mm/Clark IV, V	17.2	30.4 to 51
>6 mm	N/A	15.6
Recurrent tumor	10 to 27.5	16.3 to 30.3
Poorly differentiated histology	28.6	32.8 to 57.9
Perineural invasion	16 to 47.2	10 to 50
Host factors	**Rate of recurrence (percent)**	**Rate of metastasis (percent)**
CLL and SLL	25 to 100	18 to 100
Organ transplantation	10 to 54	6 to 31

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma.

From: Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: A systemic review of the English literature. Dermatol Surg 2006; 32:1309. DOI: 10.1111/j.1524-4725.2006.32300.x. Reproduced with permission from Lippincott Williams & Wilkins. Copyright © 2006 American Society for Dermatologic Surgery. Unauthorized reproduction of this material is prohibited.

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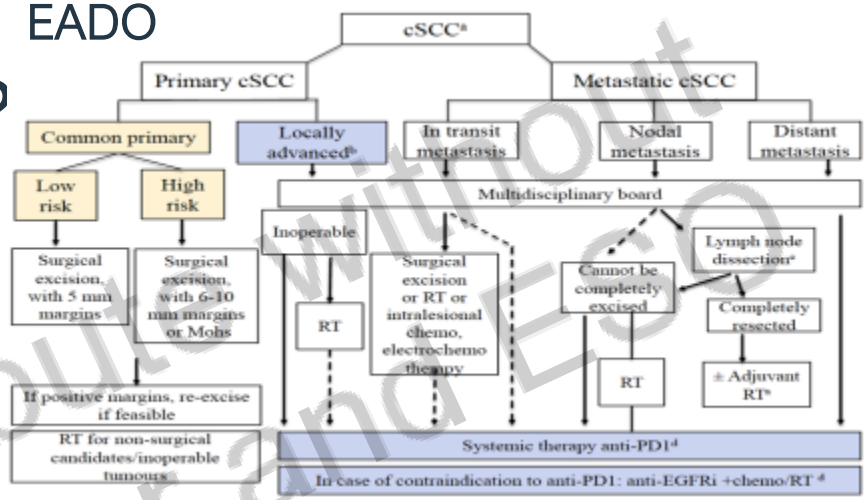
Risk factors of progression

- **Staging**
- **Clinical features:** anatomic location, T diameter, recurrent tumours, multiple tumours, neurologic symptoms
- **Histologic features:** grade and subtype, T thickness, growth pattern, PNI, PVI
- **Comorbidities:** Immunocompromised / immunosuppressed patients, comorbidities associated with chronic immunosuppression (e.g. certain malignancies, HIV) and skin conditions (epidermolysis bullosa)
- **Genetic conditions** predisposing to skin cancer (AT, Gorlin's syndrome, albinism)
- Skin cancer arising from previous burns or XRT areas
- Delays in care (denial, neglect, access inequalities, COVID)
- Gene expressions and biomarkers

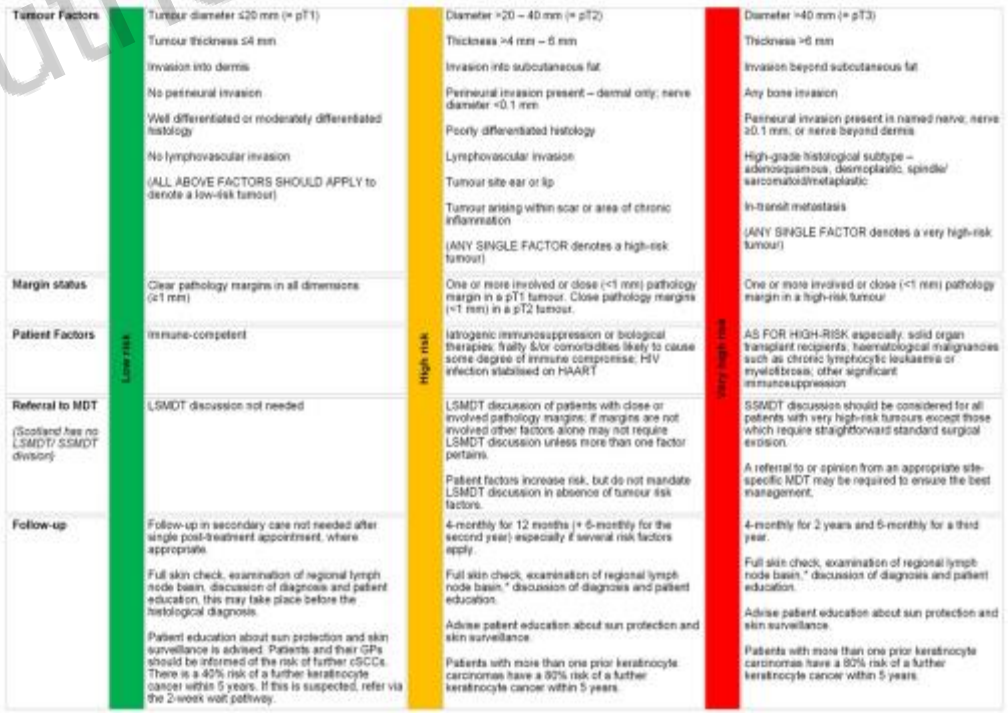
Advanced – what does it mean?

- No agreed definition
- Various risk factors (single or combination)
- Various staging systems (AJCC, UICC/TNM, Breuninger, BWH)
- EADO guidelines 2020 not based on any staging system
- UK BAD guidelines based on TNM + risk categories (cSCC 2020, BCC 2021)
- High or very high risk of ?LR, ?progression ?nodal ?distant metastases
- Locally advanced, nodal / distant metastases
- Management requiring involvement from at least two specialities or complex single multimodality treatment
- Specific for this session: radiotherapy, immunotherapy

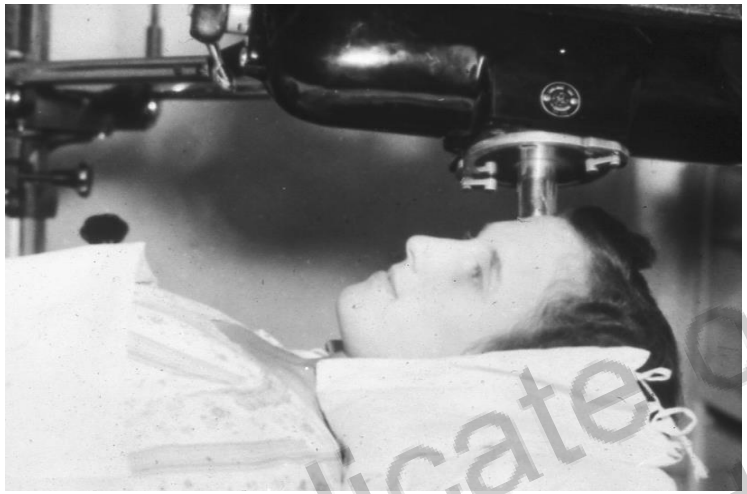
EADO

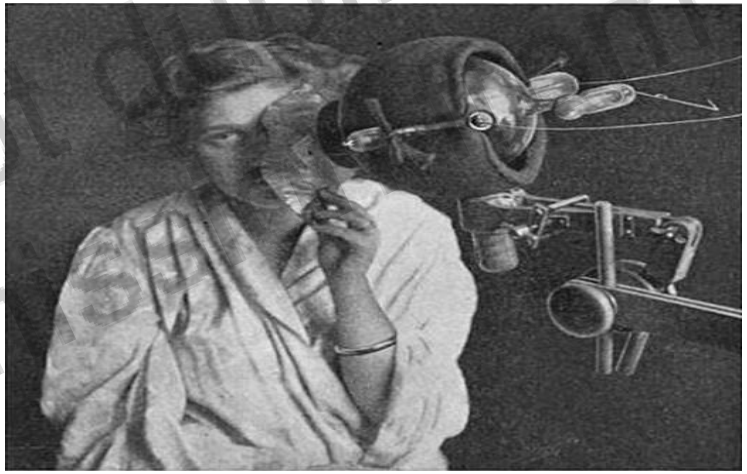


UK BAD



Skin radiotherapy





How skin radiotherapy is delivered in 21st century?

External beam radiotherapy

Grenz rays 10-20kV
Contact therapy 40-50 kV

X-rays

- Grenz (Bucky) rays 10-30 kV
- **low-energy photons**

  kV = superficial 50-150 kV
  orthovoltage 150-300 kV
- MV photons 4-25 MV

Particle radiation

- **electrons** 4-15 MeV
- protons <=250MeV

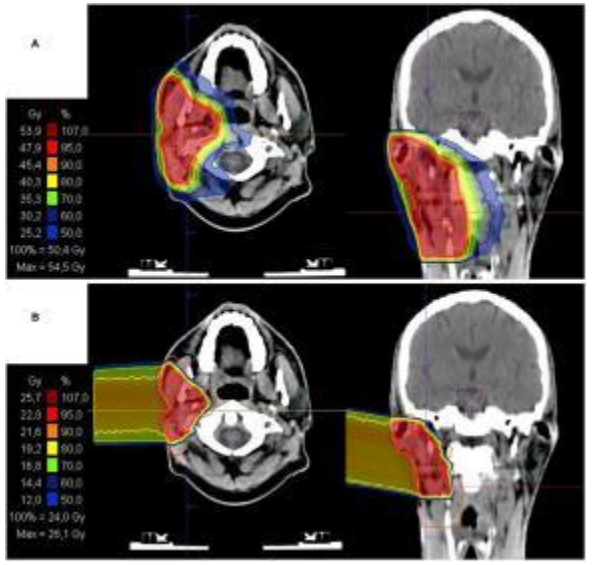
Brachytherapy (interventional radiotherapy)

Mainly gamma emitters – Ir192 0.38 MeV

- surface or contact BT

  flaps, moulds, surface applicators
- interstitial BT

IMRT / VMAT /SRT / IGRT



Evidence based – primary disease

NMSC systematic reviews:

Zaorsky (2017)
a meta analysis of hypofx RT for NMSC (9729 patients)
median LR 2% at 1 year and 14% at 5 years
good (physician assessed) cosmesis in 92%

Lansbury (2013) pooled analysis
FU up to five years
LR 6.4% in 761 cSCC patients treated with EBRT
LR 5.2% in 88 cSCCs treated with BT

Gunaratne (2018)
Hypofractionated XRT (>2 Gy per fraction)
12,000 patients with NMSC (24% cSCC), 40 publications
LR 7.9% in 33/36 studies, FU 2-77 months.
"Hypofractionated radiotherapy is an option that confers no obvious disadvantage in local control when compared to traditional more protracted radiotherapy schedules".

Zaorsky (2018) SCRiBE meta-analysis EBRT vs BT
9965 patients received EBRT, 553 received BT across 24 studies.
BT has favourable cosmesis over EBRT for skin SCCs/BCCs at common fractionation regimens.
"Prospective studies comparing EBRT vs BT are warranted".

Evidence based – primary disease

- Very little comparative data, no RCTs
  mostly retrospective studies and case series {Lansbury, 2013; Jambusaria, 2009}

- Insufficient evidence to identify high-risk features in which ART may be beneficial

- **Margin status**
  No consistency in literature what pathological margin is regarded as clear (1 mm)
  In an Australian study 9% of patients with incompletely / closely excised lip SCC relapsed following ART comparing to 57% who did not undergo ART {Veness, 2013}

- **PNI** - seen in 5% to 10% of cSCC, risk factor for LRR and DM. Postoperative RT in microscopic PNI if multifocal, diameter of nerve >0.1 mm or in named nerves {Jambusaria, 2009}. Patients with symptomatic and/or radiological PNI should be considered for conformal ART to the extended field including the whole pathway of the nerve.

Evidence based – primary disease

- Postoperative CRT vs XRT alone

There was one small cohort study
61 patients with HNcSCC
Adjuvant XRT vs CRT

Better RFS with adjuvant CRT although no difference in OS {Tanvetyanon, 2015}.

TROG 05.01 {Porceddu, 2018}
Randomized phase III trial
Concurrent post op CRT vs XRT in patients with high risk cSCC in HN (XRT to nodes allowed)

No observed benefit with the addition of weekly carboplatin

Evidence based – nodal disease

- In regional nodal metastases from SCC, including intra-parotid metastases in HNcSCC, the standard of care is nodal dissection and parotidectomy.
- There are no prospective randomised data for these treatments.
- Three within-patient cohorts, following the same group of patients, examined recurrence after surgical excision and adjuvant XRT compared to surgical excision alone. These favoured the combined treatment for loco-regional and overall survival {Wang, 2012; Oddone, 2009; Veness, 2005}
- A retrospective cohort study of parotidectomy with or without neck dissection for metastatic cSCC supported surgery and adjuvant XRT for metastatic cSCC {Hirshoren, 2018}.
- The use of SLNB has been investigated in several studies but there are no conclusive data on its use {Stratigos, 2015}

Evidence based – nodal disease

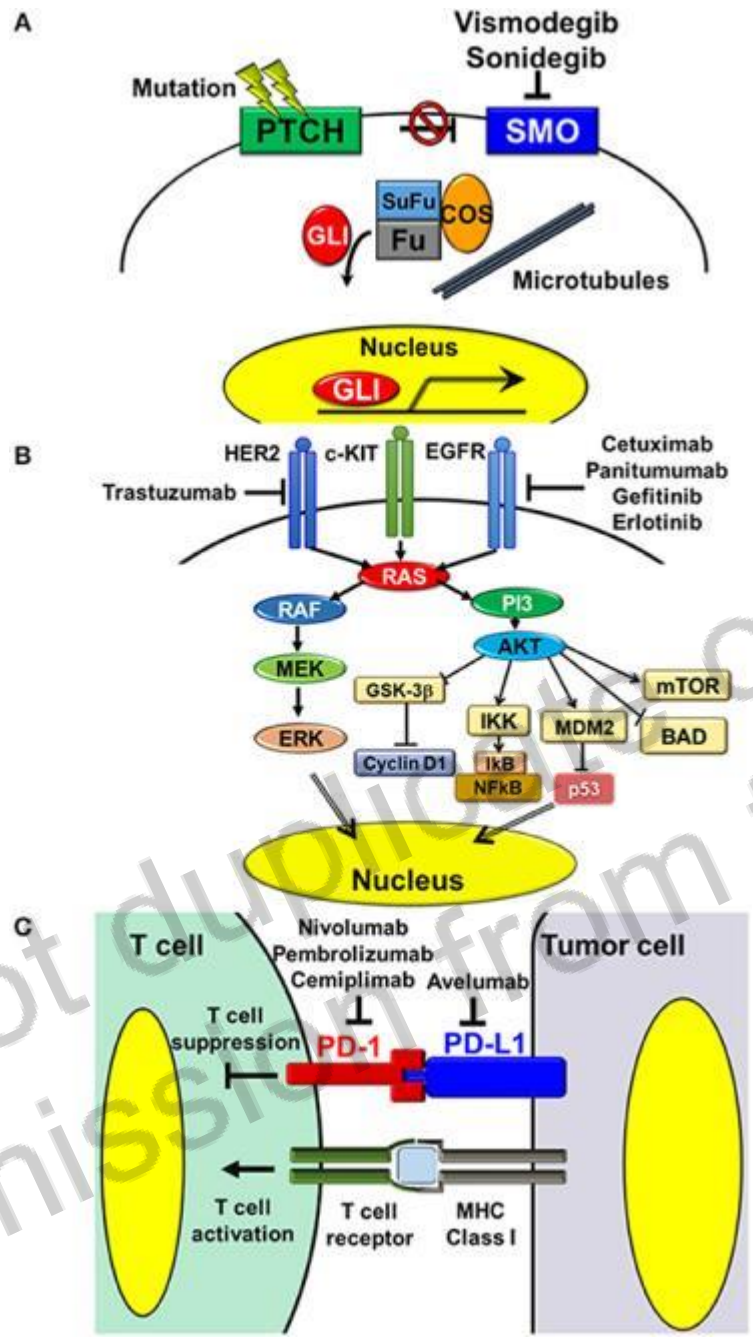
- Adjuvant XRT of the draining nodal basin is recommended in patients with multiple nodal involvement, large nodes ≥ 3cm or ECE.

- Elective nodal basin irradiation should not be routinely recommended.
  - One a single-institution study {Wray, 2015}
  - 71 consecutively treated cSCC on face, ears, or scalp
  - actuarial regional control rate at 5 years 96%
  - no grade 3 or higher complications

- The TROG 05.01 randomized phase III trial {Porceddu, 2018}. Postop concurrent CRT in patients with high risk HNcSCC. No observed benefit with the addition of weekly carboplatin

- For non-HNcSCC, regional lymphadenectomy+/-adjuvant. XRT (axilla/inguinal) may be considered as above although data is limited, mostly from single centre series {Goh, 2010}

Targeting pathways and molecules in the treatment of NMSC



(A) Hedgehog signalling pathway

(B) Receptor tyrosine kinases and downstream MAPK and PI3-AKT signalling pathways

(C) Interaction between T cells and tumor cells via the PD-1/PD-L1 axis

Cemiplimab - advanced fully human monoclonal antibody indicated for the treatment of both advanced cSCC and BCC.

https://www.frontiersin.org/articles/10.3389/fmed.2019.00160/full

Clinical trials

- **BCC**

Vismodegib: EVIRANCE, **STEVIE**, MIKIE

Sonidegib: BOLT

Side effects: alopecia, dysgeusia, muscle spasm, weight loss

STEVIE

Outcome	mBCC (n=84)	laBCC (n=1077)
Overall response, %	36.9%	68.5%
Complete response	4.8%	33.4%
Partial response	32.1%	35.1%
Stable disease	46.4%	25.1%
Progressive disease	10.7%	1.9%
Median duration of response	13.9 mos	23.0 mos
Median progression-free survival	13.1 mos	23.2 mos

- **cSCC**

cemiplimab, pembrolizumab

First cemiplimab trial: the rate of response for 76 patients with locally advanced cSCC was 43.6%, and the durable disease control rate was 62.8%#

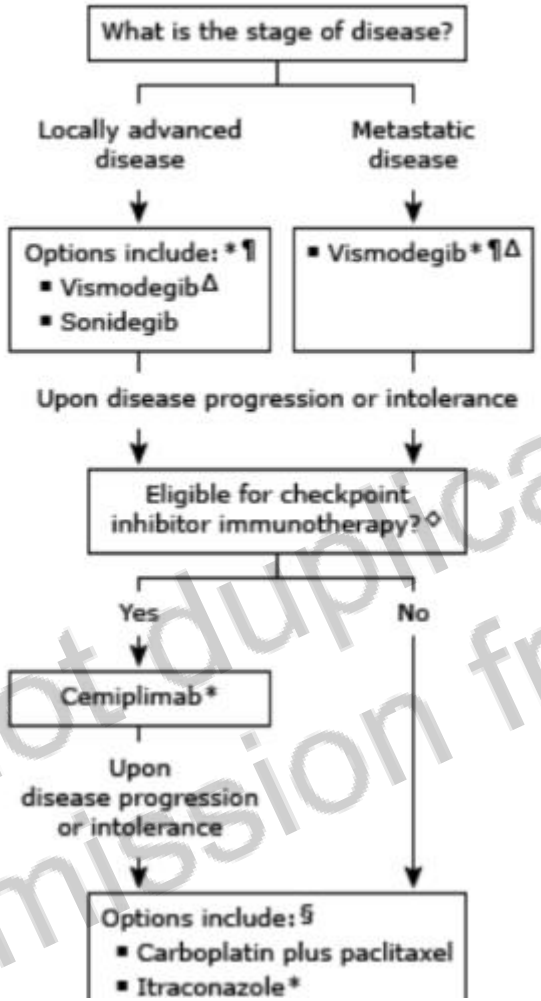
Phase 2 trial **EMPOWER-CSCC-1** (NCT02760498), up to 3 years of follow-up showed continued response rates, and a clinically meaningful survival and duration of response (DOR) for cemiplimab: an overall response rate (ORR) of 46.1%, complete response (CR) rate of 16.1%, and a median time to CR of 11.2 months in 89 responders. The DOR had not yet been reached at the time of data cutoff.

KEYNOTE-629 Pembrolizumab monotherapy for recurrent or metastatic cSCC: A Single-Arm Phase II Trial -clinically meaningful, durable responses; and acceptable safety in primarily elderly patients with R/M c

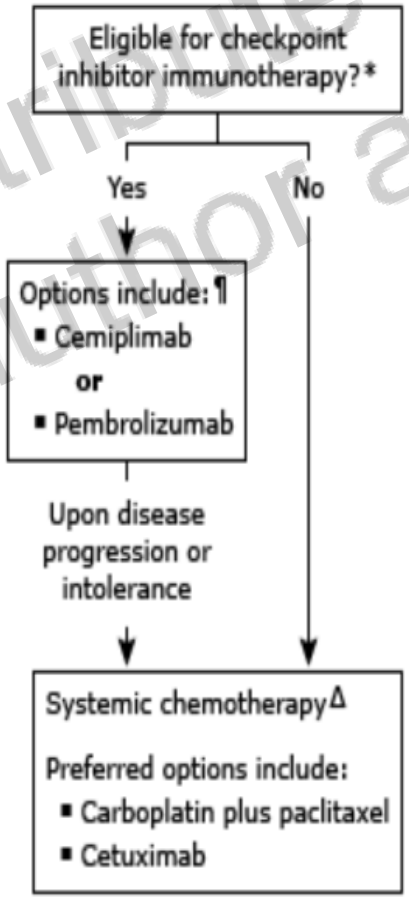
Side effects: new or worsening cough, SOB, irregular heart beat, severe headaches, confusion, hallucinations, eye pain or redness, vision problems, severe muscle pain or weakness, neck stiffness;

In February 2021 cemiplimab received approval from the FDA as the first immunotherapy indicated for treating advanced BCC who are previously treated with a hedgehog pathway inhibitor (HHI) or for whom an HHI is not acceptable.

Initial systemic therapy in locally advanced or metastatic basal cell carcinoma not amenable to locoregional therapy

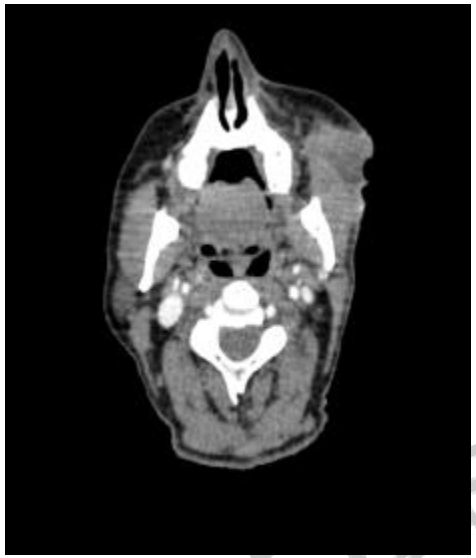


Initial systemic therapy in advanced cutaneous squamous cell carcinoma not amenable to locoregional therapy

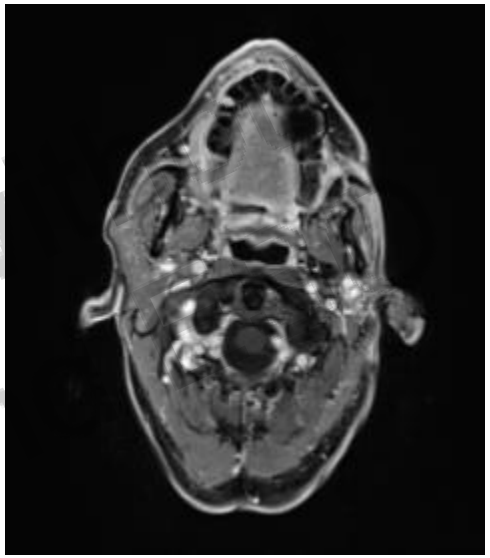


https://www.uptodate.com/contents/systemic-treatment-of-advanced-basal-cell-and-cutaneous-squamous-cell-carcinomas-not-amenable-to-local-therapies

November 2019



October 2021



- 78 year old male, PS: 0
- March 2018: Excision of ulcer and left parotidectomy (28mm G2 SCC infiltrating underlying salivary tissue and extending focally to the deep lateral margin)
- Post operative radiotherapy completed June 2018: 50Gy in 15#, 12MeV electrons with a custom made lead cut out.
- September 2019 – recurrent ulcer right cheek. Investigations confirmed recurrent cSCC with lung metastases
- November 2019 decision to treat with cemiplimab
- Following 3 cycles of cemiplimab the patient had an excellent clinical response, with resolution of the cheek recurrence. Radiological response was mixed with some areas of ?progression ?pseudo-progression
- Patient was benefiting clinically and the decision was made to continue with treatment
- Pt has now received 33 cycles of cemiplimab and has CR
- Cemiplimab has been well tolerated with no toxicity

Courtesy of Dr A. Sykes, The Christie Hospital, Manchester, UK

New challenges

EClinicalMedicine 35 (2021) 100844

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study)
Neoadjuvant Vismodegib in Locally Advanced Basal Cell Carcinoma

Nicolas Bertrand, MD[a,1,*], Pierre Guerreschi, MD, PhD[b,1], Nicole Basset-Seguin, MD, PhD[c], Philippe Saiag, MD, PhD[d], Alain Dupuy, MD, PhD[e], Sophie Dalac-Rat, MD[f], Véronique Dziwniel, PhD[g], César Depoortère, MD[b], Alain Duhamel, MD, PhD[h], Laurent Mortier, MD, PhD[i]

Current Problems in Cancer
Volume 45, Issue 6, December 2021, 100736

Neo-adjuvant Vismodegib followed by radiation in locally advanced basal cell carcinoma

Diya M Sabu [a, d], Jeska Kroes [a], Charles Gilham [b], Ann Fleming [c], Fergal C Kelleher [a, d]

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Author manuscript
Clin Cancer Res. Author manuscript; available in PMC 2022 February 15.

Published in final edited form as:
Clin Cancer Res. 2021 August 15; 27(16): 4557–4565. doi:10.1158/1078-0432.CCR-21-0585.

Pilot phase II trial of Neoadjuvant Immunotherapy in Locoregionally Advanced, Resectable Cutaneous Squamous Cell Carcinoma of the Head and Neck

Renata Ferrarotto[1], Moran Amit[2], Priyadharsini Nagarajan[3], M. Laura Rubin[4], Ying Yuan[4], Diana Bell[3], Adel K El-Naggar[3], Jason M. Johnson[5], William H Morrison[6], David I. Rosenthal[6], Bonnie S. Glisson[1], Faye M Johnson[1,11], Charles Lu[1], Frank E Mott[1], Bita Esmaeli[7], Eduardo M. Diaz Jr.[2], Paul W. Gidley[2], Ryan P. Goepfert[2], Carol M. Lewis[2], Randal S. Weber[2], Jennifer A. Wargo[8], Sreyashi Basu[9], Fei Duan[9], Shalini S. Yadav[9], Padmanee Sharma[10], James P. Allison[9], Jeffrey N. Myers[2], Neil D. Gross[2]

U.S. National Library of Medicine
ClinicalTrials.gov

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Home > Search Results > Study Record Detail

Neoadjuvant Pembrolizumab in Cutaneous Squamous Cell Carcinoma (DESQUAMATE)

Take home messages

- Rapidly risking incidence of non-melanoma skin cancer worldwide, especially in elderly
- Advanced skin cancer – unmet medical need
- Excellent outcomes in skin radiotherapy in definitive, adjuvant and palliative settings in selected patients
  - Advanced radiotherapy and brachytherapy techniques
- BCC two hedgehog pathway inhibitors approved (vismodegib and sonidegib)
  - Highly active, but resistance is common
  - Toxicities predictable but can be treatment-limiting
- cSCC
  - Immunotherapy (cemiplimab, pembrolizumab and other agents in phase 2/3 investigations)
- Emerging opportunities
  - Combination therapies

Further learning opportunities

Home / Live e-Sessions / Clinical case discussion on non-melanoma skin cancers

Clinical case discussion on non-melanoma skin cancers

E-session 634 / CME accredited

Ask the expert

06
OCT 2022
18:15
CEST

CALL FOR CLINICAL CASES

TOPIC: Complex non-melanoma skin cancer (BCC, SCC and rare keratinocyte skin cancers)

FORMAT: 10-slide presentation including three questions related to the clinical case that you would like to discuss with the experts
SUBMISSION DEADLINE: 4 September 2022 (selected authors will be notified within 10 days)
PRESENTATION DATE: 6 October 2022 – h. 18.15 CEST (you will need to be available to connect from h.17.30 CEST)
For further information and case submission contact e-ESO@eso.net

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24 November 2022 - 25 November 2022 Online

Multidisciplinary Management of Non-melanoma Skin Cancer

ESTRO

ESTRO 2022

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06 May 2022 - 10 May 2022
Copenhagen, Denmark

Multidisciplinary approach to high-risk skin cancer with special focus on brachytherapy

Friday 6 May 2022
09:00-17:00

THANK YOU