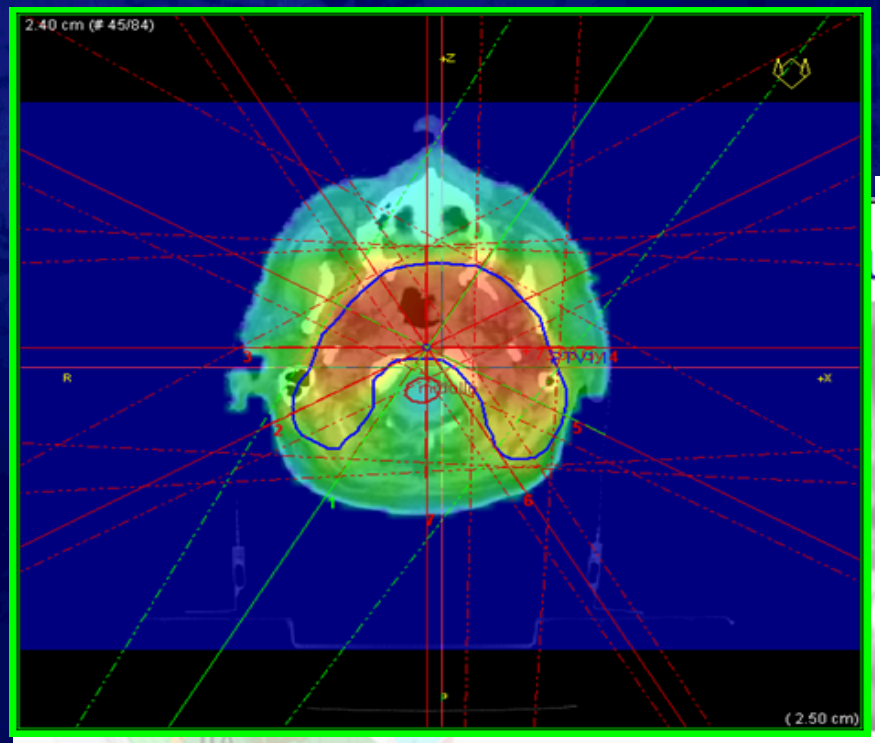
TOSSICITA' DA TARGETED THERAPIES E RADIOTERAPIA

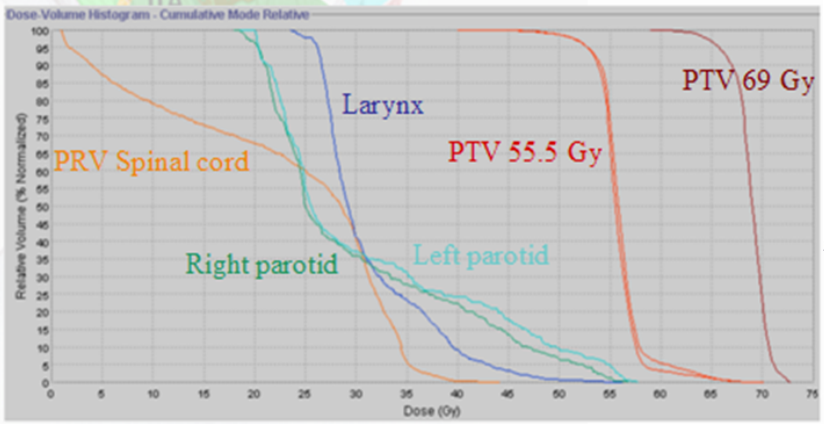
Alessandro Gava

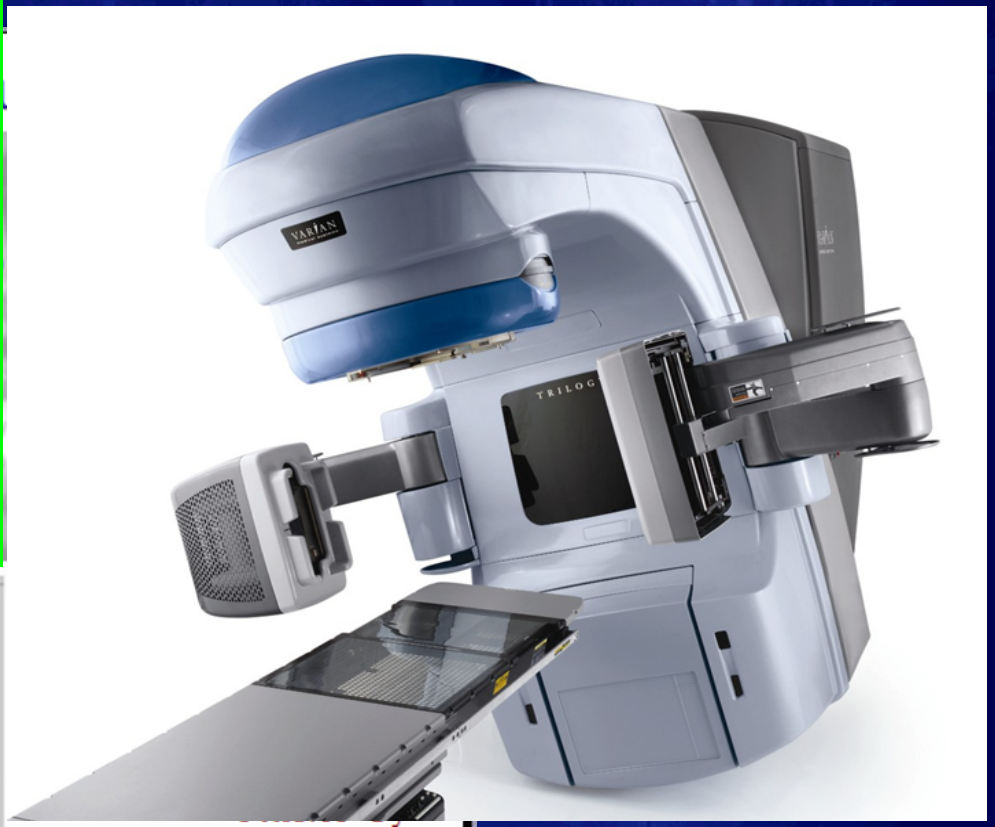
RADIOTERAPIA ONCOLOGICA TREVISO

Genova 20 novembre 2011

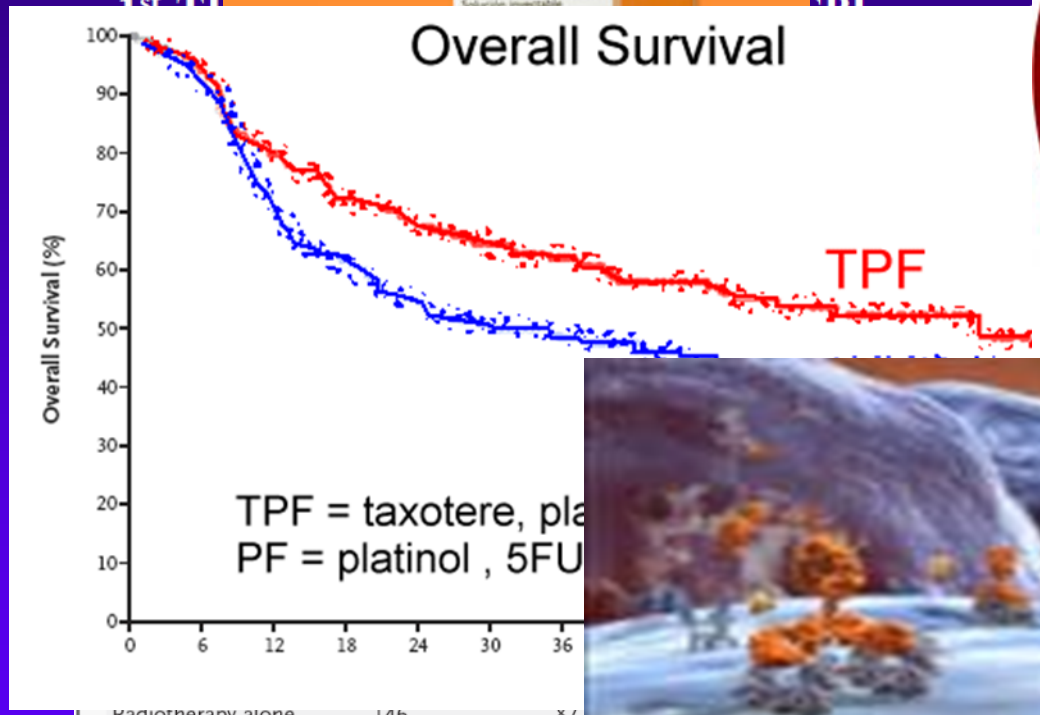
NOVITA' ULTIMO DECENNIO

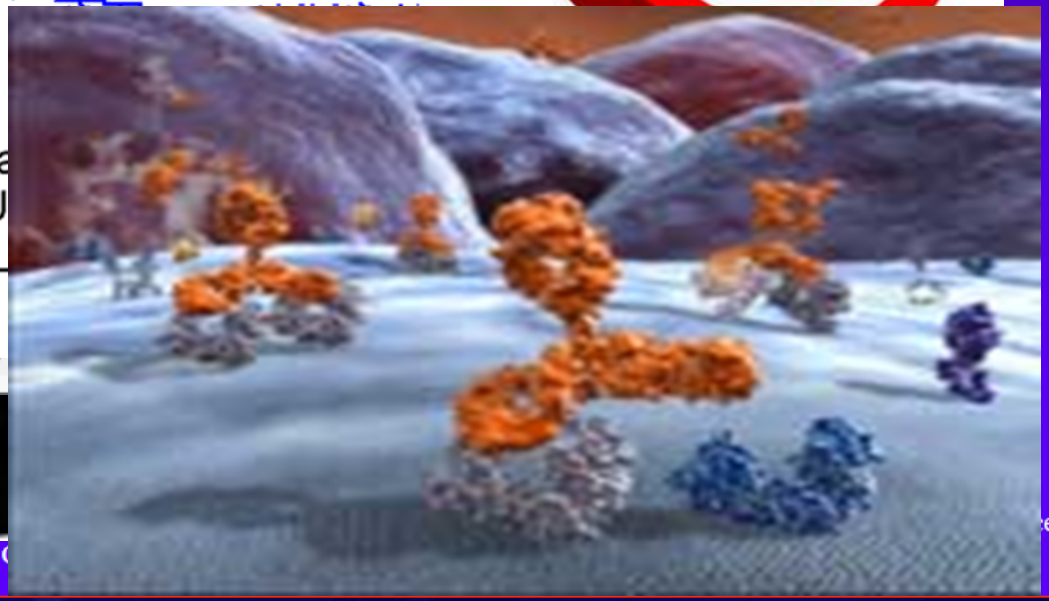






3 NOVITA' PIU' RECENTI NEL TRATTAMENTO NON CHIRURGICO DEI TUMORI DEL CAPO-COLLO





Billroth

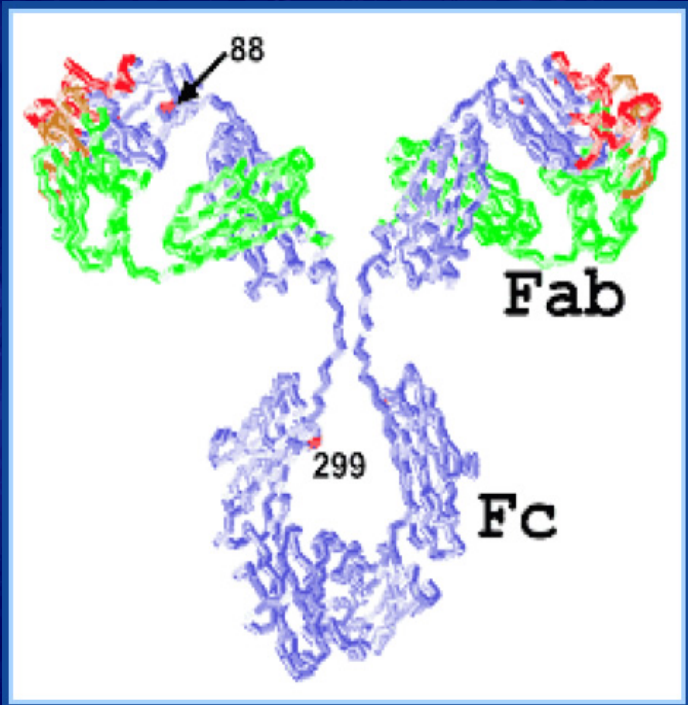
2008

TL = total lar
VA = Veteran
RTOG = Radiation Therapy

RT e CETUXIMAB: RAZIONALE

CETUXIMAB o C225

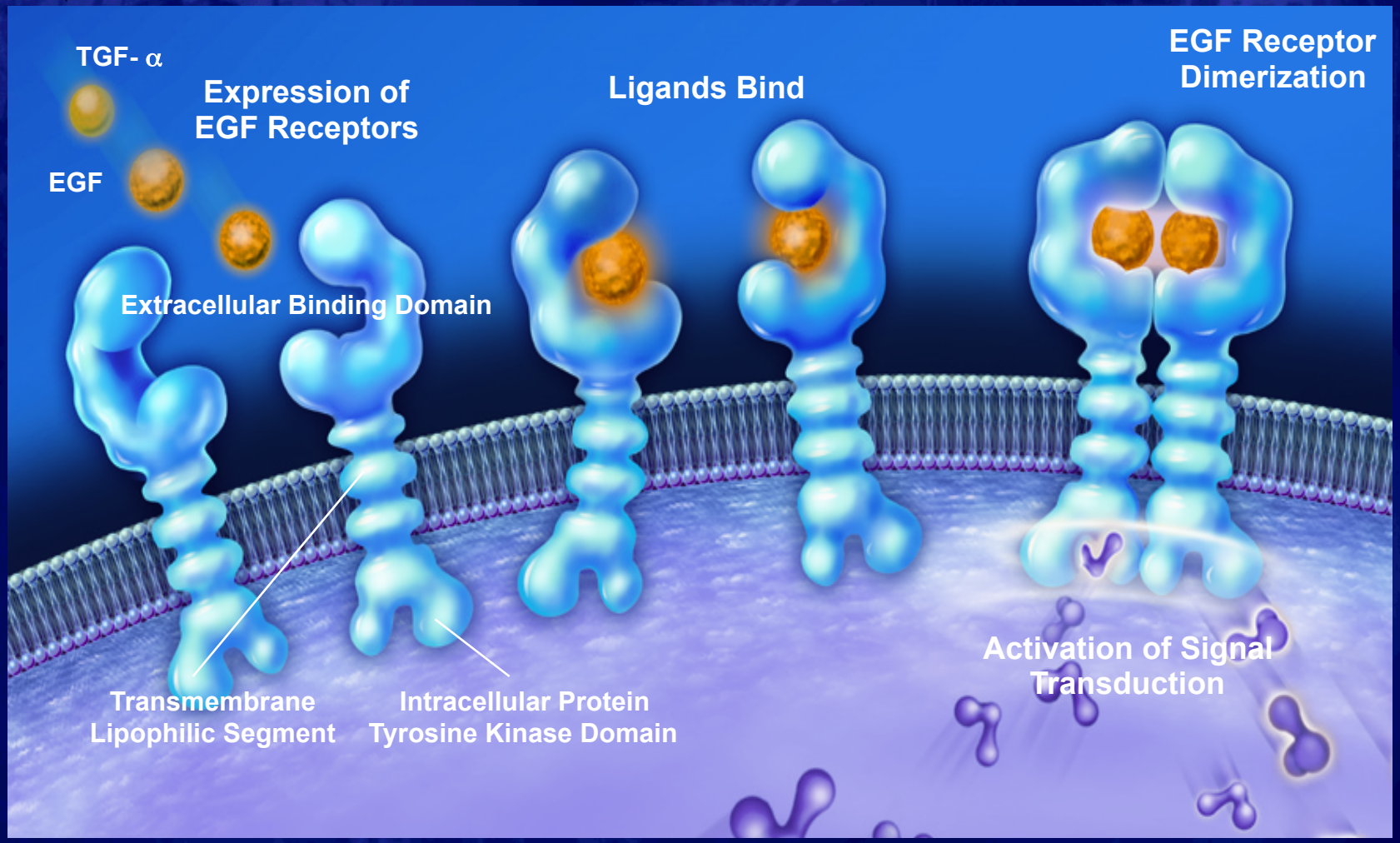
Anticorpo monoclonale umano-murino, che ha alta affinità per il EGFR. La sua storia inizia negli anni 80 nei laboratori del MD Anderson a Houston.



*Cetuximab = IMC-C225 = Erbitux®

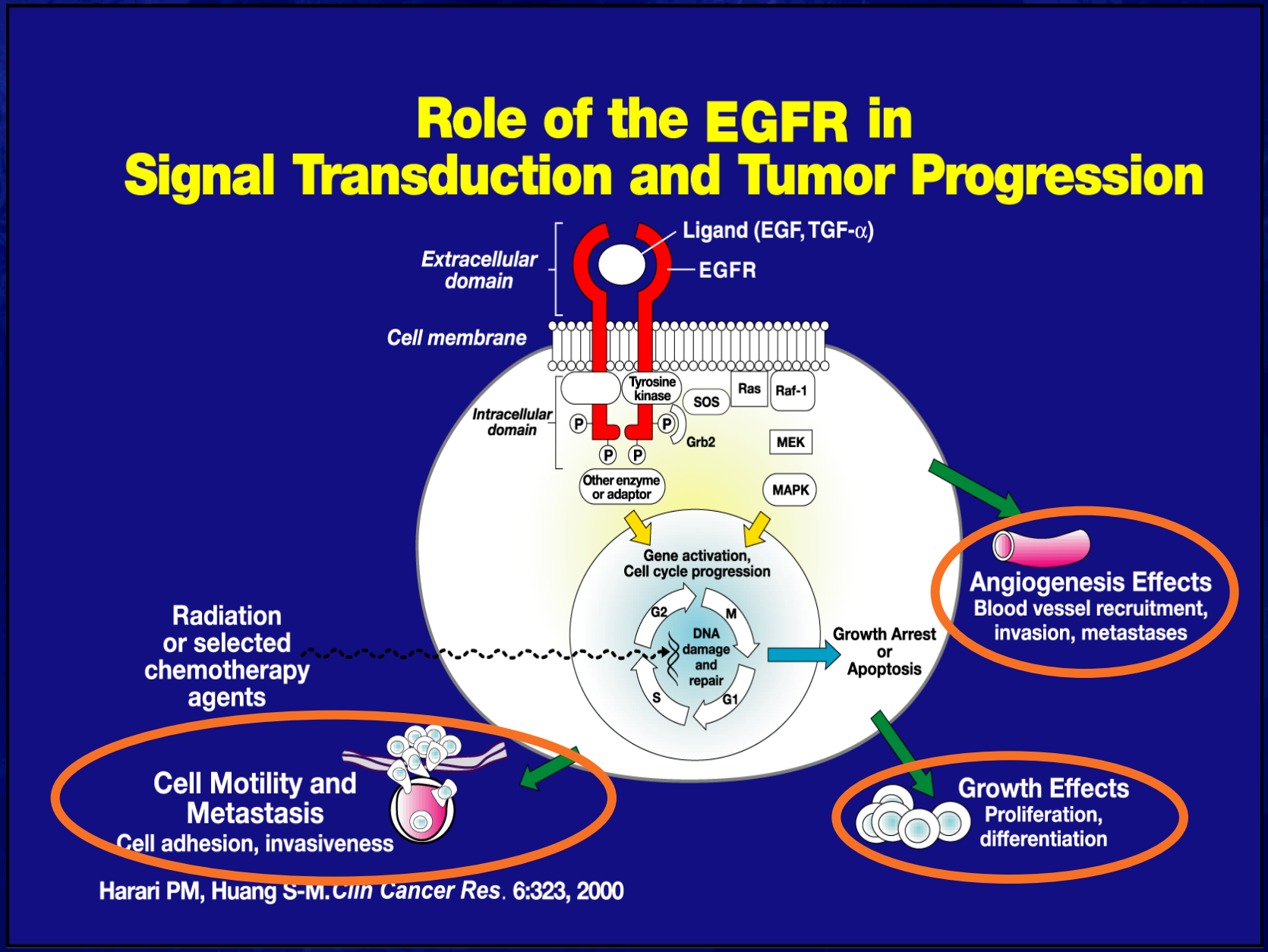
Cetuximab: Mechanism of Action

The EGF Receptor : an important Target for Cancer Therapy



Baselga J. *J Clin Oncol*. 2001;18s:41s-44s.

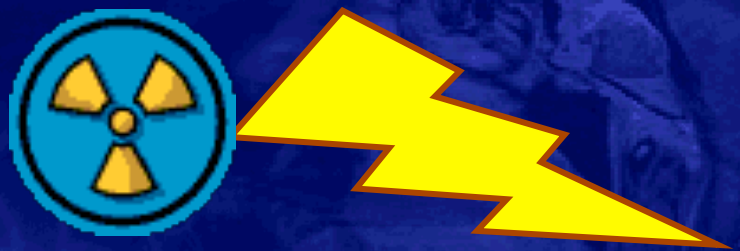
RT e CETUXIMAB: RAZIONALE

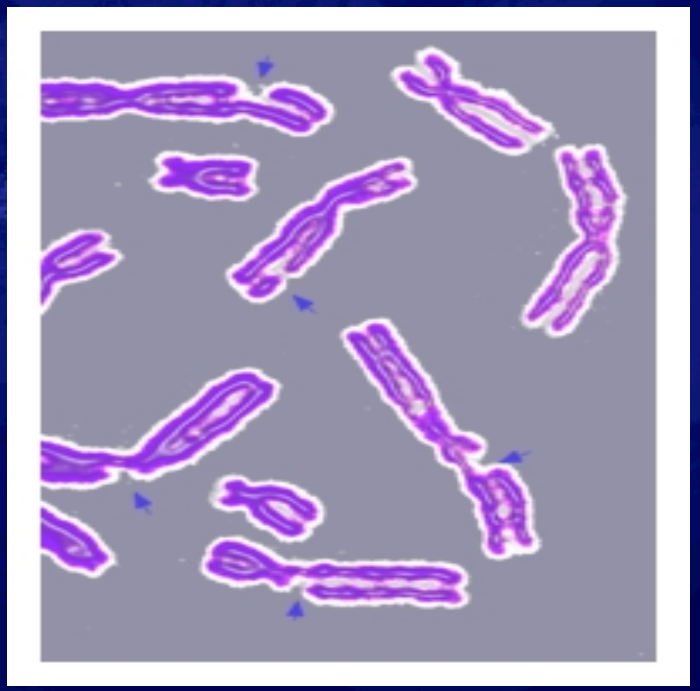


RT e CETUXIMAB: RAZIONALE

EFFETTO RADIOSENSIBILIZZANTE

Poiché il EGFR attivato favorisce la riparazione del danno radioindotto al DNA, il cetuximab inibendo tale effetto rende il tumore più radiosensibile.





RT e CETUXIMAB: STUDI CLINICI

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

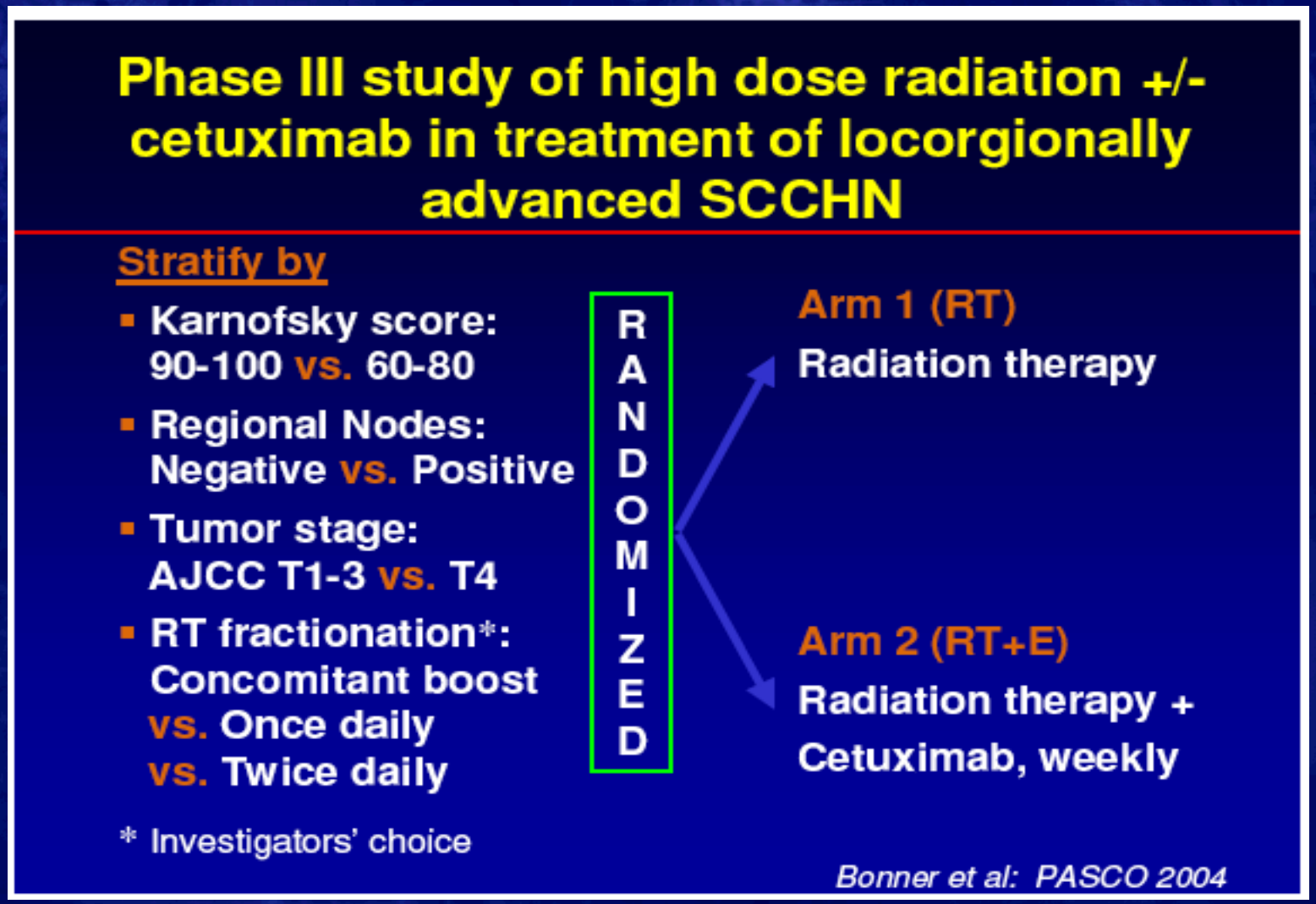
ABSTRACT

BACKGROUND

We conducted a multinational, randomized study to compare radiotherapy alone with radiotherapy plus cetuximab, a monoclonal antibody against the epidermal growth factor receptor, in the treatment of locoregionally advanced squamous-cell carcinoma of the head and neck.

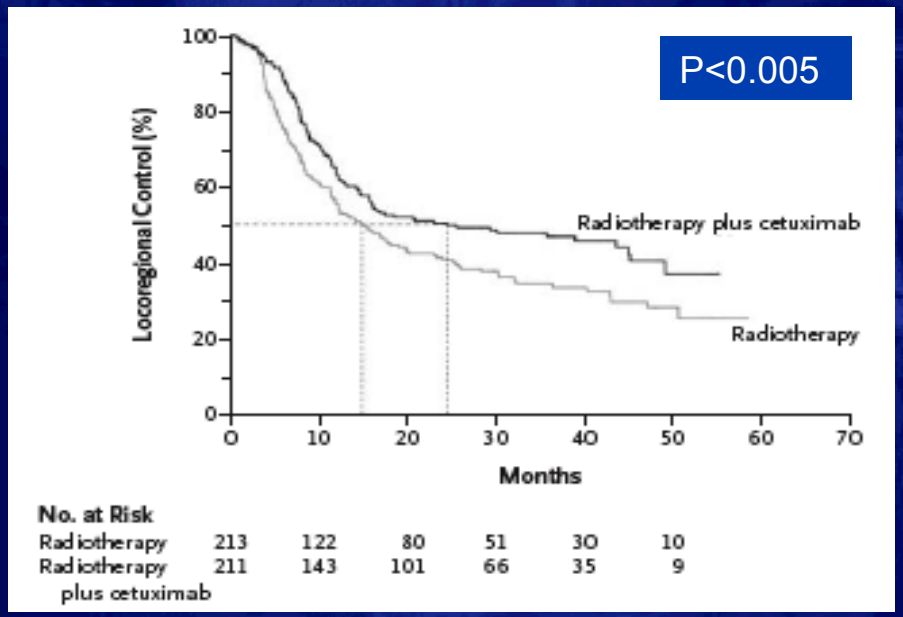
N Engl J Med 2006;354:567-78.

RT e CETUXIMAB: STUDICLINICI

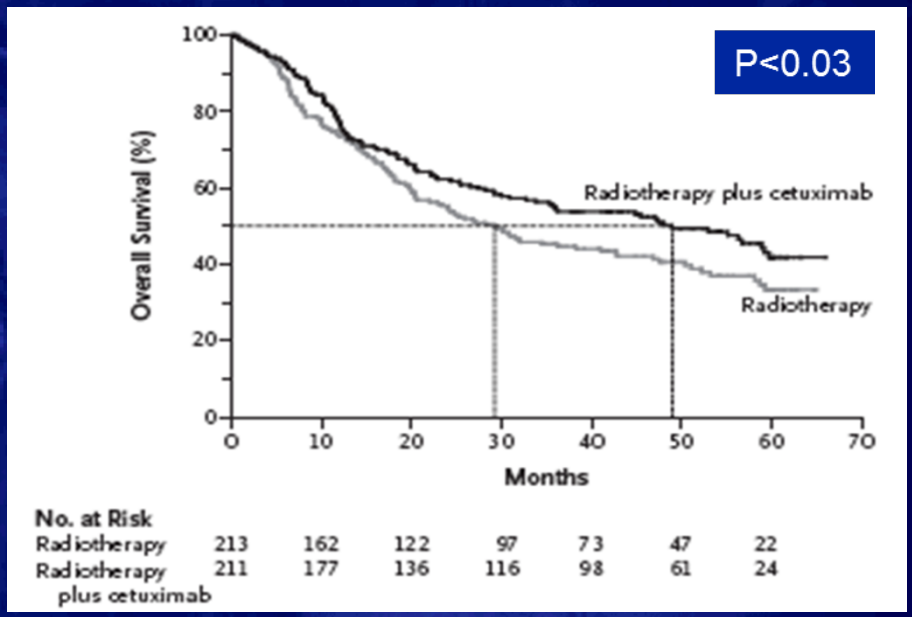


RT e CETUXIMAB: STUDI CLINICI

LOCOREGIONAL CONTROL



OVERALL SURVIVAL

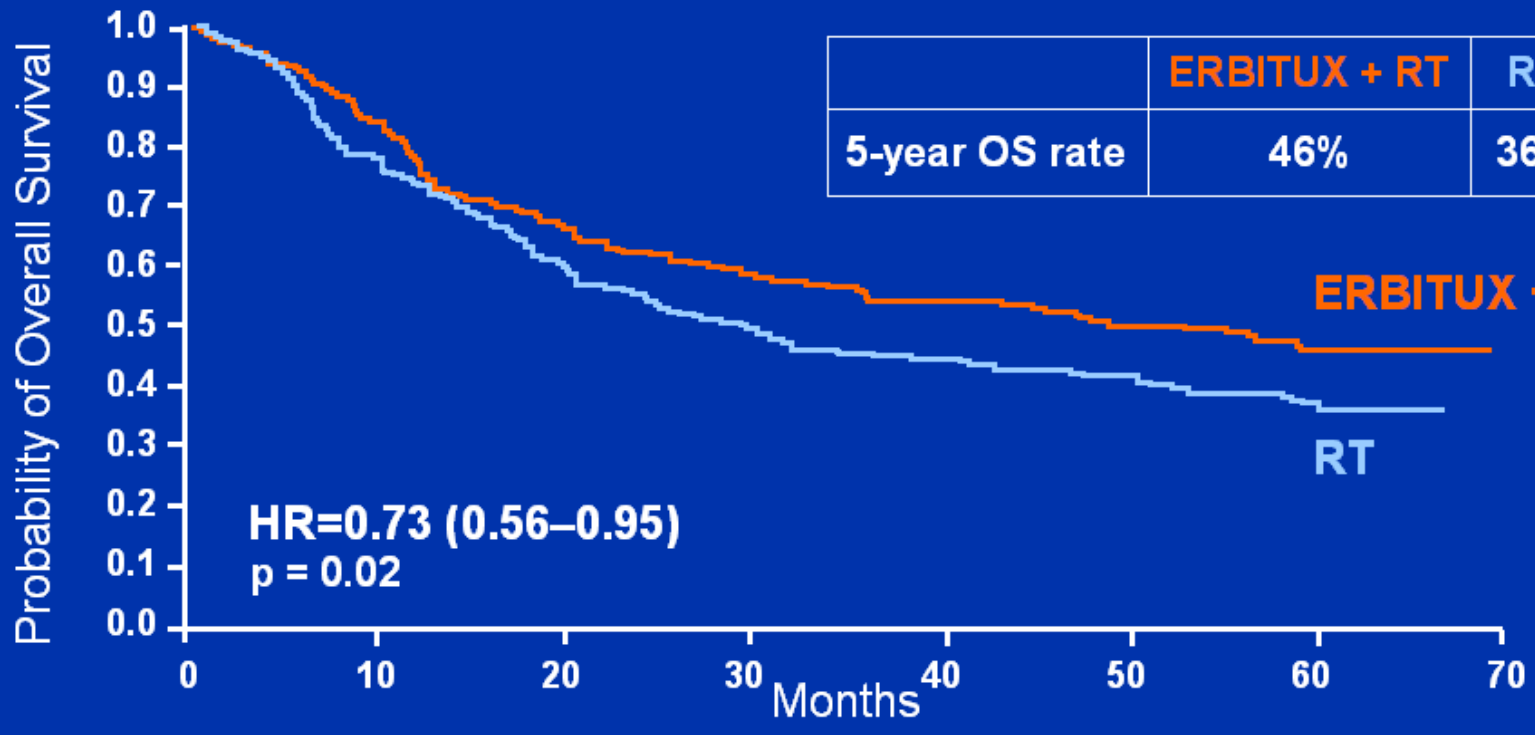


Bonner JA et al, N.Engl.J.Med. 2006;354:567-78

ERBITUX + RT: Overall survival 5 year update

ERBITUX + RT improves significantly long term survival, with nearly half of the patients alive at 5 years

	ERBITUX + RT	RT	p-value
5-year OS rate	46%	36%	0.02



Treatment	Total	Death	Alive	Median
Erbitux + RT	211	110	101	49.0
RT	213	130	83	29.3

Bonner J.A, et al. as presented ASTRO 2008

RT e CETUXIMAB: STUDI CLINICI

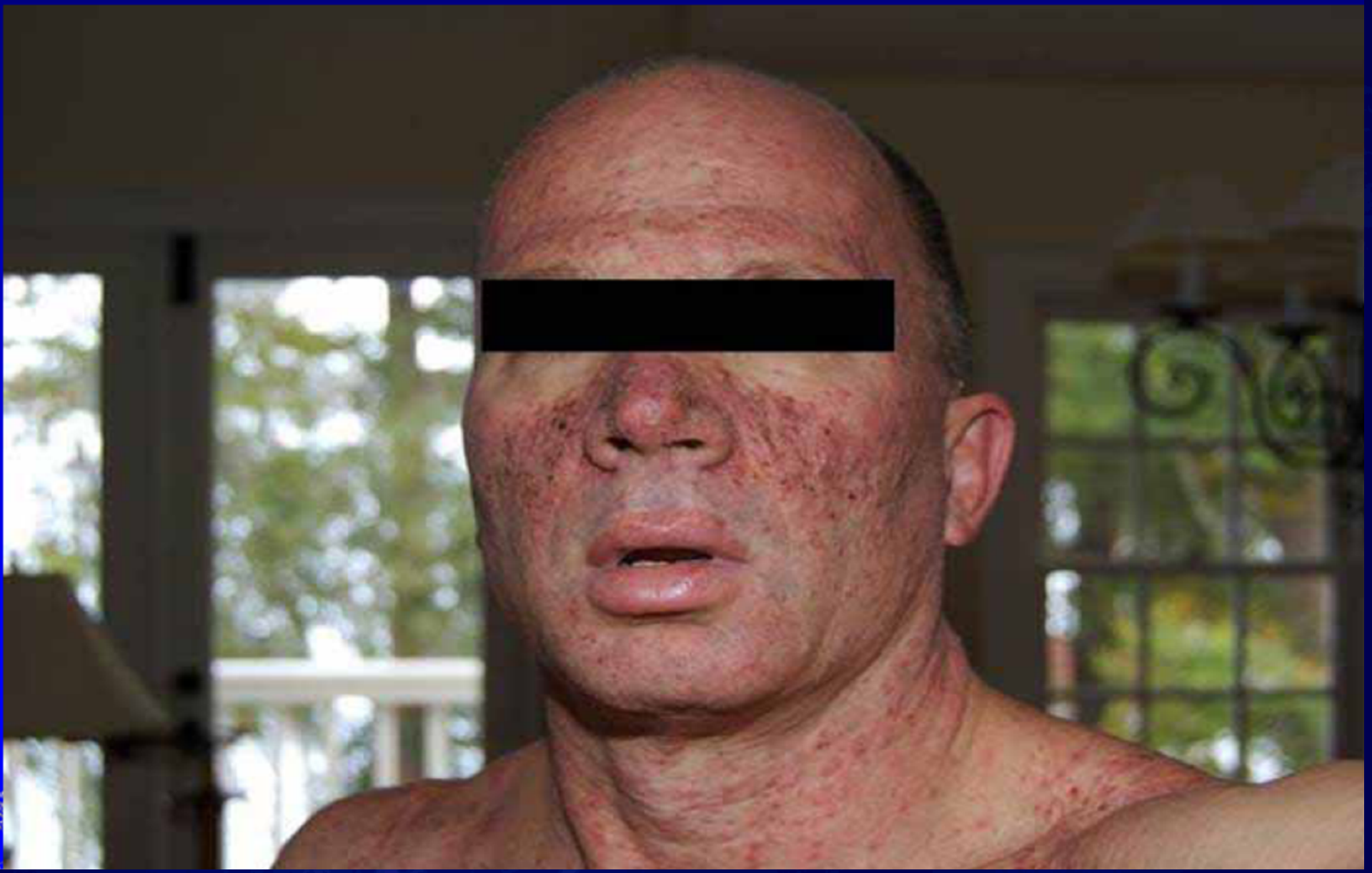
Relevant Grade 3–5 Side Effects

Side effect	RT (n=212)	ERBITUX + RT	p-value[a]
Mucositis/stomatitis	52%	56%	0.44
Dysphagia	30%	26%	0.45
Xerostomia	3%	5%	0.32
Fatigue/malaise	5%	4%	0.64
Acne-like rash	1%	17%**	<0.001
Infusion-related reactions[b]	0%	3%*	0.01

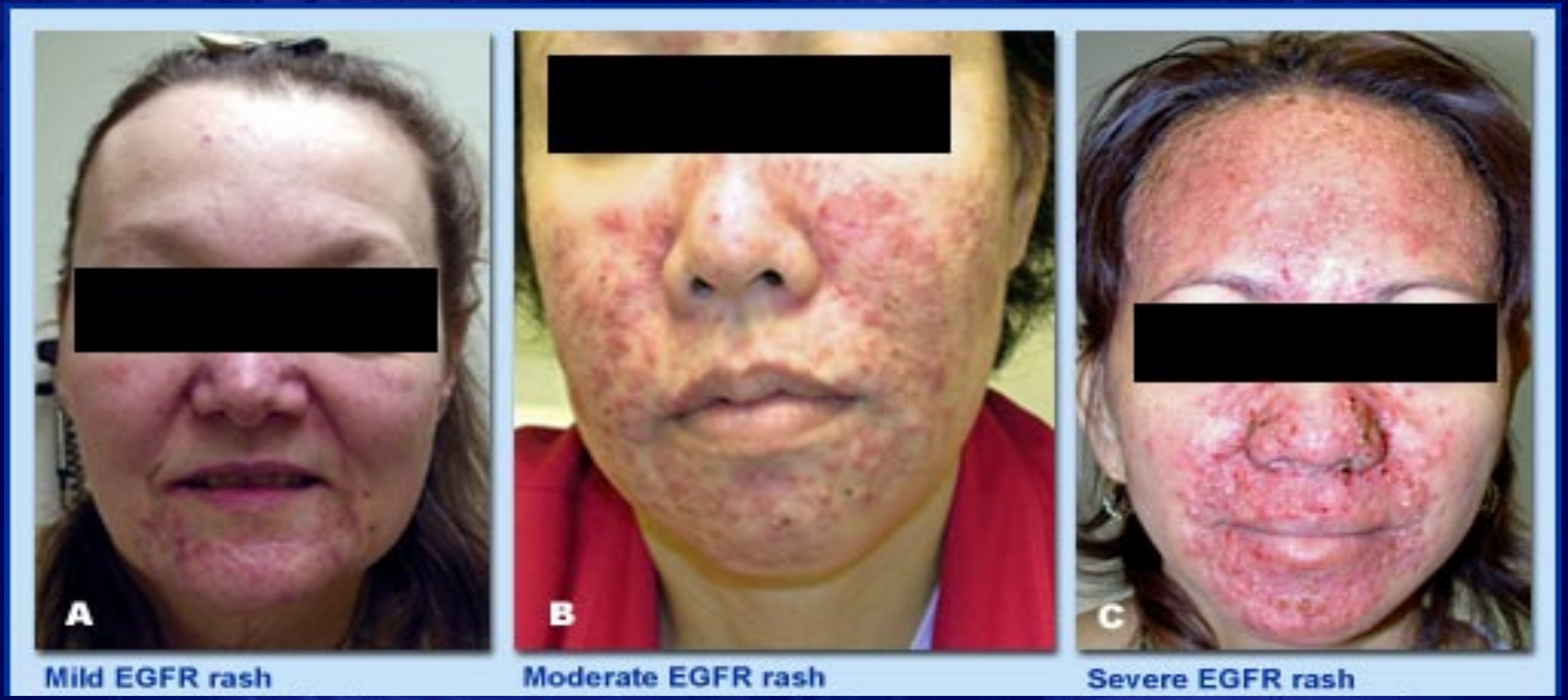
[a]Fisher's exact test
[b]Listed for its relationship to ERBITUX

Bonner J…Ang, K. N Engl J Med 2006;354:567–578

RASH ACNEIFORME



RASH ACNEIFORME

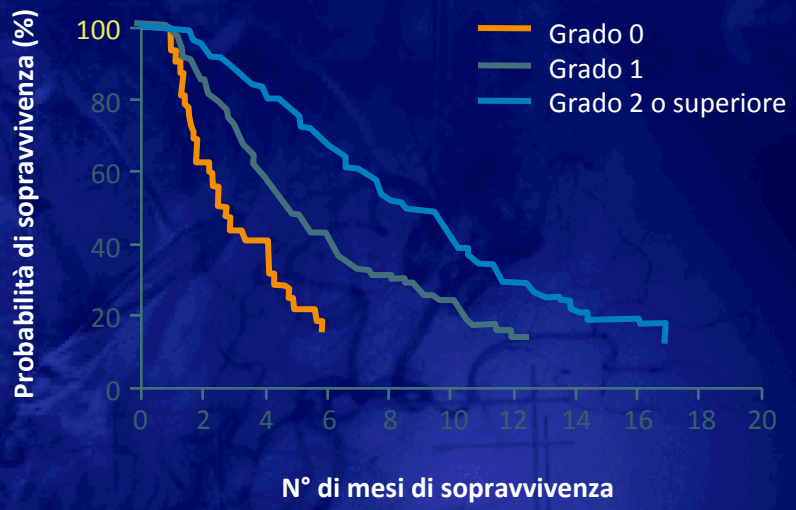


CORRELAZIONE TRA RASH CUTANEO E SOPRAVVIVENZA

Studio NCIC CTG CO.17

Cetuximab + BSC (N=287)		
Eruzione acneiforme	**N° pazienti**	**Sopravvivenza (mesi)**
Nessuna	32	2,6
Grado 1	115	4,8
Grado 2 o superiore	136	**8,4**

Eruzione acneiforme	**HR**	***p***
Grado 2 o superiore vs 0	0,33	<0,001
Grado 1 vs 0	0,61	<0,02
Grado 2 o superiore vs 1	0,54	<0,001



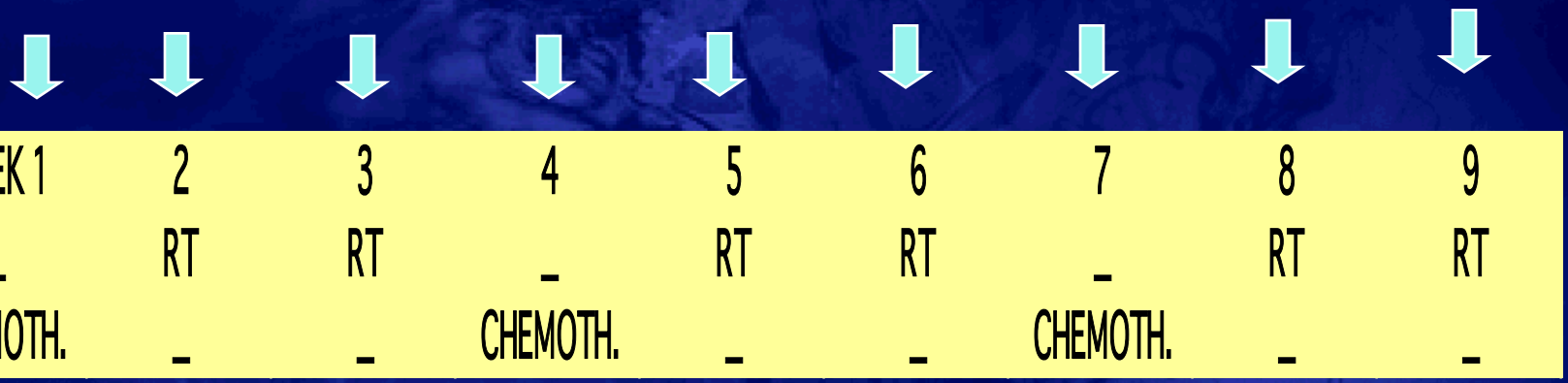
N° a rischio											
Grado 0	32	20	13	5	3	3	3	2	1	0	0
Grado 1	115	100	69	43	30	18	9	4	2	1	0
Grado 2 o superiore	136	128	110	89	55	40	25	14	10	3	1

Jonker et al. NEJM 2007;357:2040-2048

RT e CETUXIMAB: STUDI CLINICI

Studio AlteRCC
Alternating Radio-Chemotherapy plus Cetuximab

Istituto Nazionale per la Ricerca sul Cancro
Genova



RADIOTH. = 10 Gy/5 fractions/1 fraction per day

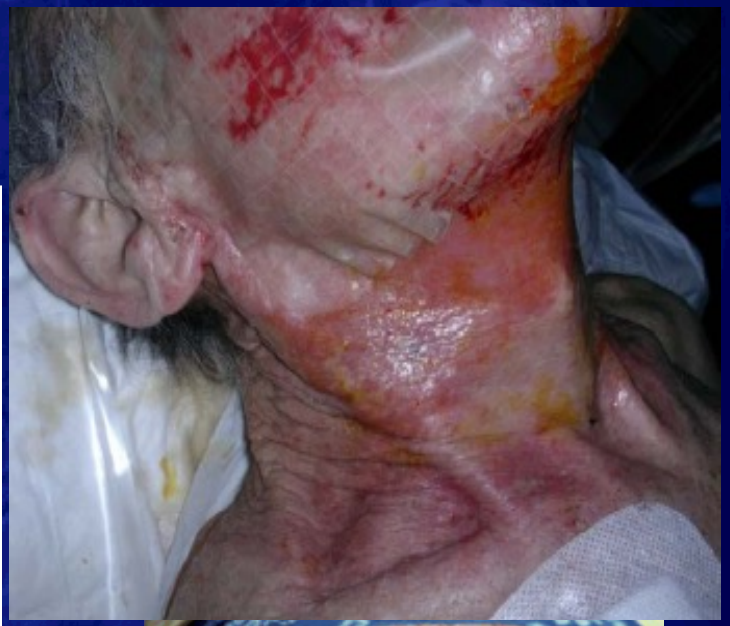
CHEMOTH. = Cis-Pt 20mg/m2/day per 5 days
5-Fu 200mg/m2/day per 5 days

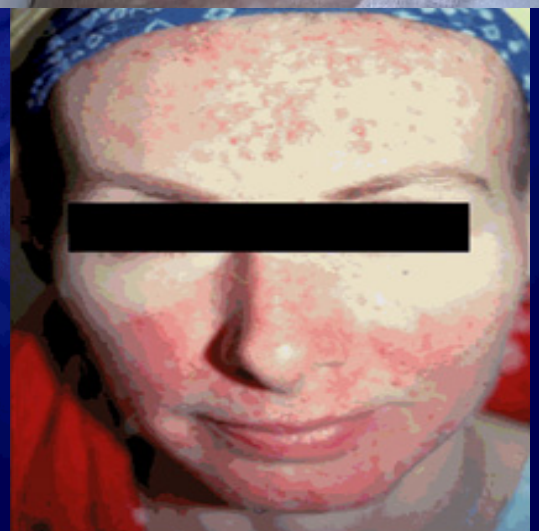
= C225

RT e CETUXIMAB: STUDI CLINICI

Tossicità'G3-G4 Studio AlteRCC

EFFETTI COLLATERALI	CETUXIMAB + RT
Mucosite/stomatite	60%
Diarrea	20%
Neutropenia febbrile	20%
Ipomagnesemia	10%
Dermatite desquamativa	90%
Decessi (IMA)	1 caso

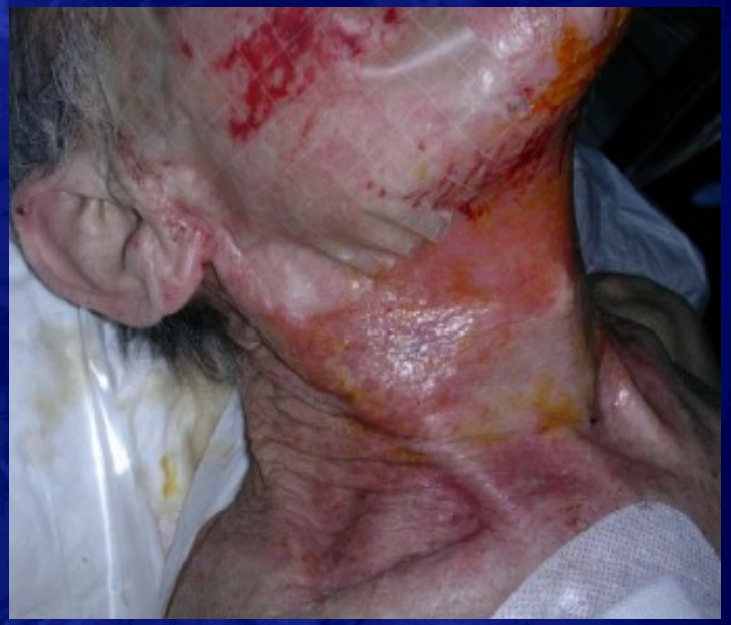


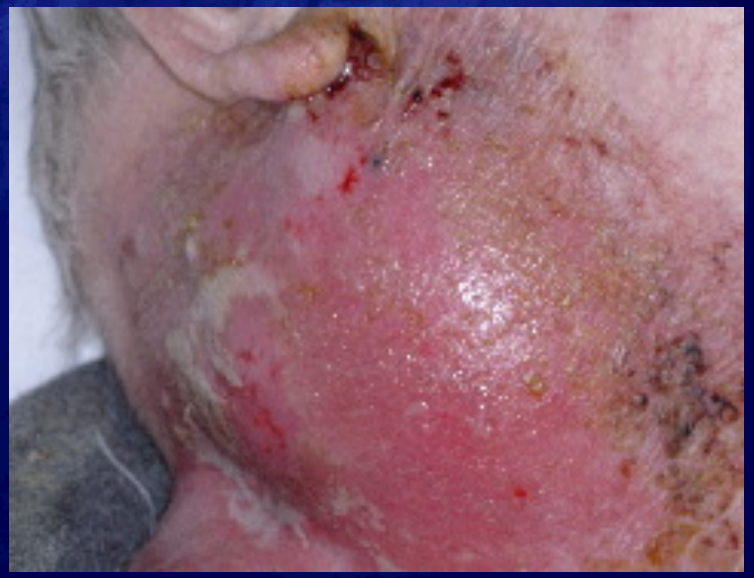


RT e CETUXIMAB: STUDI CLINICI

TOSSICITA' CUTANEA STUDIO AlteRCC

1. **Classificata "*epidermiolisi umida*" osservata esclusivamente sulla cute irradiata.**
2. **La tossicità sembra RT-dose-dipendente.**
3. **Mai comparsa prima di 45 Gy dose cumulativa.**





ERBITUX + RT: radiation dermatitis Pathophysiological differences

RT/CRT alone	ERT
Dry desquamation with clumps of exfoliated corneocytes	Marked xerosis
Moist desquamation with exposure of the inflamed dermis	Intense inflammatory response localized to the subepidermis
Skin necrosis or ulceration of the full-thickness dermis*	Obvious thinning of the epidermis
	Production of an inflammatory exudate that mixes with exfoliated corneocytes to form crusts
	Superficial ulcerations with crusty exudates
	Necrosis of the superficial dermis and epidermis

*Not reported in the acute phase with modern fractionated megavolt radiotherapy

Bernier et al. Ann Oncol 2011; May: epub ahead of print

CRT = chemoradiotherapy; ERT = ERBITUX + radiotherapy; RT = radiotherapy

ERBITUX + RT: radiation dermatitis
Clinical differences

RT/CRT alone	ERT
Onset: weeks 3+ to 5+ of treatment	Onset: weeks 1 or 2 of treatment
No crusting	Crusts can result in sustained microtrauma, bleeding and discomfort and can lead to infection

- **While ERT-associated reactions may appear more severe than the radiation dermatitis seen with RT/CRT:**
  - They resolve rapidly, patients recovering 1–2 weeks after the end of treatment, even when there is crusting
  - They generally do not leave scarring

Bernier et al. Ann Oncol 2011; May: epub ahead of print

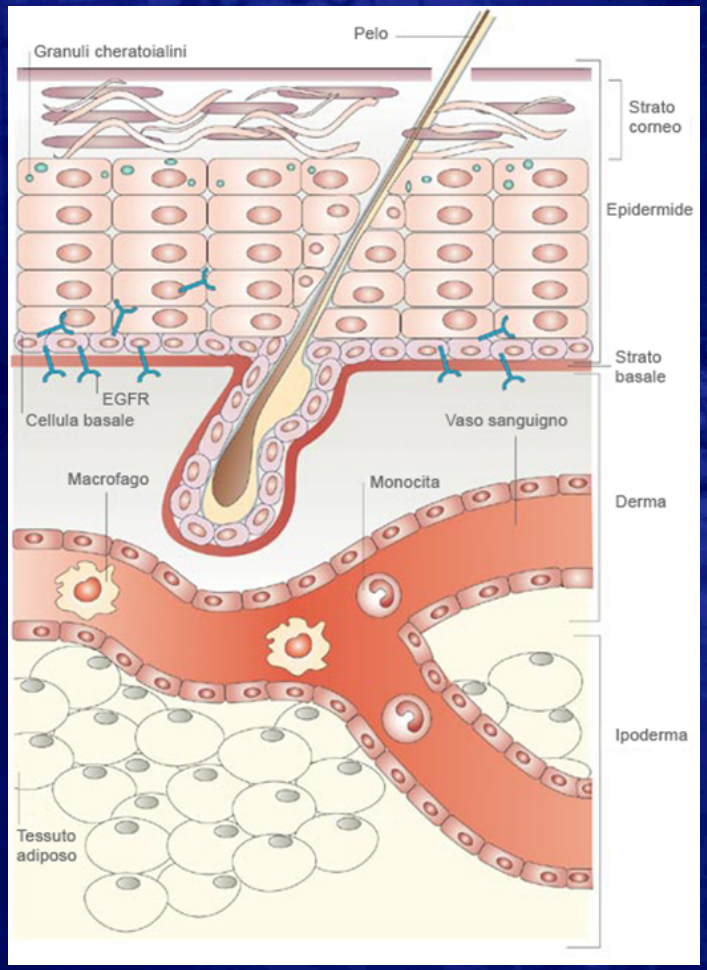
CRT = chemoradiotherapy; ERT = ERBITUX + radiotherapy; RT = radiotherapy

TIPOLOGIA DELLE LESIONI CUTANEE IN CORSO DI TRATTAMENTO CON CETUXIMB

Rash
Dermatite da radiazioni
Xerosi (fissurazioni, eczema)
Alterazioni ungueali
Alterazione dei peli

FISIOPATOLOGIA TOSSICITA' CUTANEA

ANATOMIA DELLA CUTE E FOLLICOLO PILIFERO

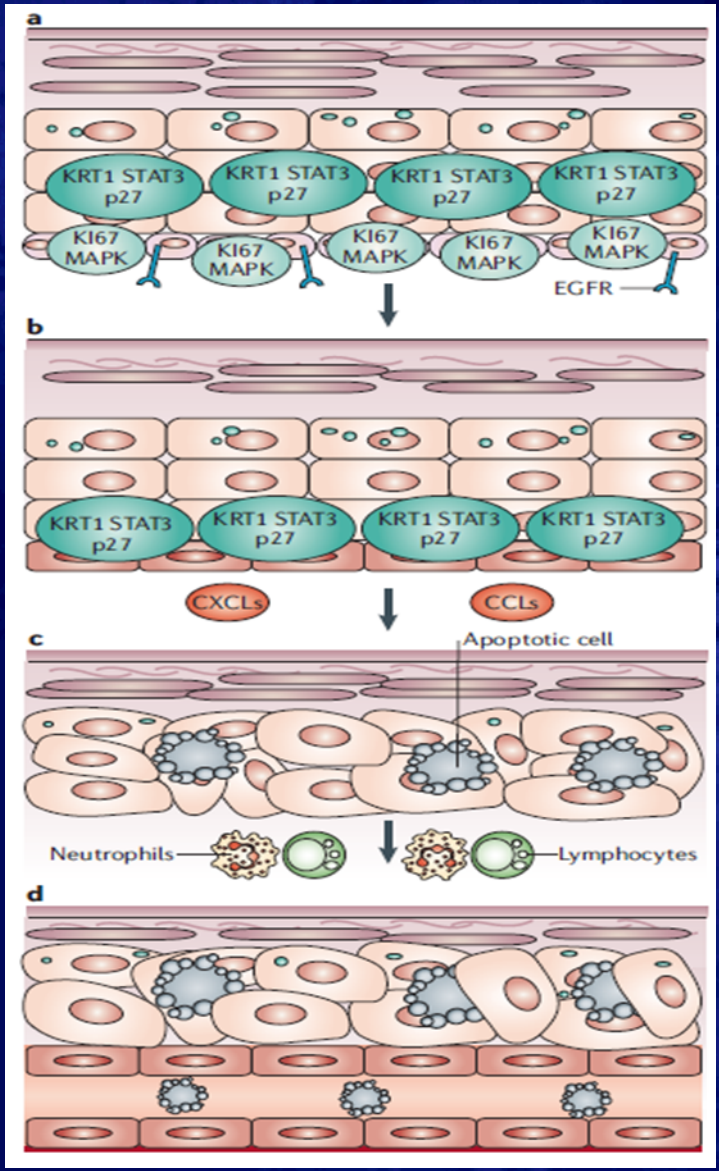


- L'epidermide è composto per il 90% da **cheratociti** che esprimono **EGFR (epidermal growth factor receptor)** in alta concentrazione negli strati basale e sovrabasale

- Lo strato basale ed il **follicolo pilifero** contengono stem-cells proliferanti che si differenziano in cheratociti e migrano in superficie formando lo strato corneo. Il **rivestimento del follicolo pilifero** è contiguo con lo strato basale, e ne condivide le proprietà biochimiche e l'alta espressione di EGFR

Lacouture, Nature Rewiews, 2006

EFFETTI CUTANEI DELL'INIBIZIONE DELL'EGFR

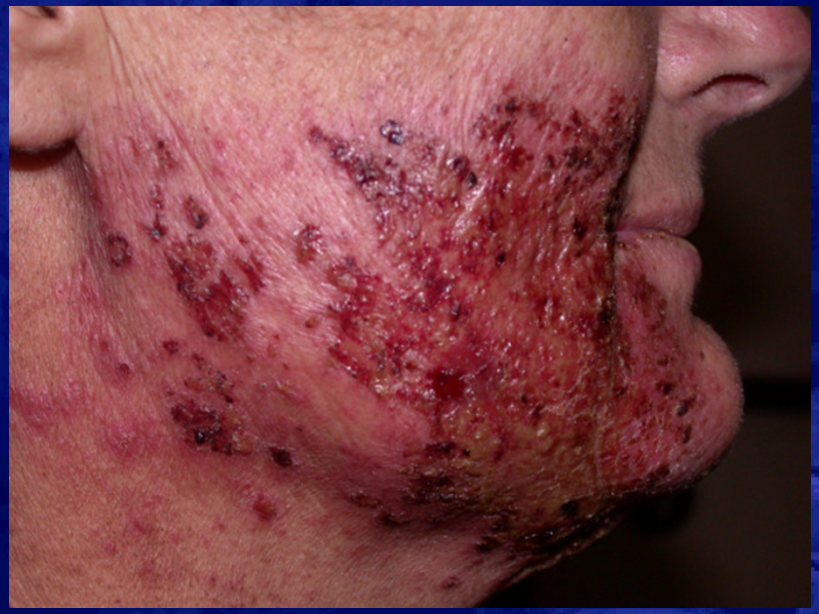


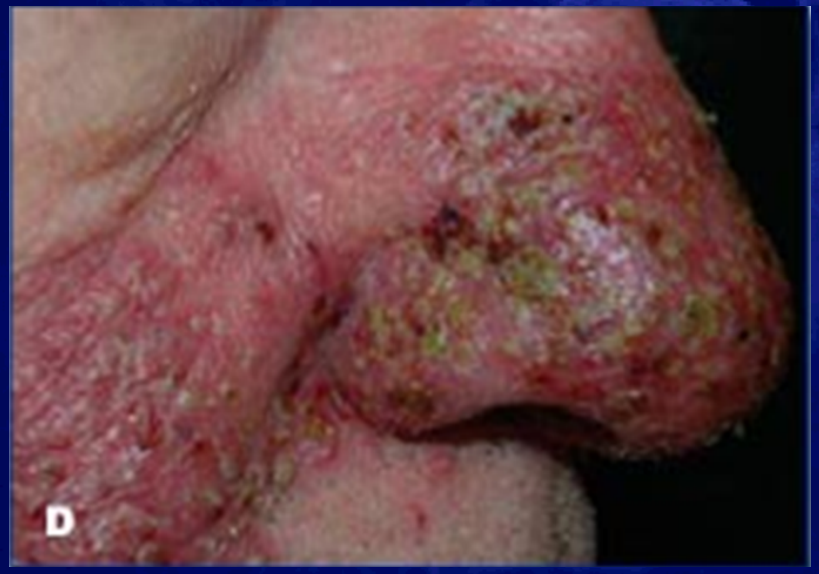
L'inibizione di EGFR nei cheratinociti basali induce:

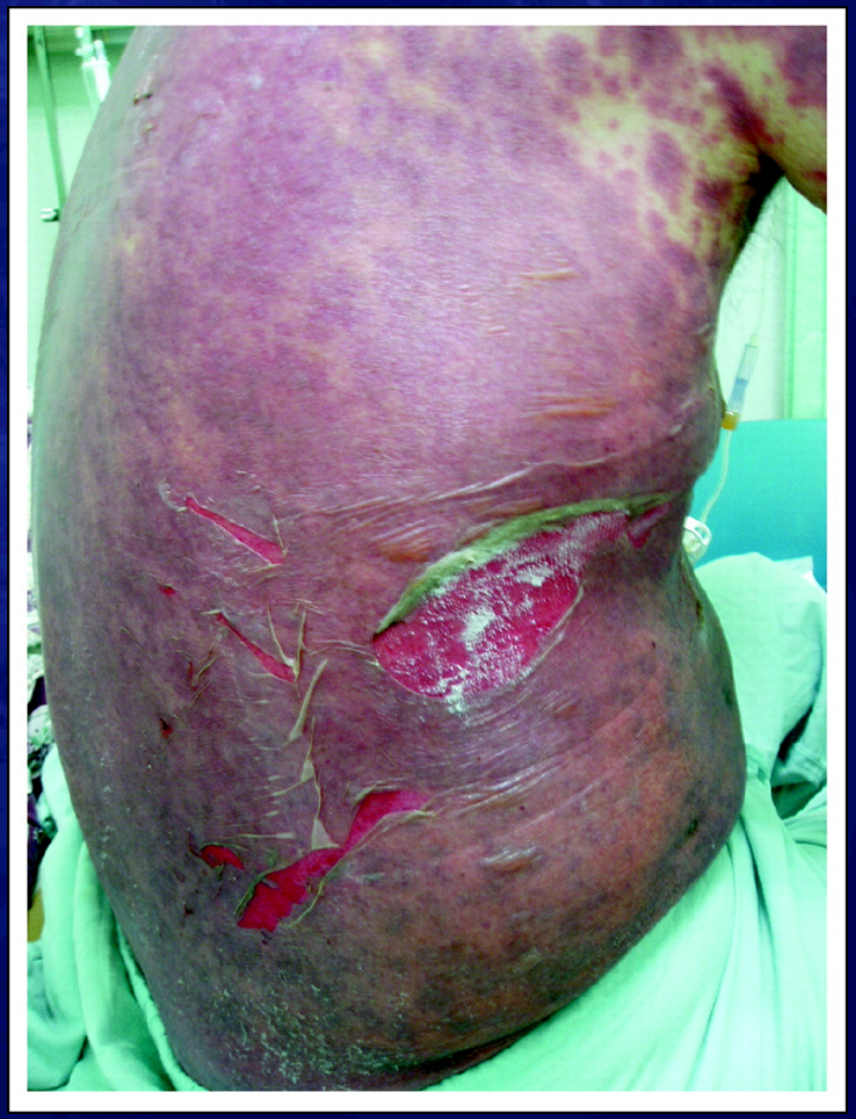
- arresto della crescita, della migrazione e induce apoptosi
- abnorme maturazione e prematura differenziazione
- rilascio di fattori chemotattici di cellule infiammatorie, produce il reclutamento dei leucociti che liberano enzimi, determinando danno cutaneo, con conseguente apoptosi dei cheratinociti e dilatazione dei vasi sanguigni
- riduzione dello spessore dell'epidermide con assottigliamento dello strato corneo

Eruzione papulo-pustolosa, xerosi, prurito, infiammazione periungueale e alterazione del pelo

ATTENZIONE ALLA TOSSICITA' CUTANEA







OXFORD JOURNALS

The Oncologist®

Symptom Management and Supportive Care

Management of Skin Toxicity Associated with Cetuximab Treatment in Combination with Chemotherapy or Radiotherapy

CARMINE PINTO,[a] CARLO ANTONIO BARONE,[b] GIAMPIERO GIROLOMONI,[c] ELVIO GRAZIOSO RUSSI,[d] MARCO CARLO MERLANO,[e] DARIS FERRARI,[f] EVARISTO MAIELLO[g]

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Key Words. Cetuximab • EGFR • Italian Expert Opinions • Skin rash • Skin toxicity

Disclosures: Carmine Pinto: None; **Carlo Antonio Barone:** *Consultant/advisory role*: Merck; **Giampiero Girolomoni:** None; **Elvio Grazioso Russi:** None; **Marco Carlo Merlano:** *Consultant/advisory role*: Merck; *Expert testimony*: Merck; **Daris Ferrari:** None; **Evaristo Maiello:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

RTOG TOXICITY SCALE

RTOG/EORTC Radiation Toxicity Grading

- RTOG Common Toxicity Criteria
  - **1995** - PMID 7713792 — "Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC)." Cox JD et al. Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1341-6.

ACUTE [edit]

For all: 0 - no symptoms, 5 - death directly related to radiation effects

RTOG ACUTE Radiation Morbidity

Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	Injection / may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Eye	Mild conjunctivitis w/ or w/o scleral injection / increased tearing	Moderate conjunctivitis w/ or w/o keratitis requiring steroids and/or antibiotics / dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis	Loss of vision (uni or bilateral)
Ear	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication / serous otitis media / hypoacusis on testing only	Severe external otitis with discharge or moist desquamation / symptomatic hypoacusis / tinnitus, not drug related	Deafness
Salivary gland	Mild mouth dryness / slightly thickened saliva / may have slightly altered taste such as metallic taste / these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness / thick, sticky saliva / markedly altered taste	(none)	Acute salivary gland necrosis
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	Mild or intermittent hoarseness / cough not requiring antitussive / erythema of mucosa	Persistent hoarseness but able to vocalize / referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic / cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic / confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

LATE [edit]

For all: 0 - no symptoms, 5 - death directly related to radiation effects

RTOG/EORTC LATE Radiation Morbidity

Tissue	Grade 1	2	3	4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Salivary glands	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Spinal cord	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia
Brain	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headache; severe CNS dysfunction (partial loss of power or dyskinesia)	Coma
Eye	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment	Panophthalmitis / blindness
Larynx	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Lung	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency / Continuous oxygen / assisted ventilation
Heart	Asymptomatic or mild symptoms; transient T wave inversion & ST changes; sinus tachy > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade / severe heart failure; severe constrictive pericarditis
Esophagus	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis / perforation fistula

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Publish Date: August 9, 2006

Quick Reference

The NCI Common Terminology Criteria for Adverse Events v3.0 is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each AE term is mapped to a MedDRA term and code. AEs are listed alphabetically within CATEGORIES.

Short AE Name

The 'SHORT NAME' column is new and it is used to simplify documentation of AE names on Case Report Forms.

Supra-ordinate Terms

A supra-ordinate term is located within a CATEGORY and is a grouping term based on disease process, signs, symptoms, or diagnosis. A supra-ordinate term is followed by the word *'Select'* and is accompanied by specific AEs that are all related to the supra-ordinate term. Supra-ordinate terms provide clustering and consistent representation of Grade for related AEs. Supra-ordinate terms are not AEs, are not mapped to a MedDRA term and code, cannot be graded and cannot be used for reporting.

REMARK

A 'REMARK' is a clarification of an AE.

ALSO CONSIDER

An 'ALSO CONSIDER' indicates additional AEs that are to be graded if they are clinically significant.

NAVIGATION NOTE

A 'NAVIGATION NOTE' indicates the location of an AE term within the CTCAE document. It lists signs/symptoms alphabetically and the CTCAE term will appear in the same CATEGORY unless the 'NAVIGATION NOTE' states differently.

Grades

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening or disabling AE
Grade 5	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

An 'Em dash' (—) indicates a grade not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

The DEATH CATEGORY is new. Only one Supra-ordinate term is listed in this CATEGORY: 'Death not associated with CTCAE term – *Select*' with 4 AE options: Death NOS; Disease progression NOS; Multi-organ failure; Sudden death.

Important:

- Grade 5 is the only appropriate Grade
- This AE is to be used in the situation where a death
  1. cannot be reported using a CTCAE v3.0 term associated with Grade 5, or
  2. cannot be reported within a CTCAE CATEGORY as 'Other (Specify)'

Contents

CLASSIFICAZIONE NCI-CTCAE 3.0: TOSSICITÀ DERMATOLOGICA

DERMATOLOGY/SKIN						Page 2 of 3
		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Nail changes	Nail changes	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nailbed(s)	Interfering with ADL	—	—
NAVIGATION NOTE: Petechiae is graded as Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) in the HEMORRHAGE/BLEEDING CATEGORY.						
Photosensitivity	Photosensitivity	Painless erythema	Painful erythema	Erythema with desquamation	Life-threatening; disabling	Death
Pruritus/itching	Pruritus	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	—	—
ALSO CONSIDER: Rash/desquamation.						
Rash/desquamation	Rash	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
REMARK: Rash/desquamation may be used for GVHD.						
Rash: acne/acneiform	Acne	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	—	Death
Rash: dermatitis associated with radiation – *Select*: – Chemoradiation – Radiation	Dermatitis – *Select*	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Erythema multiforme	—	Scattered, but not generalized eruption	Severe (e.g., generalized rash or painful stomatitis); IV fluids, tube feedings, or TPN indicated	Life-threatening; disabling	Death
Rash: hand-foot skin reaction	Hand-foot	Minimal skin changes or dermatitis (e.g., erythema) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema) or pain, not interfering with function	Ulcerative dermatitis or skin changes with pain interfering with function	—	—

CLASSIFICAZIONE NCI-CTCAE 3.0: TOSSICITÀ DERMATOLOGICA

	GRADO1	GRADO 2	GRADO 3	GRADO 4	GRADO 5
SECCHEZZA CUTANEA	Asintomatica	Sintomatica, non interferisce con ADL	Interferisce con ADL	-	-
MODIFICAZIONI UNGUEALI	Alterazioni del colore, coilonichia, infossamento	Parziale o completa perdita di unghie; dolore nel letto ungueale	Interferisce con ADL	-	-
PRURITO	Lieve o localizzato	Intenso o diffuso	Intenso o diffuso e Interferisce con ADL	-	-
RASH/ DESQUAMAZIONE	Eruzione maculare o papulare o eritema senza sintomi associati	Eruzione maculare o papulare o eritema con prurito o altri sintomi associati; desquamazione localizzata o altre lesioni che interessano <50% della superficie corporea	Grave, eritrodermia generalizzata o eruzione maculare, papulare o vescicolare; desquamazione che interessa ≥50% della superficie corporea	Generalizzata, esfoliativa, ulcerativa o dermatite bollosa	Morte

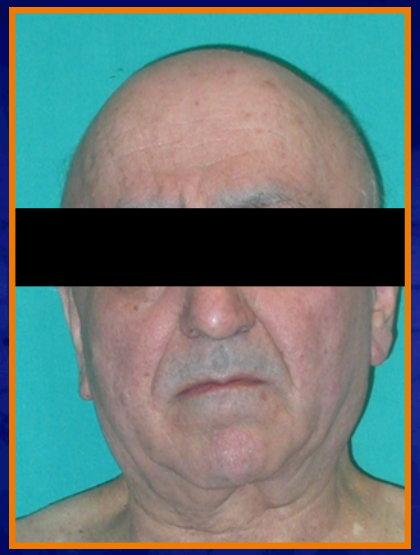
CLASSIFICAZIONE NCI-CTCAE 4.0: TOSSICITÀ DERMATOLOGICA

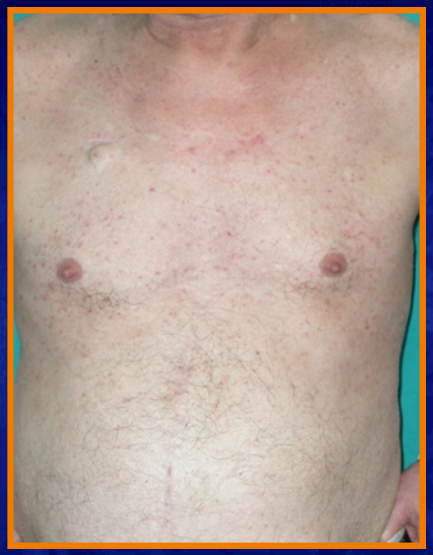
La classificazione NCI-CTCAE- 2009 vs 4 è la più completa con 34 eventi avversi contro 27, comprende le manifestazioni cutanee tipiche degli anti-EGFR ed è più accurata per quanto riguarda la superficie corporea interessata

Disordini dell'epidermide e del tessuto sottocutaneo					
	GRADO				
EVENTO AVVERSO	1	2	3	4	5
RASH ACNEIFORME	Papule e/o pustole **estese per <10% della BSA**, che possono essere o meno associate a sintomi di prurito o dolore	Papule e/o pustole **estese per il 10-30% della BSA**, che possono essere o meno associate a sintomi di prurito o dolore, associate a impatto psicosociale, limitando l'AD L strumentale ***ADL:** Activities Daily Living	Papule e/o pustole **estese per >30% della BSA**, che possono essere o meno associate a sintomi di prurito o dolore, limitando la cura personale nell'ADL; associata a sovra infezione locale con l'indicazione di antibiotici orali	Papule e/o pustole estese per qualunque % della BSA, che possono essere o meno associate a sintomi di prurito o dolore, limitando l'ADL; associata a estesa sovra infezione con l'indicazione di antibiotici e.v; conseguenze sulla mortalità	Decesso

TRATTAMENTO DELLE LESIONI CUTANEE DA RT + CETUXIMB

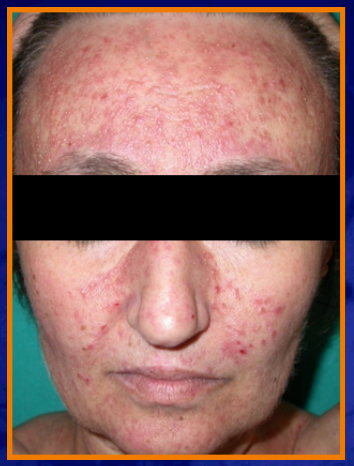
Rash
Xerosi (fissurazioni, eczema)
Alterazioni ungueali
Alterazione dei peli
Dermatite da radiazioni

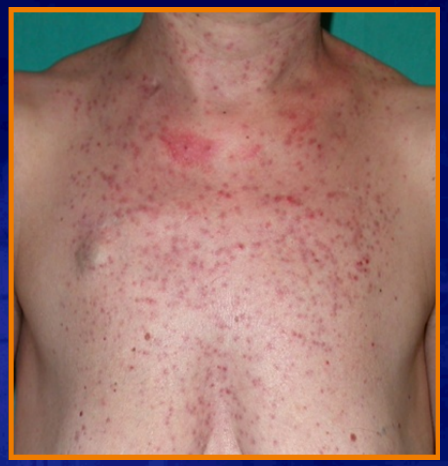




TRATTAMENTO DEL RASH CUTANEO DI GRADO 1

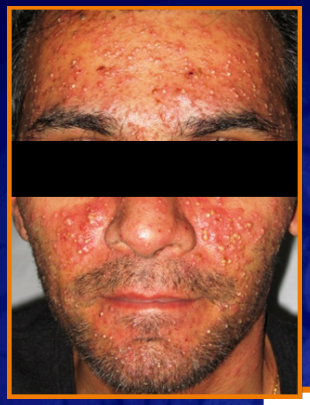
Lesioni cutanee e sintomi	Eruzione di papule minima senza sintomi
Indicazioni	Non sono necessari provvedimenti terapeutici

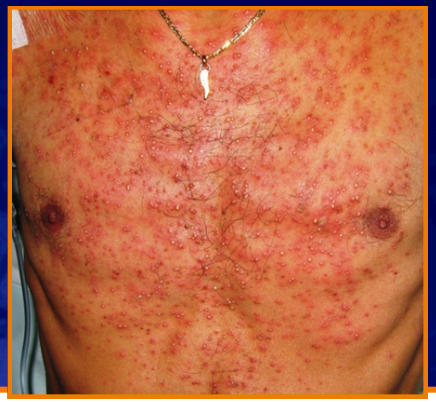




TRATTAMENTO DEL RASH CUTANEO DI GRADO 2

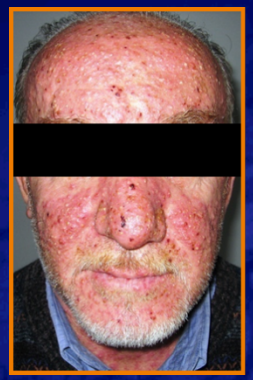
Lesioni cutanee e sintomi	Eruzione di papule (Grado 2A) o di pustole (Grado 2B) che interessano <30% della superficie corporea; sintomi moderati che non interferiscono con le attività quotidiane della vita
Modifiche dose cetuximab	No
Trattamento topico	Antibiotici: clindamicina 1% gel*;* eritromicina 3% gel/crema*;* metronidazolo 0,75-1% crema/gel 2 volte al giorno fino a regressione a grado 1 (evitare prodotti a base di benzoilperossido) *Manifestazioni del cuoio capelluto:* eritromicina 2% lozione
Trattamento sistemico	*Nelle forme a prevalenza di papule (Grado 2A):* nessuno ***Nelle forme a prevalenza di pustole (Grado 2B). Antibiotici:*** minociclina 100 mg 1 volta al giorno os*;* doxiciclina 100 mg 1 volta al giorno os per un minimo di 4 settimane e proseguendo fino a quando il rash rimane sintomatico

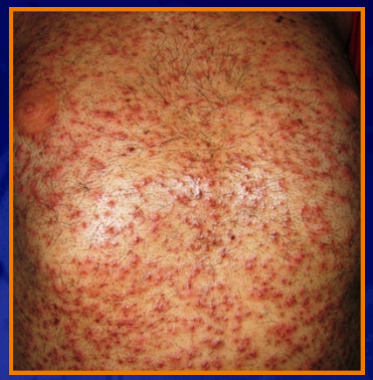




TRATTAMENTO DEL RASH CUTANEO DI GRADO 3

Lesioni cutanee e sintomi	Eruzione di papule (Grado 3A) o di pustole (Grado 3B) che interessano >30% della superficie corporea; segni di infezione e presenza di sintomi severi che interferiscono con le attività quotidiane della vita
Modifiche dose cetuximab	**Interrompere per un periodo ≤21 giorni fino a regressione a grado ≤2 Se non c'è regressione a grado ≤2 dopo 21 giorni Interrompere definitivamente**
Trattamento topico	**Antibiotici:** clindamicina 1% gel; eritromicina 3% gel/crema; metronidazolo 0,75-1% crema/gel 2 volte al giorno fino a regressione a grado 1 (evitare prodotti a base di benzoilperossido) ***Manifestazioni del cuoio capelluto*:** eritromicina 2% lozione
Trattamento sistemico Paziente fortemente sintomatico/ non responsivo	**Retinoidi os:** isotretinoine *0,3-0,5 mg/Kg* **Corticosteroidi ev:** metilprednisolone; dexametasone **Antistaminici im/ev:** clorfenamina **Antibiotici ev:** amoxicillina/acido clavulanico; gentamicina **Idratazione ev può essere considerata**





TRATTAMENTO DEL RASH CUTANEO DI GRADO 4

Lesioni cutanee e sintomi	Rash generalizzato; sintomi gravi che richiedono un trattamento urgente
Modifiche dose cetuximab	Interrompere immediatamente e definitivamente

Trattamento topico e sistemico come per il grado 3

+ ev. OSPEDALIZZAZIONE

NUOVE EVIDENZE - VITAMINA K

Riattivazione del recettore EGF

L'applicazione topica di Vitamina K (K1 e K3), sulla cute del topo trattato con cetuximab, inverte l'inibizione della fosforilazione dell'EGFR e delle molecole del segnale a cascata

NUOVE EVIDENZE - VITAMINA K

Dati clinici
L'applicazione topica di Vitamina K1 può prevenire e ridurre la tossicità cutanea indotta dagli inibitori anti-EGFR

L'applicazione topica 2 volte al dì della Vitamina K1 riduce gradualmente l'intensità del grado del rash cutaneo

L'applicazione della Vitamina K1 non induce alcun tipo di tossicità

Il trattamento con cetuximab può continuare per tutto il periodo di utilizzo della Vitamina K1

Topical application of vitamin K1 (RECONVAL®K1) cream for cetuximab-related skin toxicities

J Ocvirk, M Rebersek
Institute of Oncology Ljubljana, Slovenia

Ocvirk Abs. 15087 - ASCO 2009
*Ocvirk et al. Abstr. 20750 ASCO 2008

79 pazienti con mCRC, pretrattati, ricevono cetuximab + CT

La comparsa del rash cutaneo (NCI CTCAE v.3) è stata gestita con :

**Applicazioni topiche 2 volte al dì
di una crema contenente
UREA e VITAMINA K1 (0,1%)**

Dei 20 pazienti con rash G3, 12 pts ricevono anche clindamicina topica

I pazienti sono stati monitorati settimanalmente per almeno 12 settimane

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L'applicazione della crema è associata a graduale riduzione della tossicità cutanea. Tempo mediano di miglioramento: 1,2 settimane nel caso di reazioni i tutti i gradi
Tempo mediano di miglioramento di 2,3 settimane per ottenere una regressione del rash di almeno 1 grado
L'applicazione di Vitamina K1 non ha indotto alcun tipo di tossicità

Lo studio dimostra che l'applicazione topica della Vitamina K1 è un'efficace trattamento per gestire il rash indotto da cetuximab

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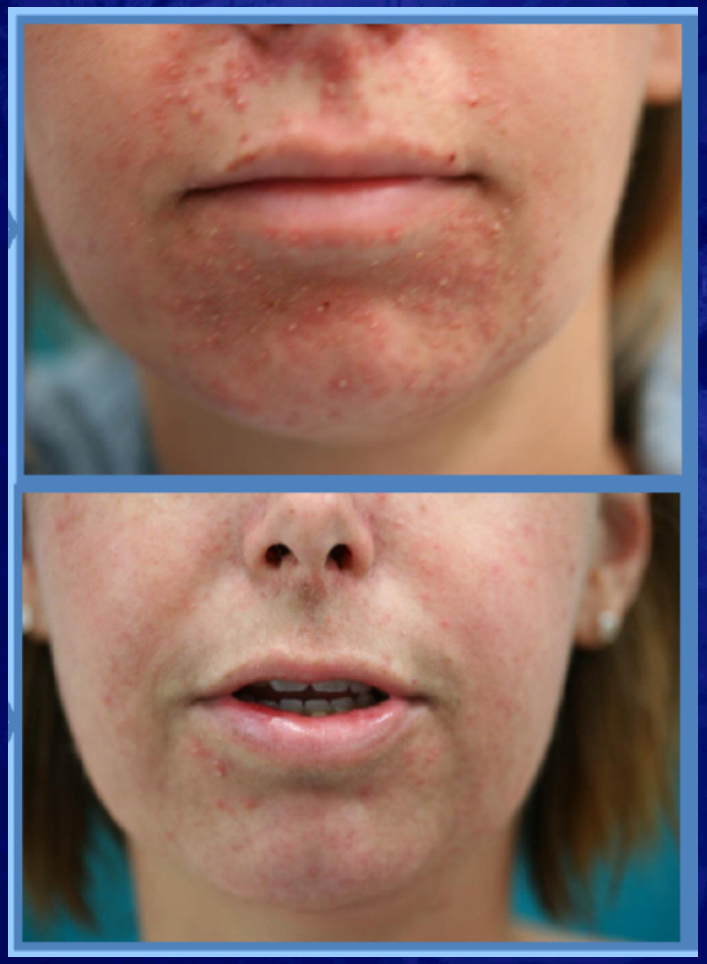

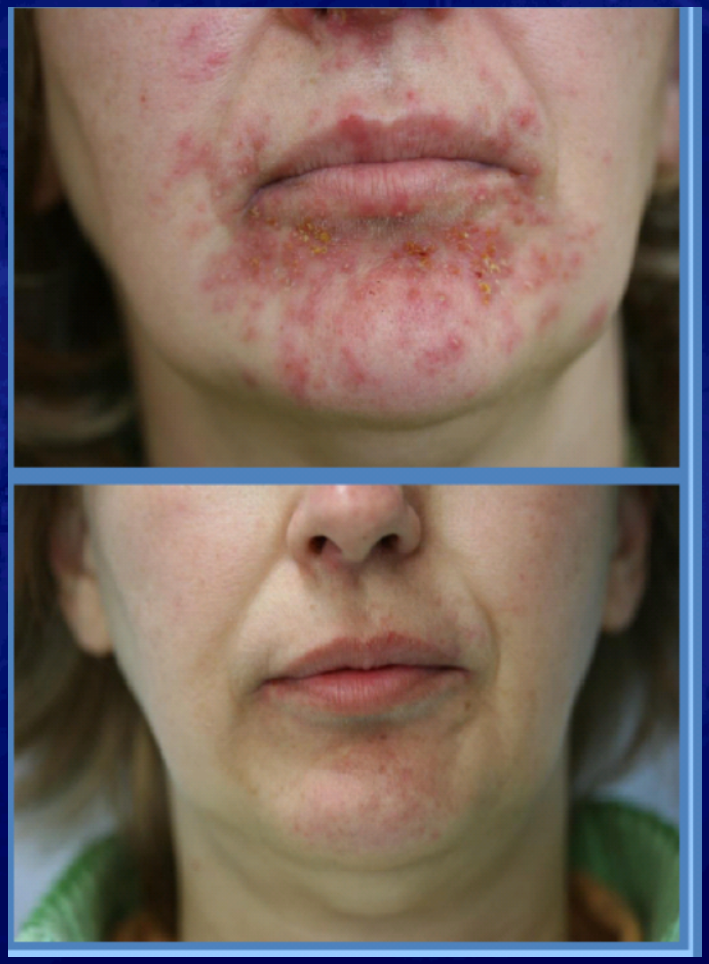

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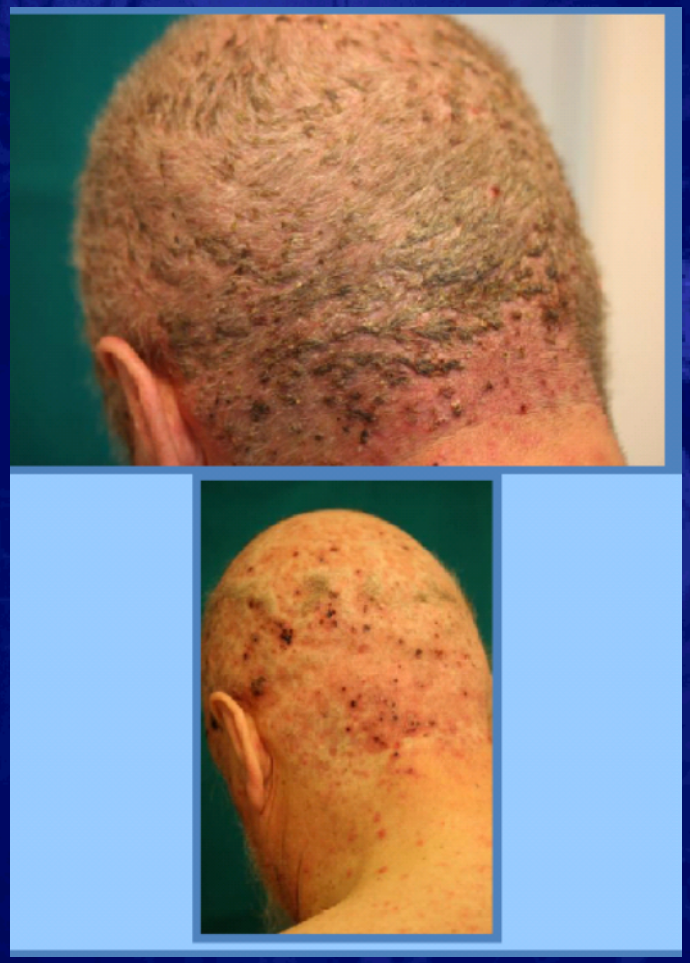
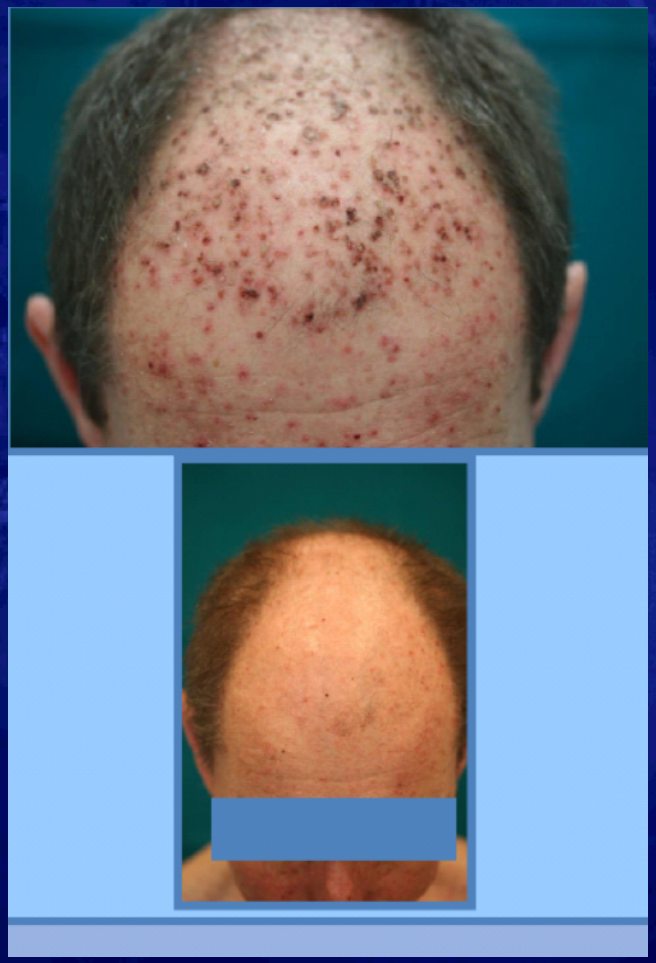
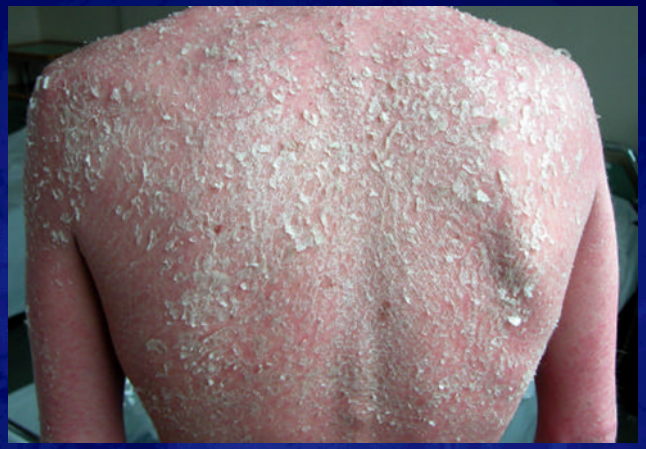






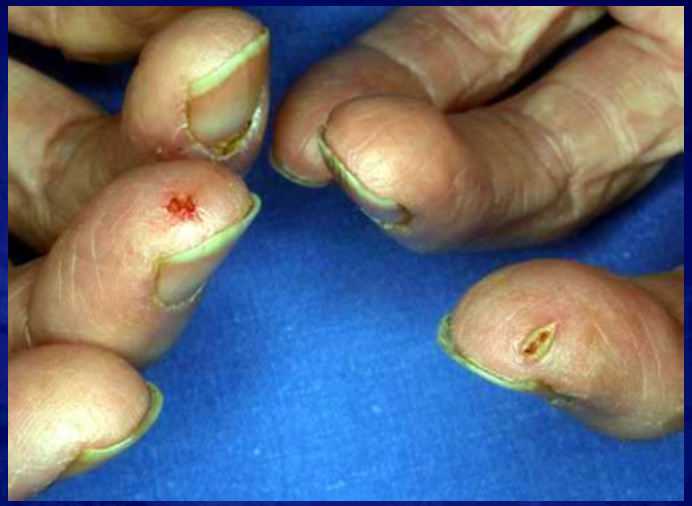
XEROSI

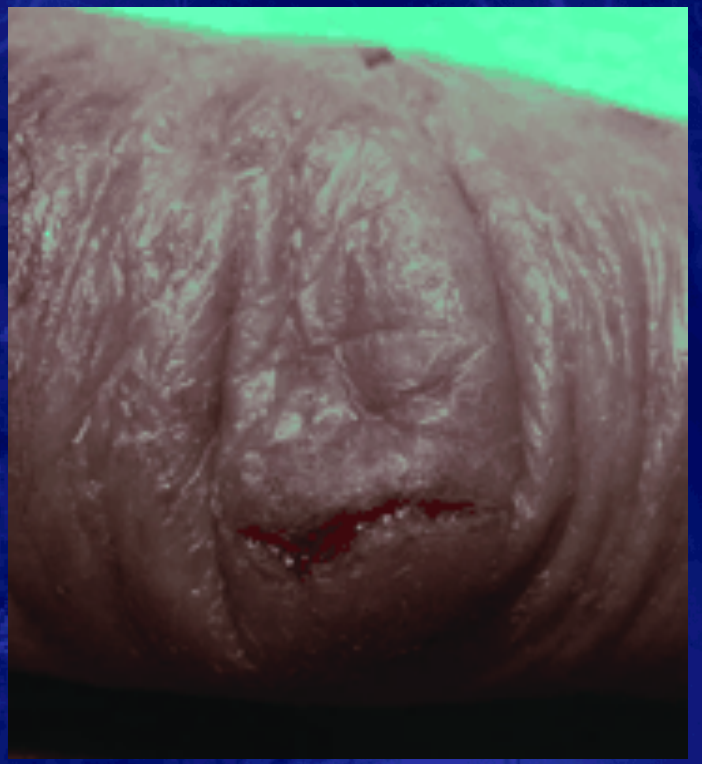
	Grado1	Grado 2	Grado 3	Grado 4	Grado 5
Secchezza cutanea	Asintomatica	Sintomatica, non interferisce con ADL	Interferisce con ADLADL= Activies of daily living	-	-

(ADL= Activties of daily living)

Frequenza/ Tempo di insorgenza	Caratteristiche patologiche	Effetti associati
• 35% dei pazienti • La xerosi compare dopo alcune settimane di trattamento*	• Secchezza e desquamazione → può evolvere in eczema cronico secco (specialmente nelle aree con eruzione papulo-pustolosa)	• Secchezza delle mucose (vagina,perineo) • Fissurazioni delle dita di mani e piedi associate a dolore

FISSURAZIONI





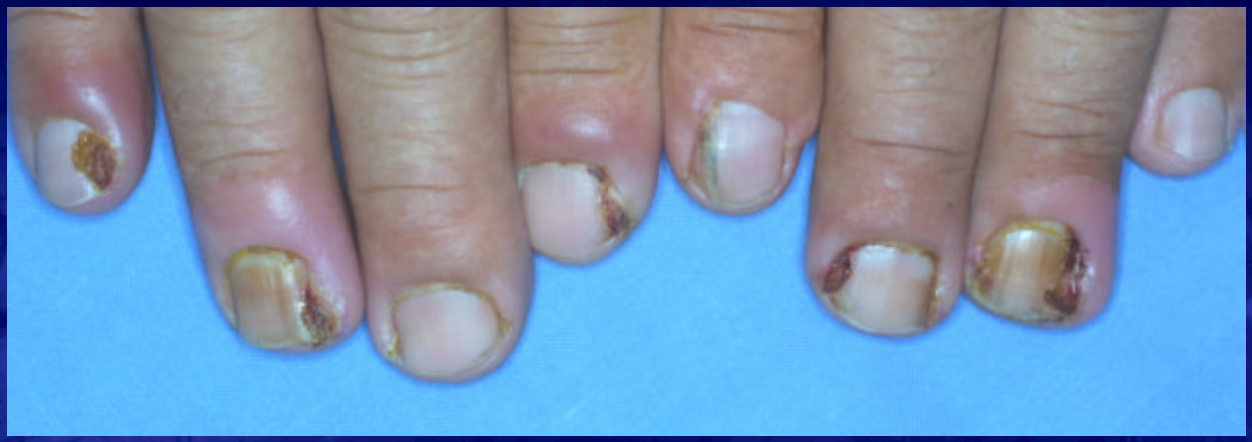
Come conseguenza della xerosi dopo circa 20 giorni da inizio terapia

TRATTAMENTO DI XEROSI, FISSURAZIONI ED ECZEMA

Misure educazionali e preventive generali
Pomate emollienti
Olio di mandorle, preparati a base di polietilenglicoli (PEG)
Corticosteroidi di media potenza per uso topico per brevi periodi (1-2 settimane) per l'eczema

- Betametasone dipropionato 0,05%, 0,1% crema
- Clobetasone 0,05% crema
- Fluocinolone acetonide pomata
- Idrocortisone butirrato 0,1% crema

Medicazione semplice o occlusiva nel caso di interessamento delle estremità
Antibioticoterapia per via topica per le sovrainfezioni
Acido fusidico 2% crema
Bacitracina crema
Mupirocina 2% crema



ALTERAZIONI UNGUEALI

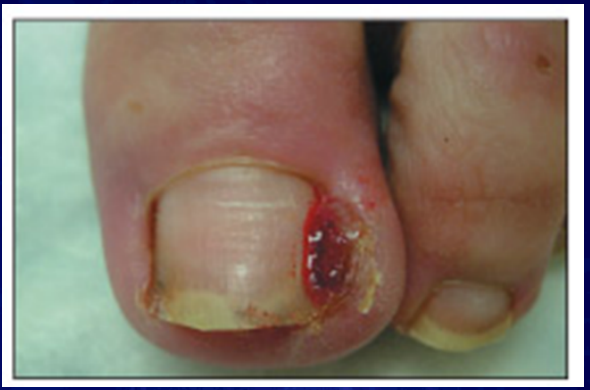
	Grado1	Grado 2	Grado 3	Grado 4	Grado 5
Modificazioni ungueali	**Alterazioni del colore, coilonichia, infossamento**	**Parziale o completa perdita di unghie; dolore**	**Interferisce con ADL**	**-**	**-**

- 10-20% dei pazienti
- Si riscontra, di solito, in pazienti che ricevono un trattamento per un periodo >2 mesi°
- Le alterazioni ungueali possono persistere per lungo tempo dopo l'interruzione del trattamento con un anti-EGFR

- Paronichia (che interessa soprattutto le dita dei piedi), può evolvere in granuloma piogenico*
- Causata principalmente dall'infiammazione*

- Onicolisi, pitting o scolorimento
- Colture batteriche negative ma più comune l'infezione secondaria

TRATTAMENTO DELLA PARONICHIA



Misure generali preventive (evitare scarpe strette)

Lavaggi con antisettici :

- soluzione di acido borico al 3%

Creme contenenti corticosteroidi e antisettici

- Betametasone 0,05% + cliochinol 3% crema
- Betametasone 0,1% + gentamicina 0,1% crema
- Betametasone valerato 0,1% + acido fusidico 2% crema
- Triamcinolone acetonide 3% + clortetraciclina 0,1% pomata
- Triamcinolone benetonide 2% + acido fusidico 0,03% crema

Antibioticoterapia os per sovrainfezione

- Amoxicillina/Acido Clavulanico
- Cefalexina capsule
- Clindamicina capsule

Anti-infiammatori non steroidei (FANS) per os per il dolore

RIASSUMENDO

L'IMPIEGO DEL CETUXIMAB IN ASSOCIAZIONE ALLA RT NEI TUMORI DEL CAPO COLLO RICHIEDE:

- MAGGIOR ATTENZIONE ALL'IGIENE DELLA CUTE
- PREVENZIONE INFEZIONE
- MAGGIORE ATTENZIONE ALLA TERAPIA DELLE ALTERAZIONI CUTANEE E AL RISCHIO DI INFEZIONI
- MAGGIOR COLLABORAZIONE TRA SPECIALISTI
- CONTROLLO DEL DOLORE

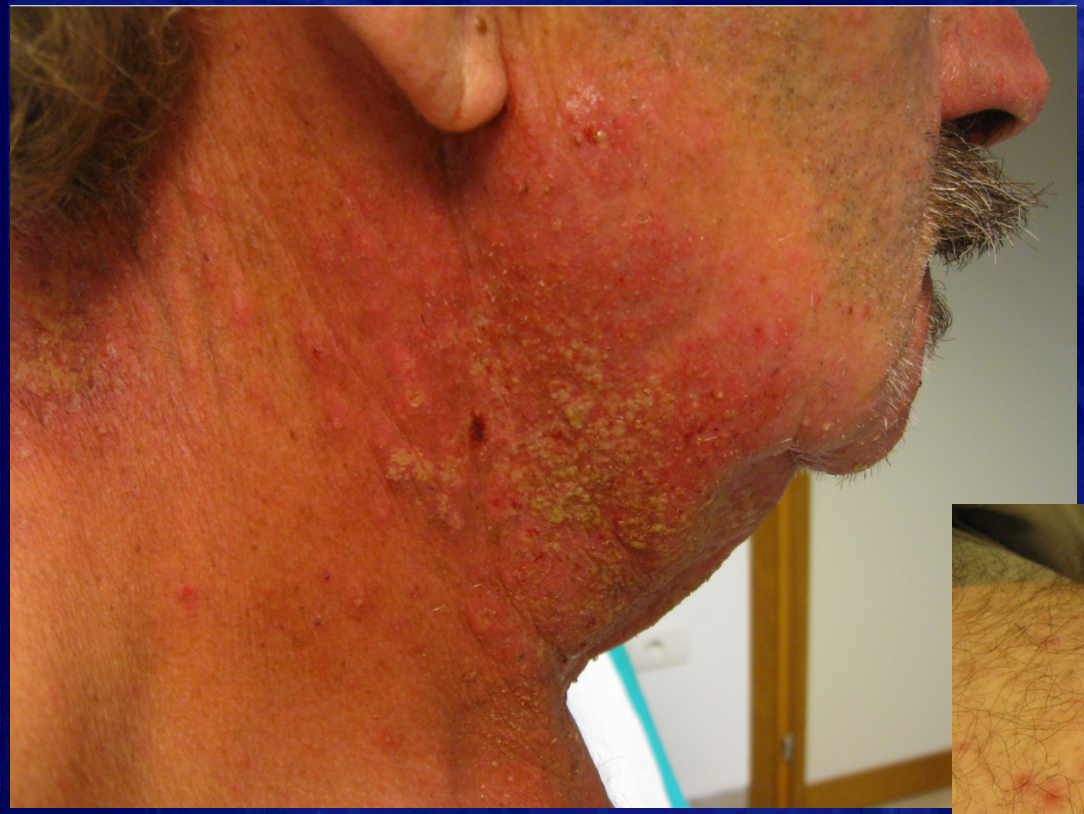
LA MORTALITÀ PER TRATTAMENTO CT-RT DATI DAGLI STUDI RANDOMIZZATI

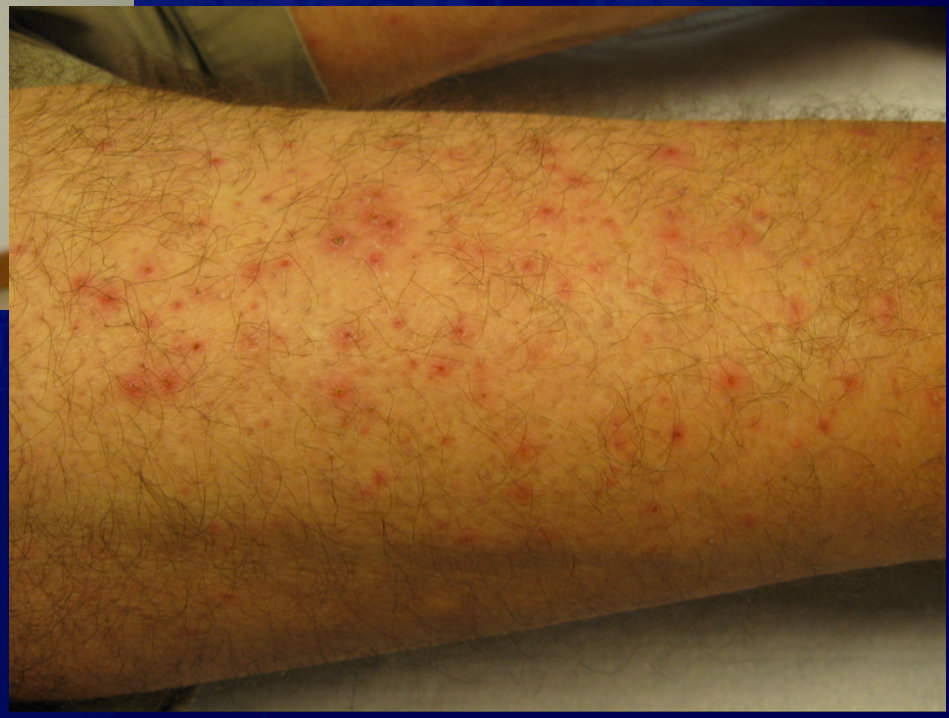
Studio	CT	RT	Mortalità
Calais	CbF	Conv	**1%**
Britzel	PF	HF	2%
Wendt	PFL	HF – split	2%
Adelstein	PF	Conv – split	2%
Adelstein	P	Conv	4%
Forastiere	P	Conv	**5%**
Bonner	C	Conv / HF	**5%**

NELLA PRATICA

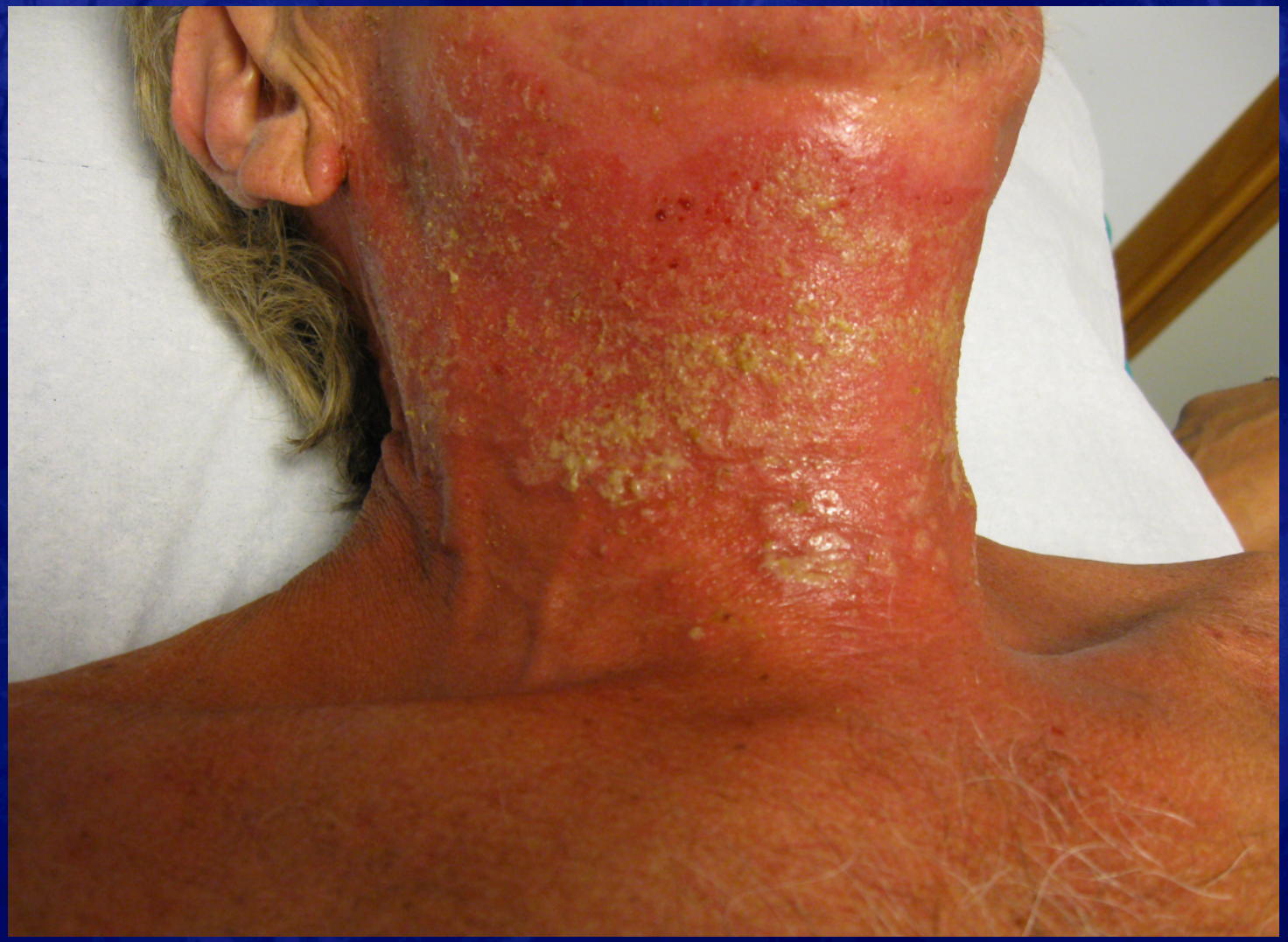
NELL'80% DEI CASI LA TOSSICITA' PRINCIPALE (RASH E DERMATITE DA RADIAZIONI) E' DI GRADO 1-2 E VIENE GESTITA NORMALMENTE DA PERSONALE INFERMIERISTICO ESPERTO NEL TRATTAMENTO RADIO-CHEMIOTERAPICO DEI TUMORI DEL CAPO-COLLO

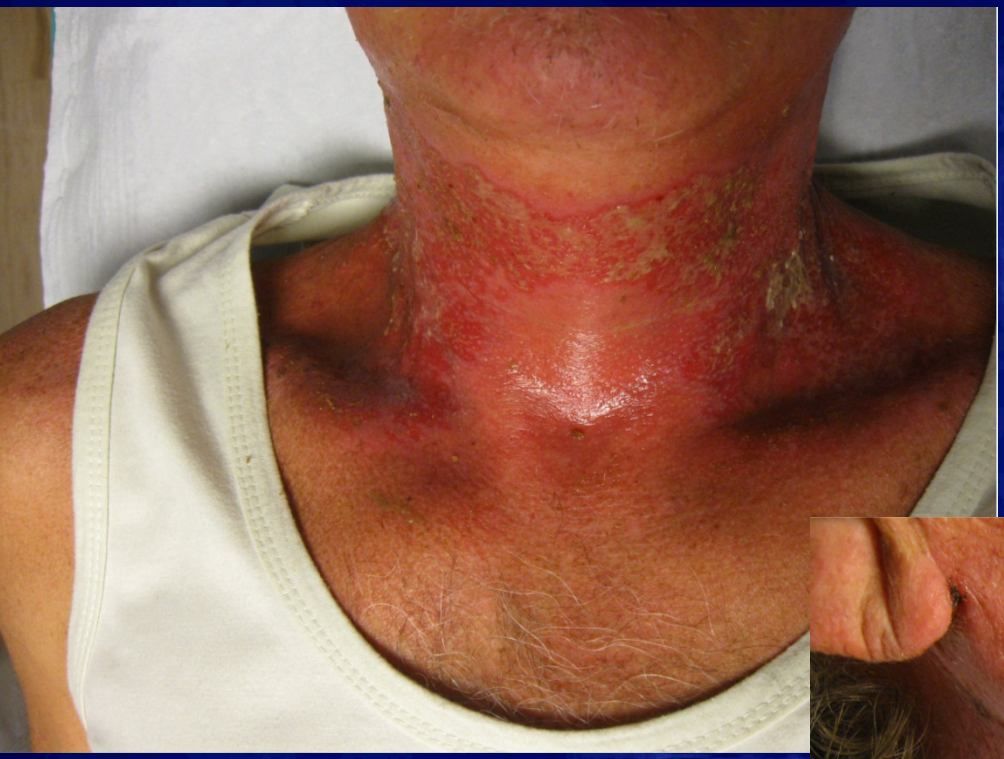
TOSSICITA' CUTANEA A 30 GY



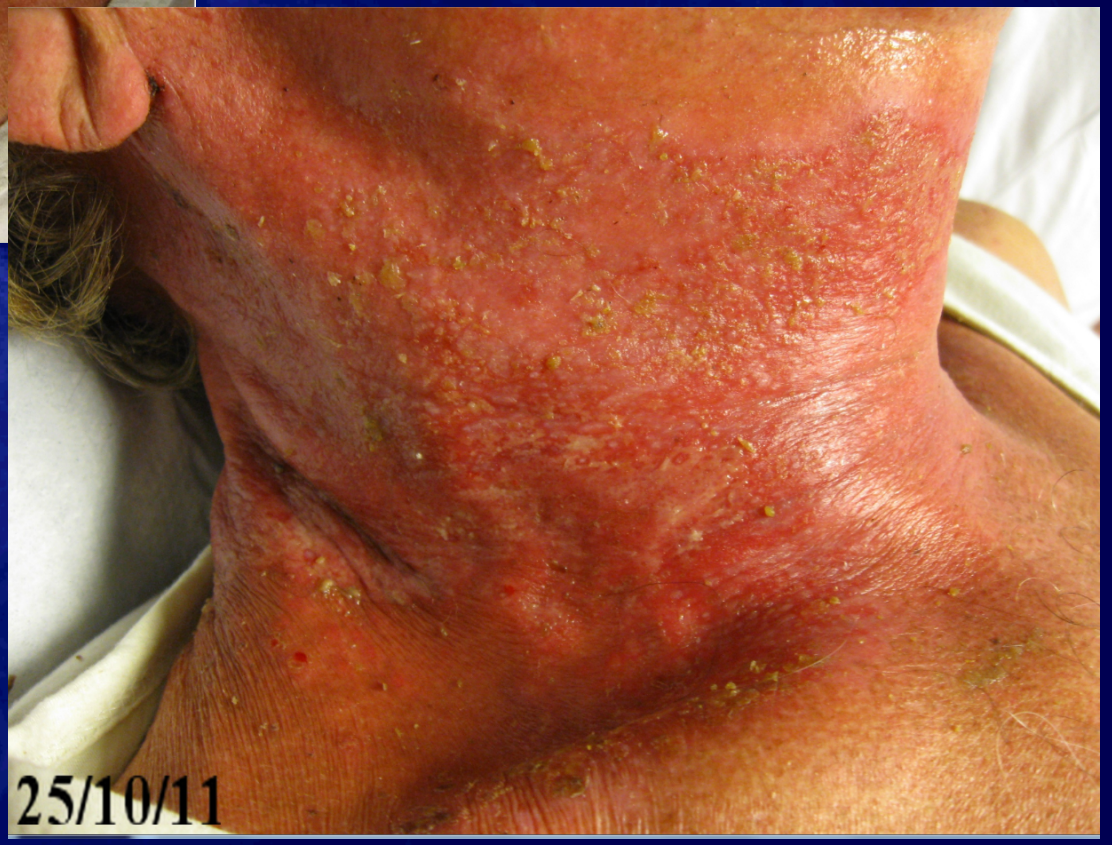


TOSSICITA' CUTANEA A 66 GY

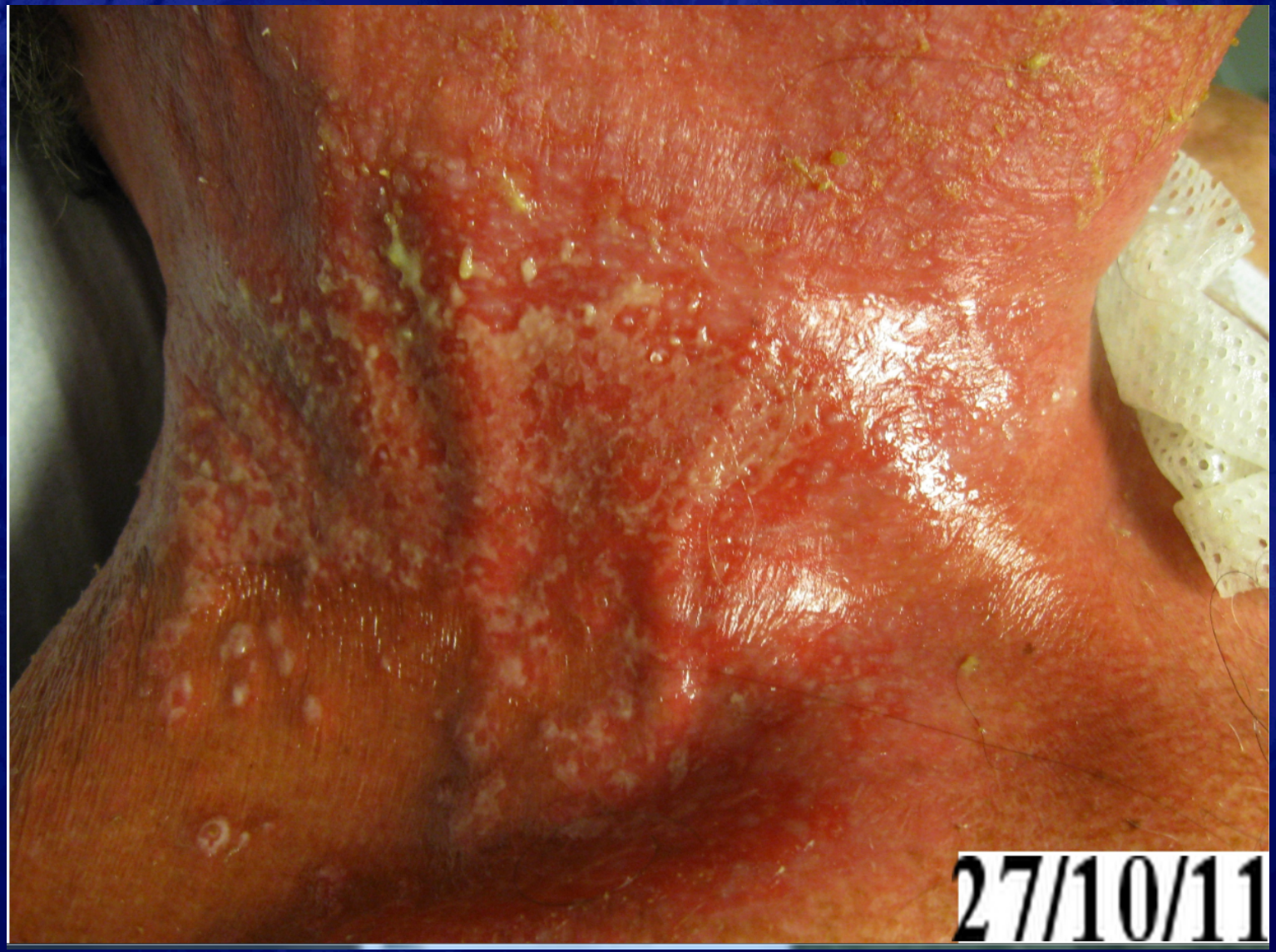




FOLLOW UP
1 settimana dalla fine della RT



FOLLOW UP



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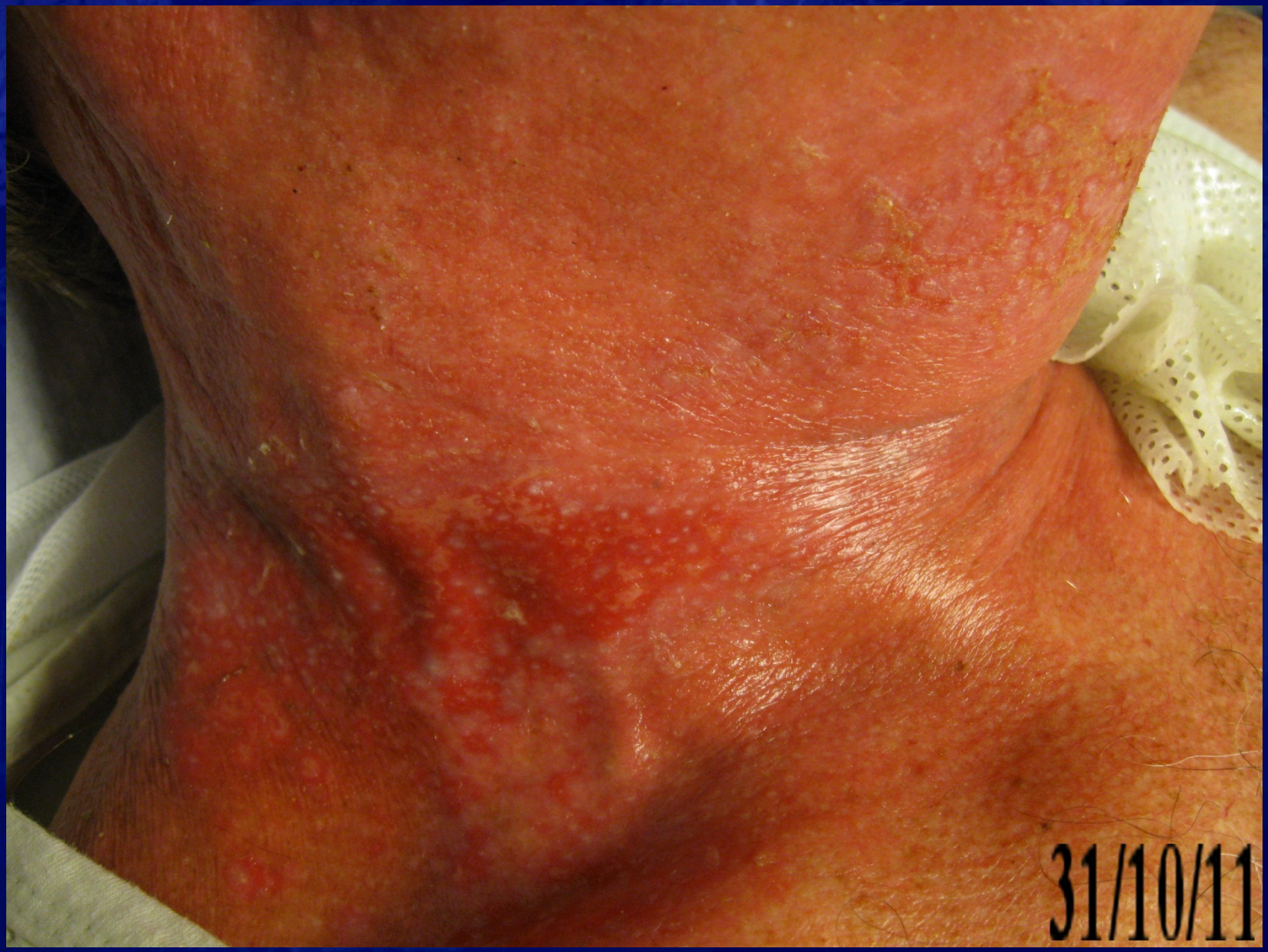

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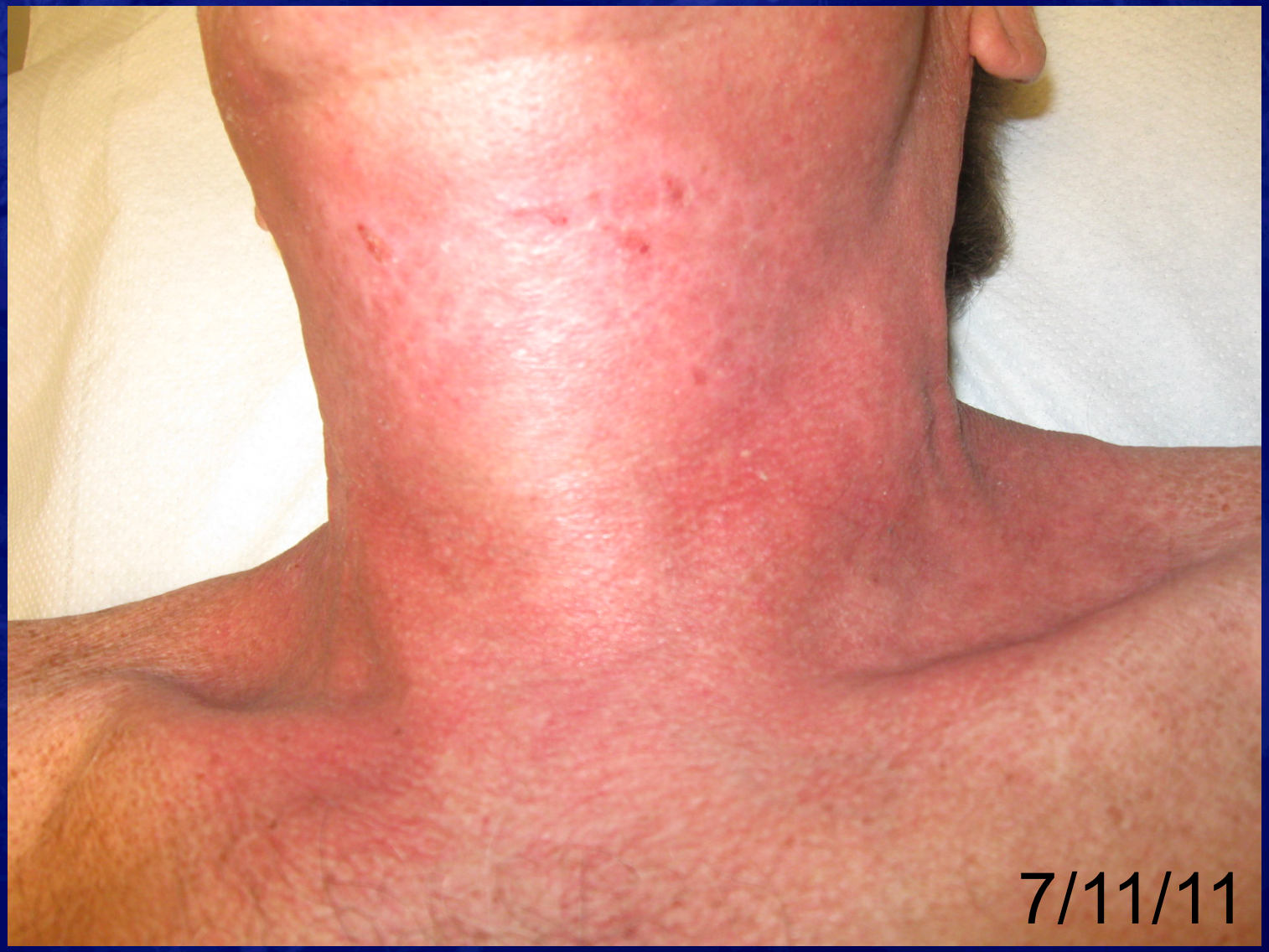
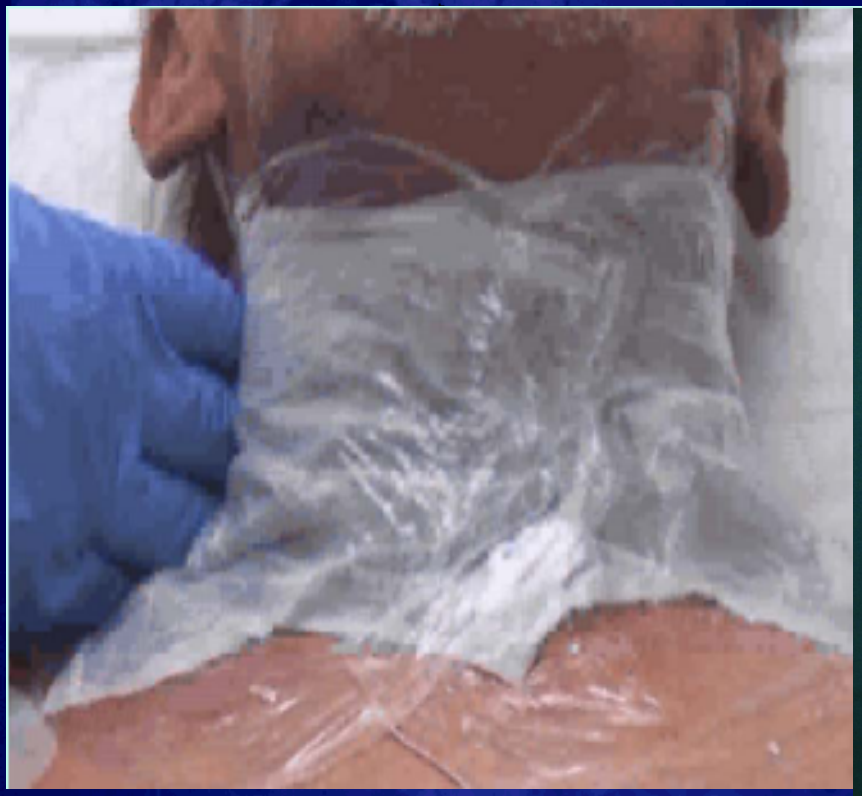
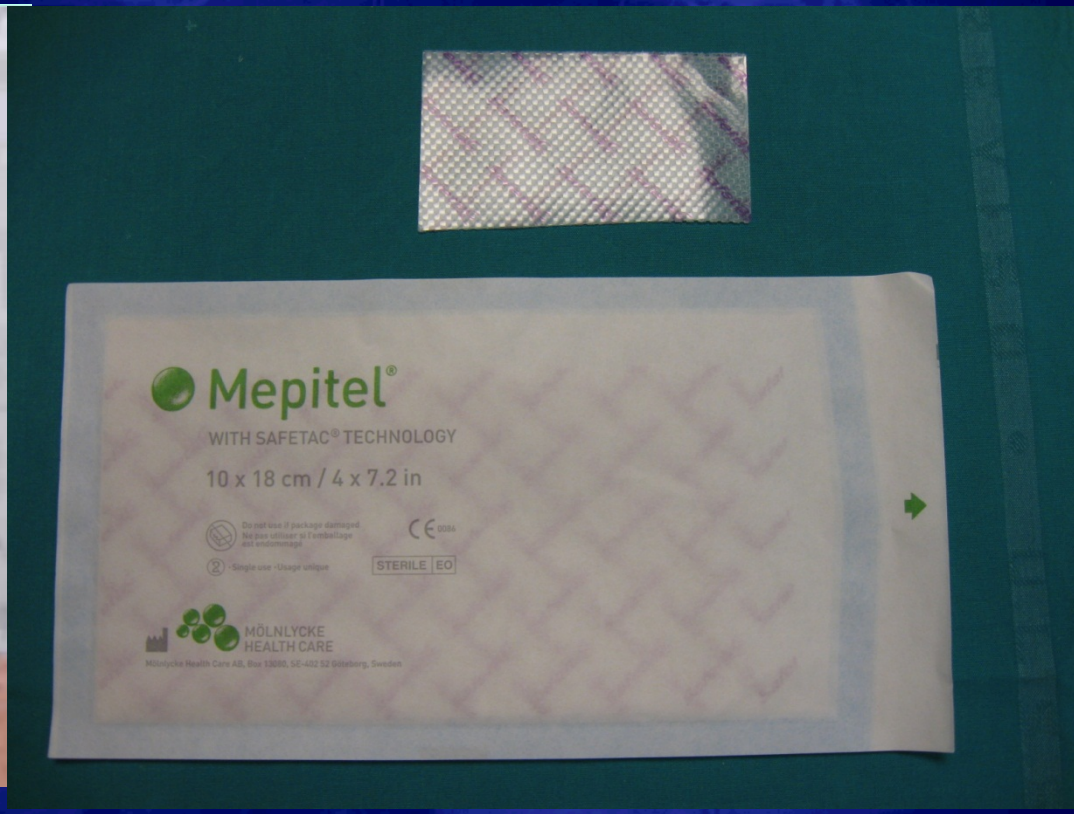


MEDICAZIONI SPECIALISTICHE





"LA NATURA È UN BUON MEDICO,
PERCHÉ GUARISCE I TRE QUARTI DELLE MALATTIE
SENZA PARLAR MALE DEI SUOI COLLEGHI"

(CLAUDIO GALENO)

Azienda ULSS 9
Treviso

GRAZIE PER L'ATTENZIONE

Non ci può essere amore per la scienza se non c'è amore per l'uomo."

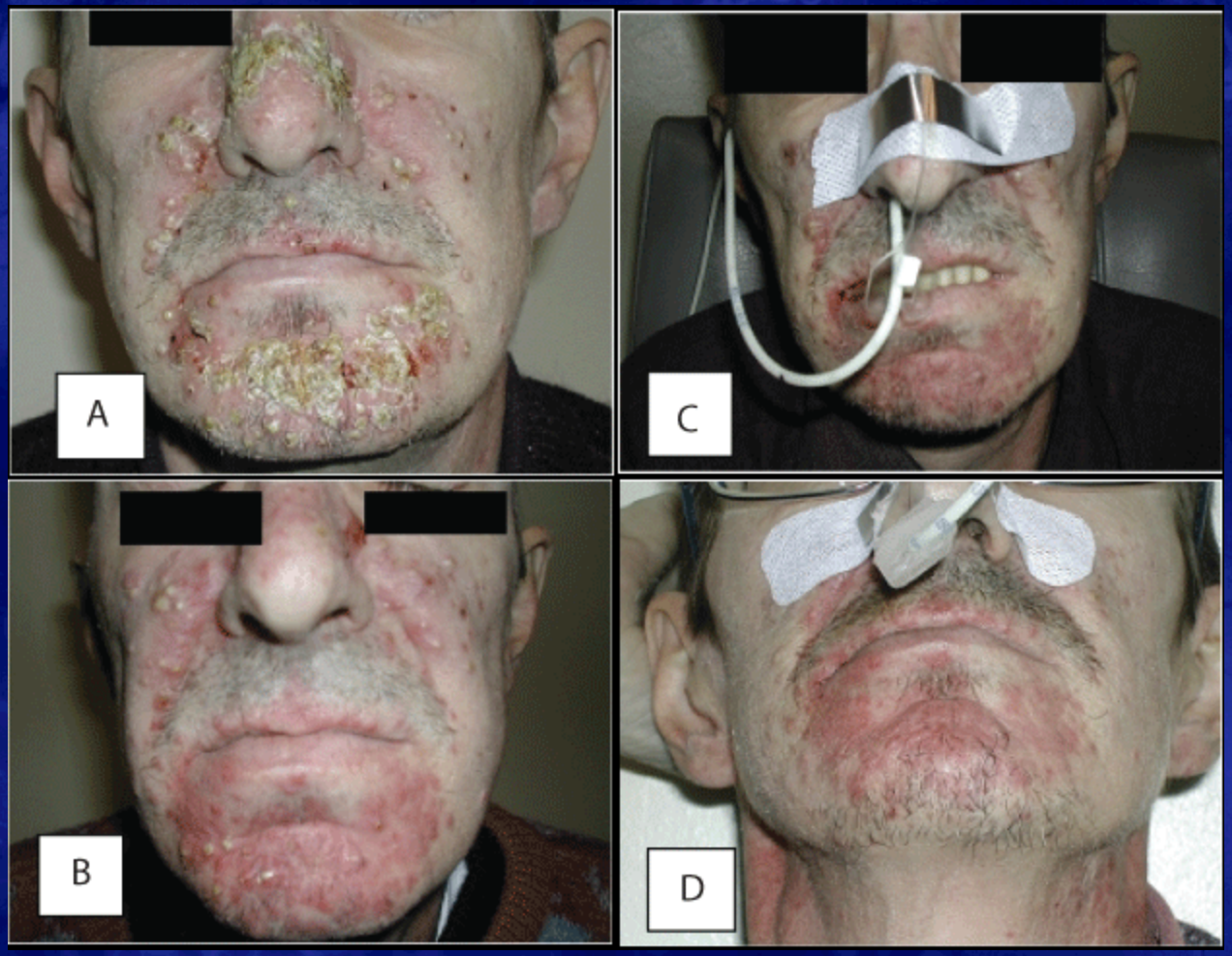
Ippocrate

GRAZIE PER L'ATTENZIONE

Table 5. Grade-specific management of skin toxicity (radiation dermatitis) from radiotherapy and cetuximab

Grade	1	2–3	3	4
Radiotherapy	Continue	Continue	Continue	Discontinue and verify that radiation dose and distribution are correct
Cetuximab	Continue	Continue	Reduce the dosage	Discontinue
Maintain hygiene with soft detergent	Yes	Yes	Keep the irradiated area clean even when ulcerated	Multispecialist evaluation: radiation oncologist, oncologist, dermatologist and nurse
Topical moisturizers	Yes	Yes (limited to not abraded skin)	Yes (limited to not abraded skin)	
Normal saline solution (+/− not aggressive disinfectants: sodium hypochlorite 1%–3%)	No	Yes (on abraded skin)	Yes (on abraded skin)	
Occlusive wound dressing (polyurethane with safetac)	No	Useful in cases of crusty exudates; if it is thin, it is not removed before radiation treatment.		
Hydrogel wound dressing and burn dressing	No	Yes in case of xerosis as a lenitive treatment; it helps debridement in case of crusty exudates	Debridement of crusty exudates	
Hydrocolloids, hydrofibers	No	No	Use to cover and protect moist desquamated area; if they are ultrathin, it is not necessary to remove before radiation treatment	
Topical antibiotics	Should not be used prophylactically		Use on suspected area after swabbing (if possible)	
Antibiotics	In the presence of SIRS[a] with suspected infection. When feasible, culture data should always be obtained prior to initiating antibiotic therapy. Empiric antibiotic therapy should be guided by available practice guidelines and knowledge of the local antibiogram			

[a]SIRS, Systemic Inflammatory Response Syndrome. It is defined as 2 or more of the following variables: fever >38°C or <36°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or $PaCO_2$ level <32 mmHg, abnormal white blood cell count (>12,000 per μL or <4,000 per μL or >10% bands).


A
C
B
D

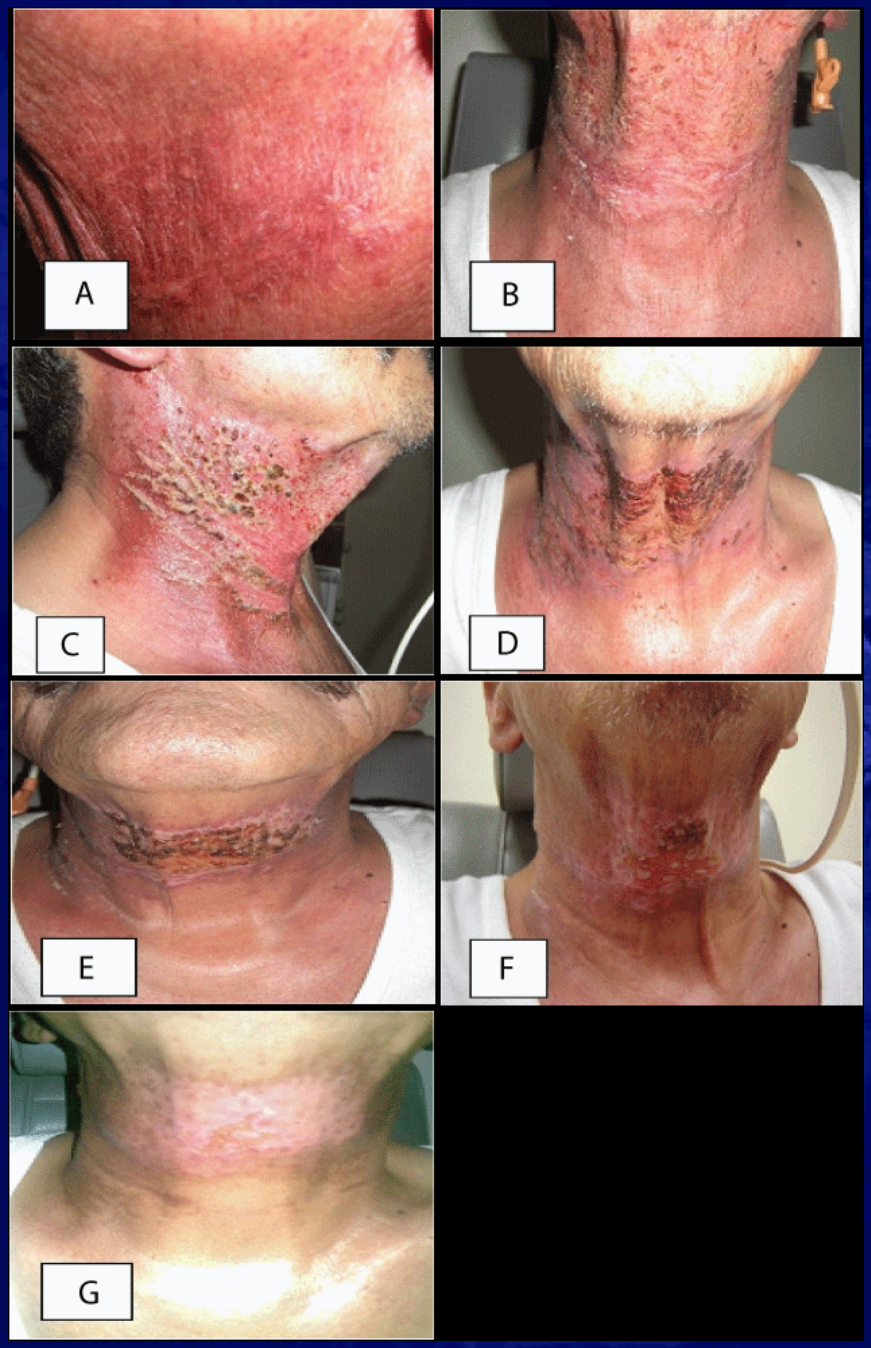
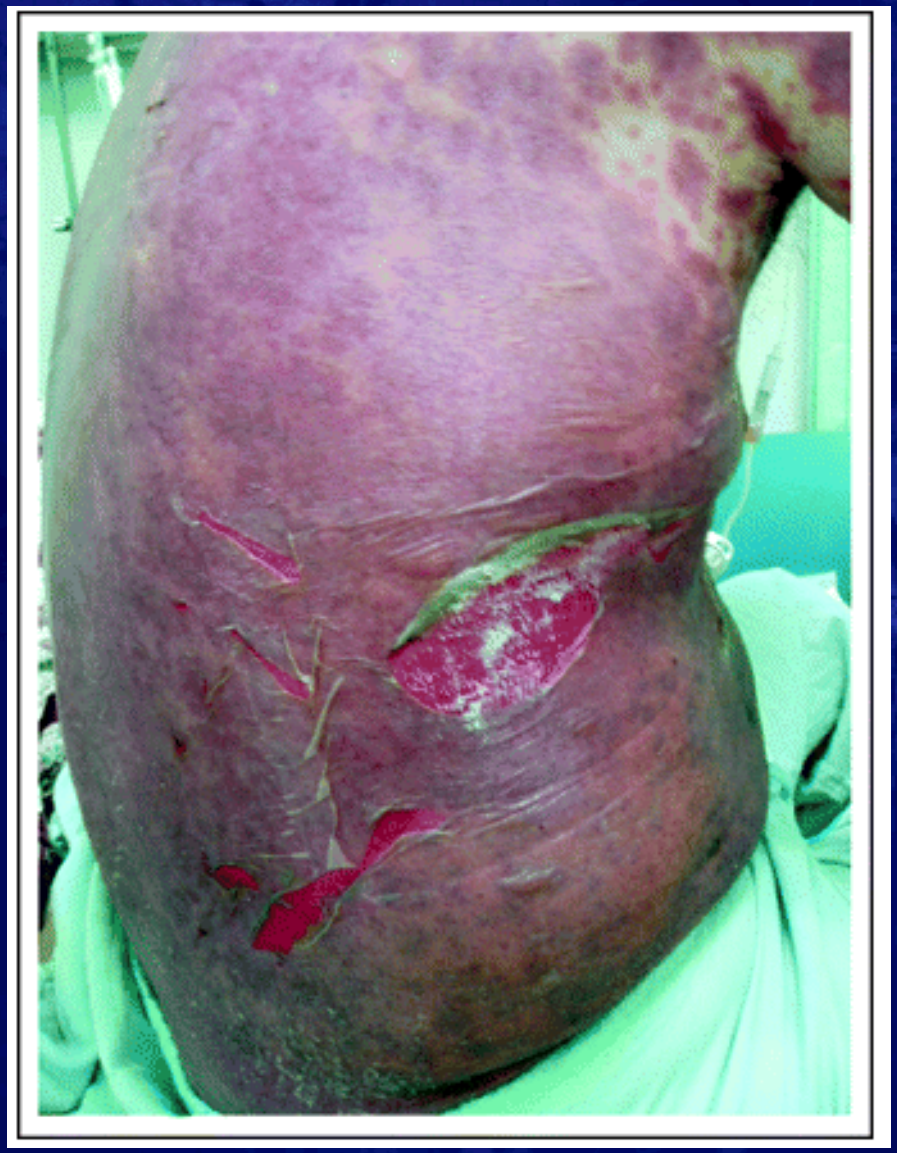


Figure 4: Case report 4: Evolution of skin lesions from the 6th week of concomitant radiotherapy and cetuximab treatment

4A: 6th week of treatment with radiotherapy + Cetuximab.
4B: 7th week of treatment.
4C: 1 week after the end of radiotherapy.
4D: 2 weeks later.
4E: 3 weeks later.
4F: 4 weeks later.
4G: 5 weeks later.



JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

Journal of Clinical Oncology, Vol 26, No 16 (June 1), 2008: pp. 2779-2780

DOI: 10.1200/JCO.2007.15.7883

DIAGNOSIS IN ONCOLOGY

Fatal Toxic Epidermal Necrolysis Associated With Cetuximab in a Patient With Colon Cancer

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Ya-Ching Chang, Hsin-Chun Ho, Li-Cheng Yang, Chih-Hsun Yang

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Wen-Hung Chung

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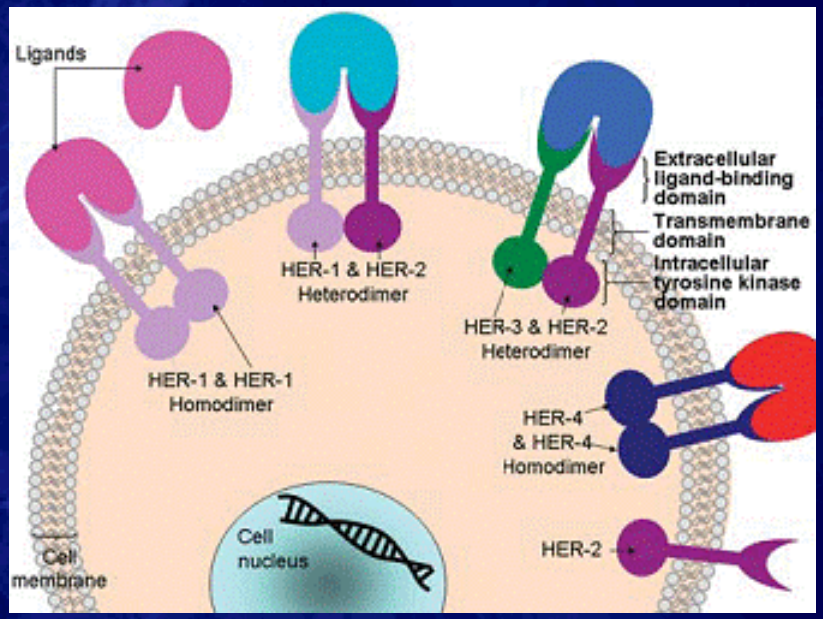
In August 2006, a 74-year-old man was admitted to our hospital for toxic epidermal necrolysis (TEN). He had been diagnosed with moderately differentiated adenocarcinoma of the proximal sigmoid colon, with hepatic metastases, in November 2004. He had received a regimen of bevacizimab 5 mg/kg, oxaliplatin 65 mg/m^2, leucovorin 200 mg/m^2, and fluorouracil 300 mg/m^2 from November 2004 to October 2005. In March 2006, he received three cycles of irinotecan 125 mg/m^2, leucovorin 20 mg/m^2, and fluorouracil 500 mg/m^2 treatment. There were no adverse reactions during the previous treatment course. Because of advanced hepatic metastases, he received additional cetuximab (250 mg/m^2) weekly, from May 30 to July 19, 2006. Progressive paronychia and acneiform papules on the four limbs developed after the eighth course (mid-July). These cutaneous reactions continued to progress, turning into large blisters with extensive epidermal shedding on the trunk; he was sent to our emergency department on July 31. On physical examination, there were generalized confluent purpuric maculopapular lesions with blisters and large epidermal detachment. Severe oral ulcers were also present. Stevens-Johnson syndrome was diagnosed through clinical morphology.[1] However, this case

LAPATINIB



- Lapatinib is a dual inhibitor of EGFR and ErbB2.
- It prevents dimerization.
- Phase I trials have shown response and phase II trials are currently recruiting.

VANDETANIB (ZD6474)

oral TKI with activity against both EGFR and VEGFR

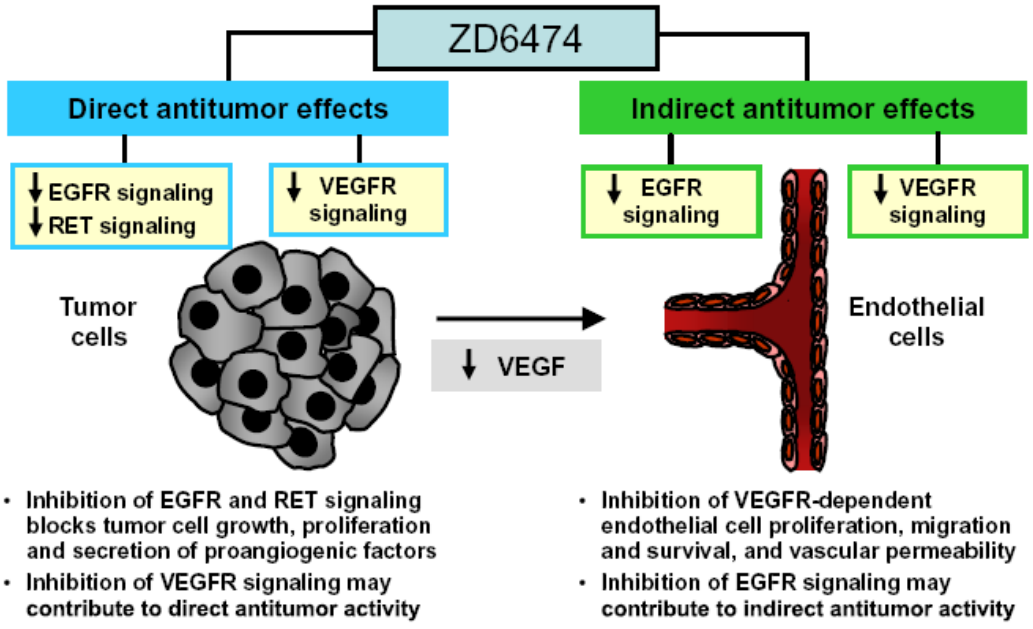


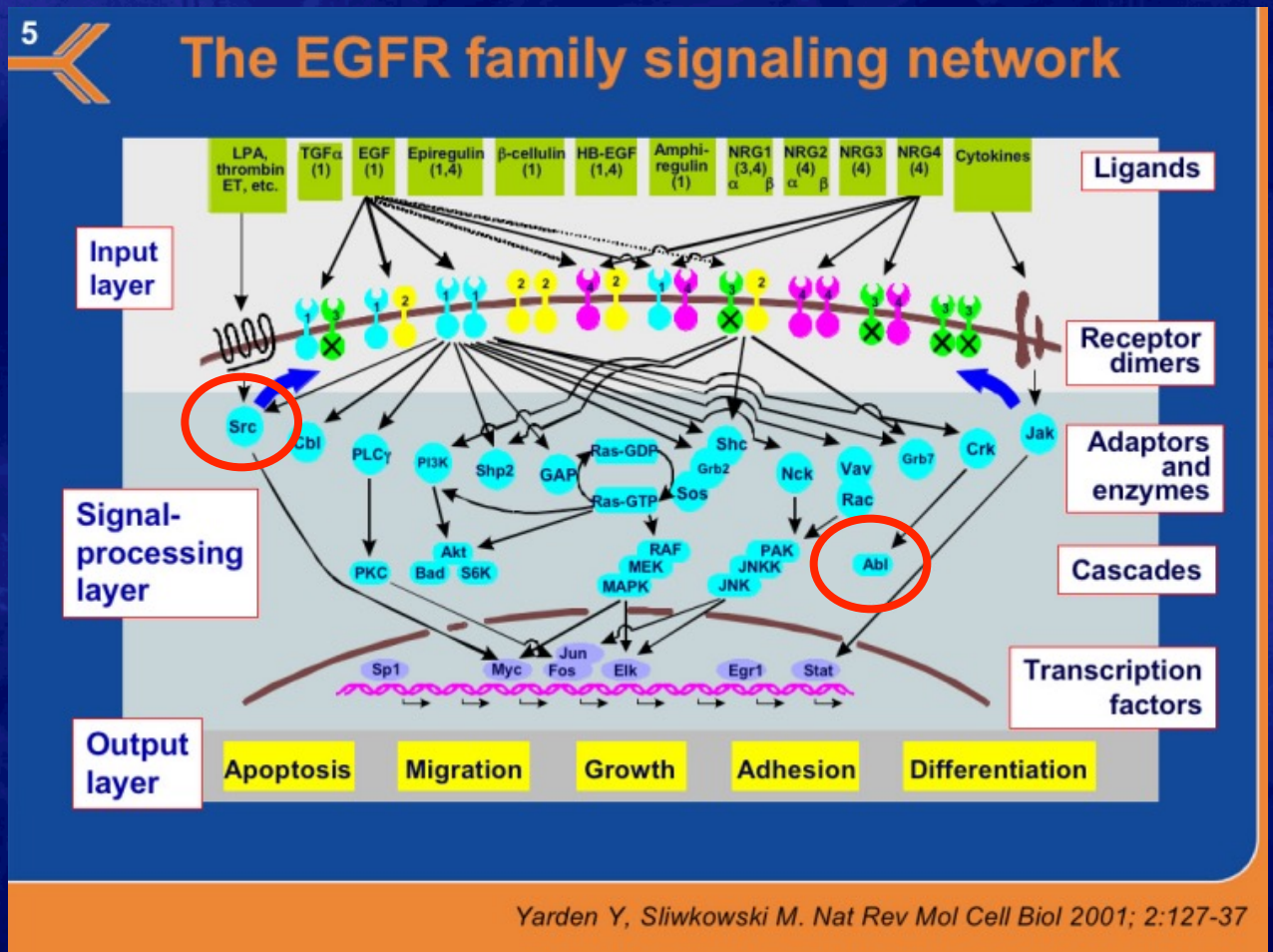
Figure 3 ZD6474: targeting EGFR and VEGFR signaling pathways in cancer. (Reproduced with permission from Anderson Ryan, Ph.D.) (Color version of figure is available online.)

RTOG has submitted a proposal to test ZD6474 in combination with CRT in a randomized phase II study of HNSCC patients with high risk postoperative features.

ALTRI APPROCCI

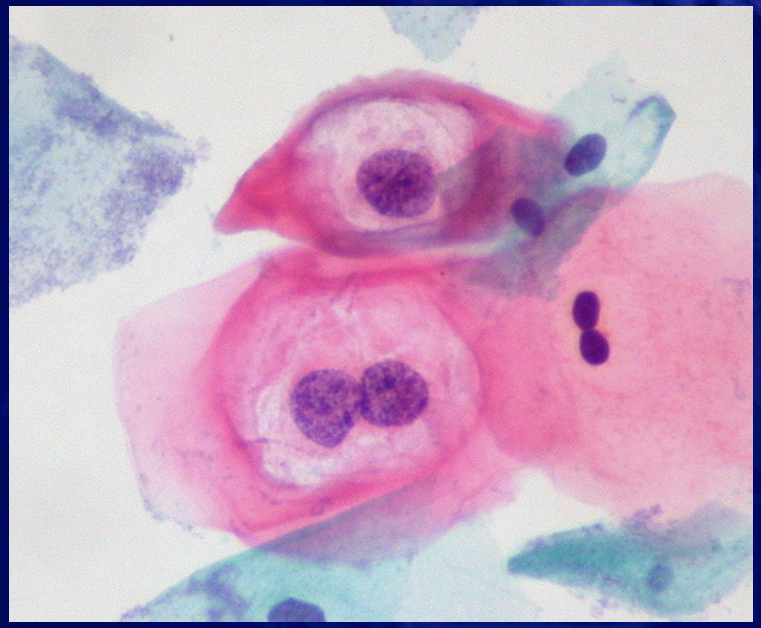
- **DESATINIB : dual c-Src and Abl kinase inhibitor, reduce migration and invasion in HNSCC and NSCLC cell lines.**

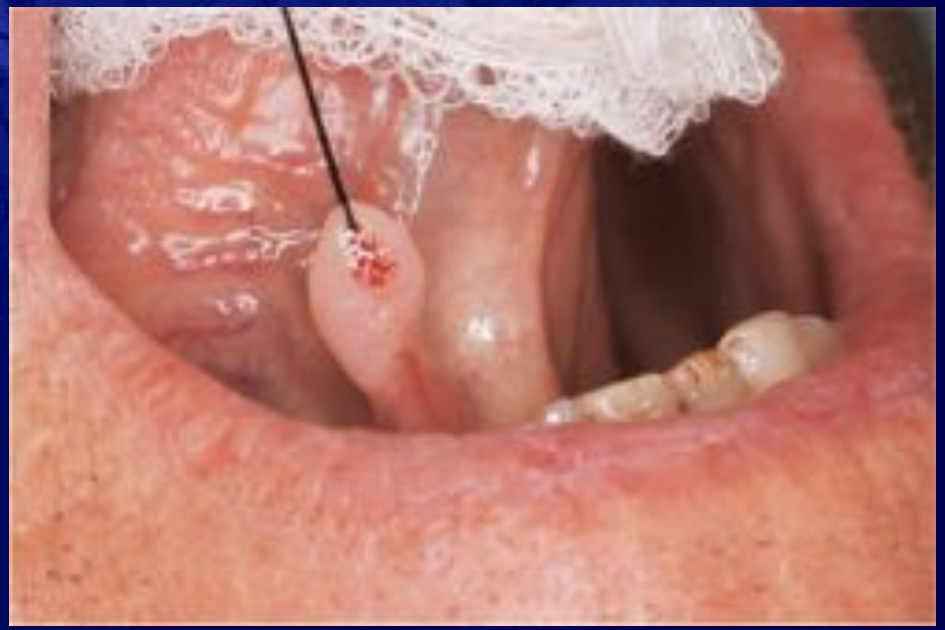
- **AZD0530: dual c-Src and Abl kinase inhibitor, reduce the growth and several HNSCC cell lines.**

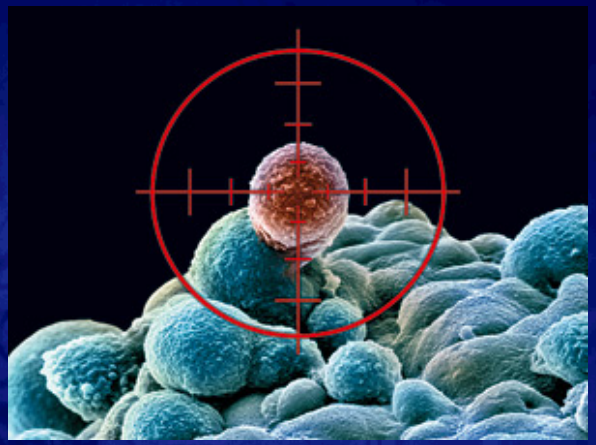


PAPILLOMA VIRUS

1. HPV has a strong association with oropharyngeal SCC (particularly tonsil)
2. HPV has weaker associations with oral and laryngeal cancer
3. Pts with HPV + ve oropharynx tumors:
    1. Present at a relatively younger age
    2. Do not have excessive tobacco/EtOH use
    3. Appear to have better survival







ELSEVIER

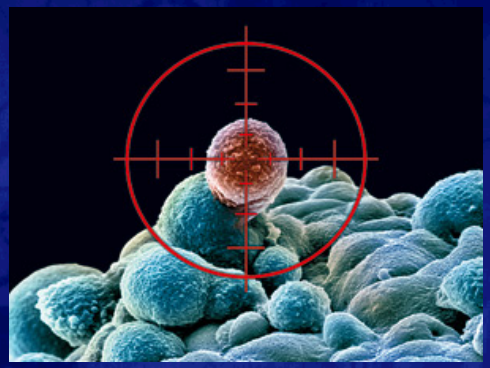
Seminars in
RADIATION ONCOLOGY

Cancer Stem Cells in Solid Tumors: An Overview

Catherine Adell O'Brien, MD,* Antonija Kreso, BSc,† and John E. Dick, PhD*,†

It has long been appreciated that significant functional and morphologic heterogeneity can exist within the individual cells that comprise a tumor. Increasing evidence indicates that many solid tumors are organized in a hierarchical manner in which tumor growth is driven by a small subset of cancer stem cells (CSCs) or tumor-initiating cells. Although these cells represent a small percentage of the overall tumor population, they are the only cells capable of initiating and driving tumor growth. Emerging evidence indicates that these cells are also resistant to chemotherapy and radiation therapy, which has led to much speculation and interest surrounding the potential clinical applicability of CSCs.
Semin Radiat Oncol 19:71-77

STEM CELLS



Vari studi hanno dimostarato che all'interno di una massa tumorale vi è una eterogeneità cellulare (morfologica, proliferativa, funzionale)

Cancer Stem Cells (CSC)
cellule caratterizzate da:

- capacità di rigenerarsi,
- crescere all'interno della massa tumorale,
- guidare l'espansione della popolazione cancerogena.

.

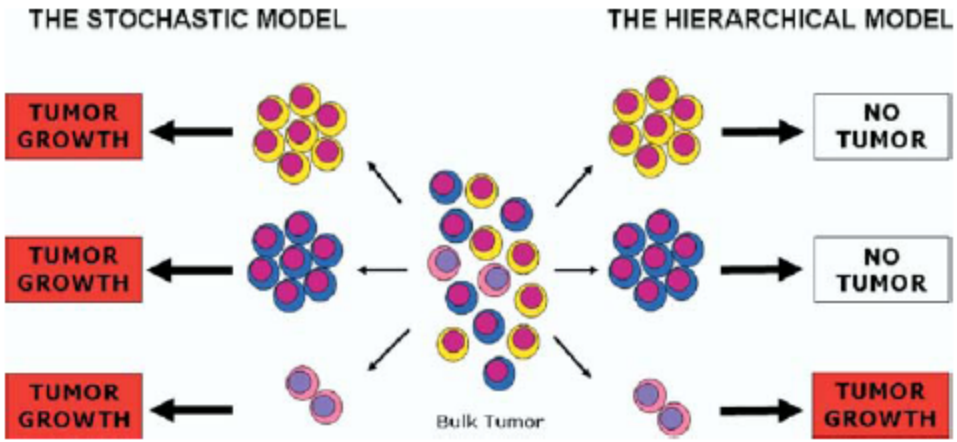


Figure 1 Two models were described to explain the heterogeneity of tumor cells. The first being the stochastic model, which states that all cells within a tumor have the potential to regenerate the tumor; however, this is determined by entry into the cell cycle, a low probability stochastic event. According to this model, it would not be possible to prospectively isolate the tumorigenic fraction. The alternative explanation for tumor heterogeneity is the hierarchical or cancer stem cell model, which postulates that tumors possess a subset of CSCs that are the only cells capable of initiating and maintaining tumor growth. According to this model, it should be possible to prospectively isolate CSCs (tumorigenic cells) from the bulk of the tumor.

IMPLICAZIONI CLINICHE

Table 1 Markers Used to Enrich for Solid Tumor CSCs

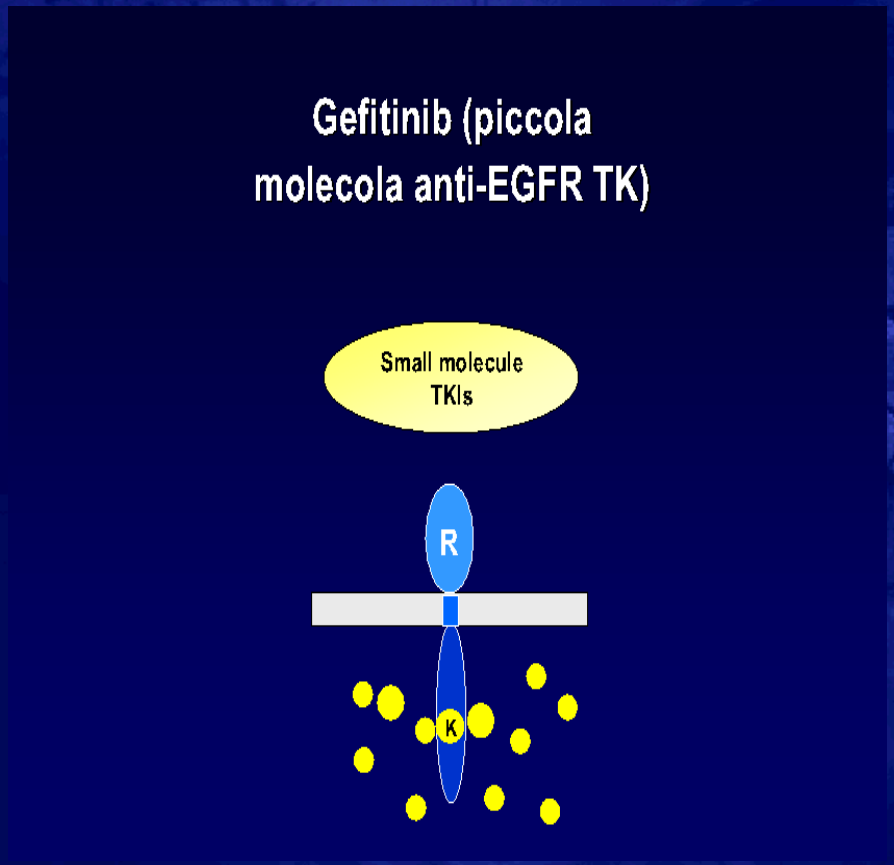
CD133	
Brain	
Glioblastoma	($CD133^+$)
Medulloblastoma	($CD133^+$)
Colon	($CD133^+$)
Pancreas	($CD133^+$)
Lung	($CD133^+$)
CD44	
Breast (Edinburgh, Scotland)	($CD44^+CD24^-$)
Head and neck	($CD44^+$)
Colon	($CD44^+EpCAM^+$)
Pancreas	($CD44^+CD24^+$ ESA+.)
CD90	
Hepatocellular	($CD90^+$)
ABC proteins	
Melanoma	($ABCB5^+$)
Functional markers	
Side Population	
Mesenchymal	(SP^+)[46]
ALDH	
Breast	(ALDH+)
Colon	($CD44^+EpCAM^+ALDH1^+$)

Evidenze preliminari sembrerebbero documentare che le CSC sono più radio - chemio resistenti rispetto le non CSC.

Non ricercare più agenti contro tutta la massa tumorale bulky, ma Agenti specifici contro sottopopolazioni CSC

Ricercare differenti terapie solo contro queste sottopopolazioni.

GEFINITIB



High levels of VEGF and cycloxygenase 2 have been associated with enanced tumor dissemination and worse survival.

WIRTH et al. 2005

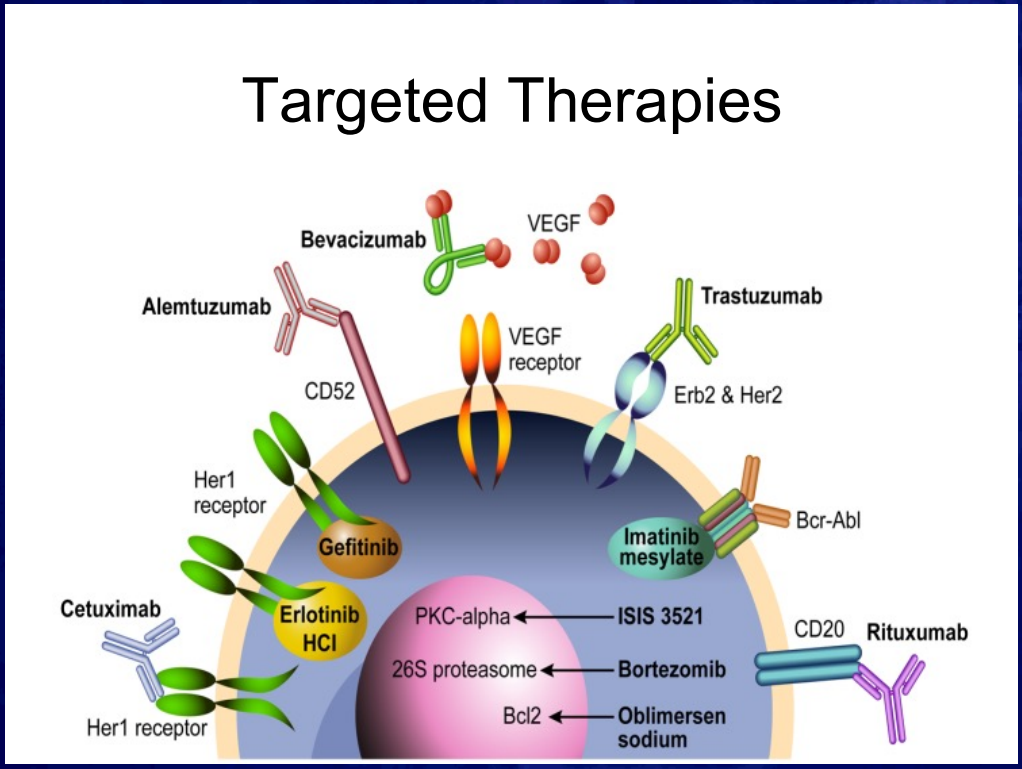
18 patients with recurrent or metastatic HNSCC : 4 partial response

GEFINITIB 250-500 mg +

CELECOXIB 200-400 mg twice x day

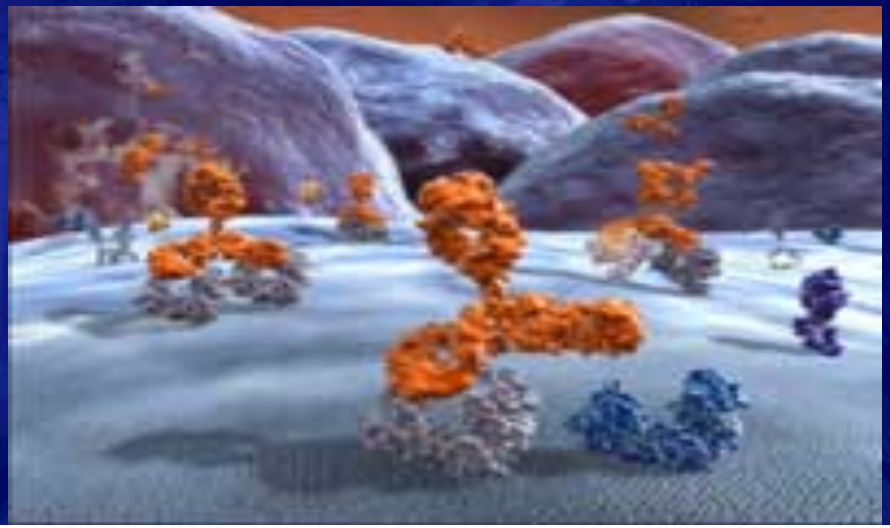
TARGETED THERAPIES

compaiono ….umab e inib



- **Monoclonal antibodies**: proteine che si legano a recettore o altra molecola di segnale extracellulare
- **Tyrosine Kinase Inhibitors**: molecola che lega e inibisce attività enzimatiche intracellulari

NEW CHEMOTHERAPY AGENT



The NEW ENGLAND JOURNAL of MEDICINE

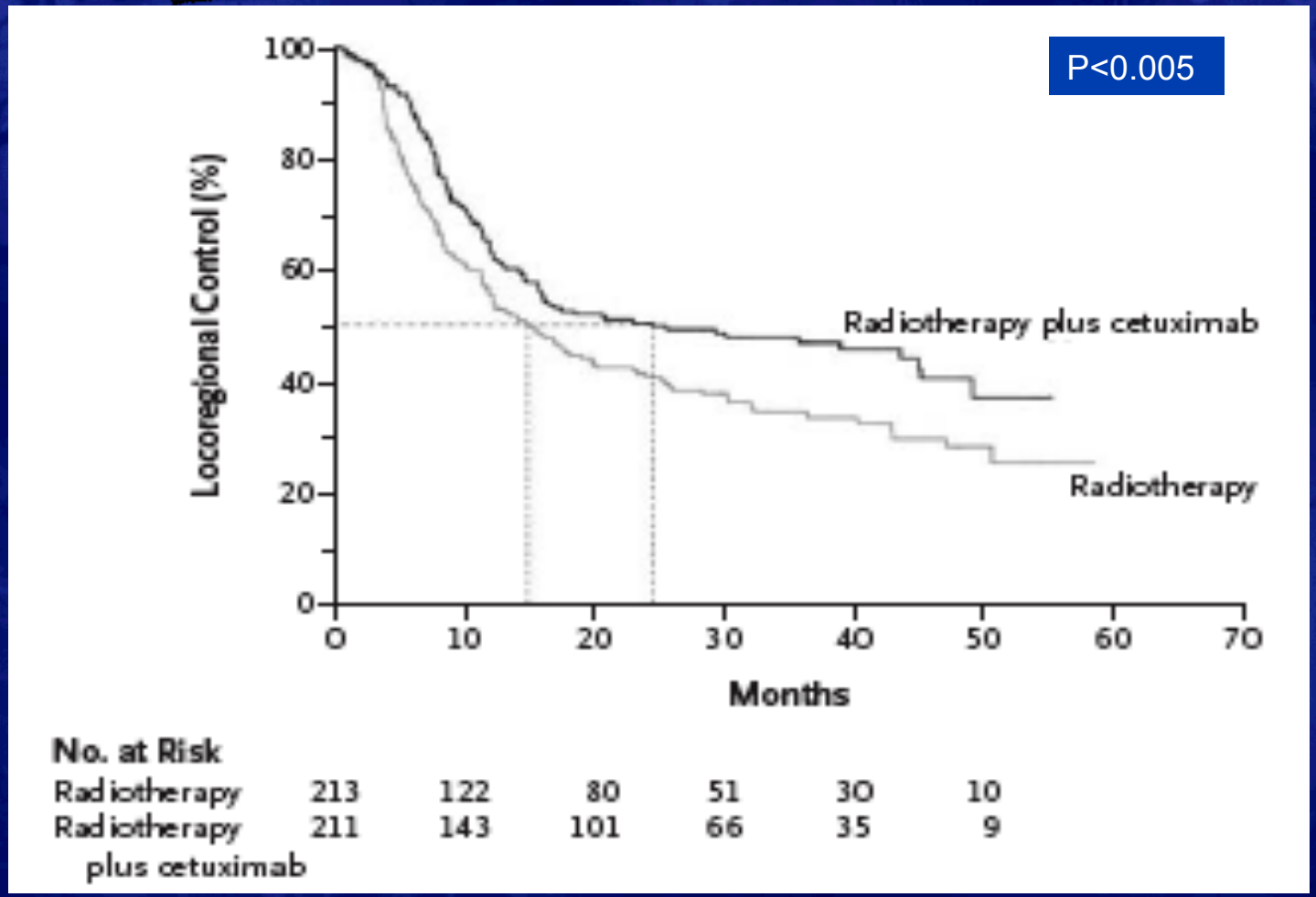
ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

RT e CETUXIMAB: STUDI CLINICI

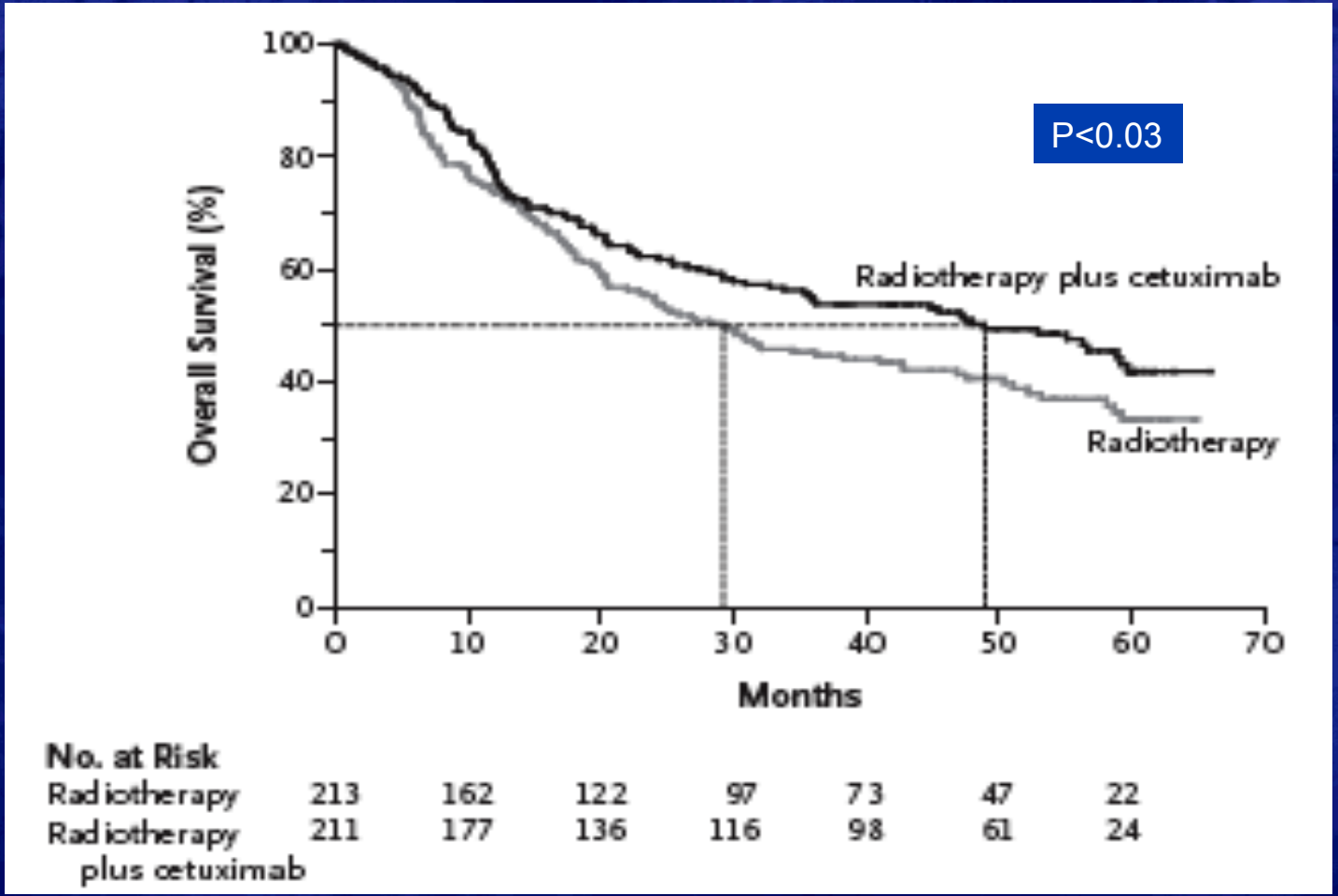
LOCOREGIONAL CONTROL



Bonner JA et al, N.Engl.J.Med. 2006;354:567-78

RT e CETUXIMAB: STUDI CLINICI

OVERALL SURVIVAL



Bonner JA et al, N.Engl.J.Med. 2006;354:567-78

RT e CETUXIMAB: STUDI CLINICI

OVERALL SURVIVAL

	RT (*n*=213)	Cetuximab + RT (*n*=211)	*p*-value
Median overall survival	29.3 months	49.0 months	0.03
Survival rate 3-year	45%	55%	0.05

Bonner J, Ang K. N Engl J Med 2006; 354:567-78

Bonner JA et al, N.Engl.J.Med. 2006;354:567-78

Phase III study: RT vs ERBITUX + RT (1)

Subset of 171 patients with laryngeal and hypopharyngeal SCC

Treatment	Laryngeal preservation	
	2-year rate	3-year rate
RT alone (n=78)	80%	77%
ERBITUX + RT (n=93)	90%	87%

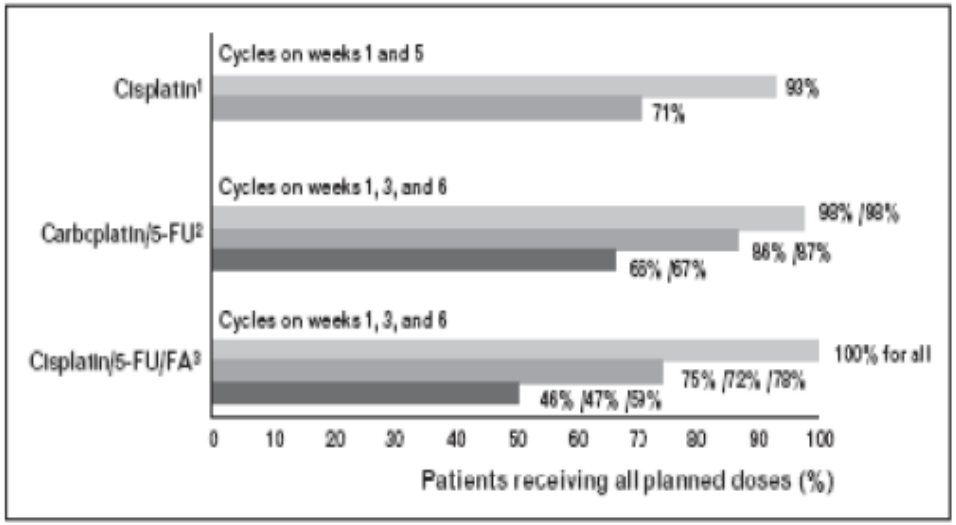
Bonner J, et al. ASCO Annual Meeting. Orlando 2005 [Abstract No. 5533]

Prolongation of Survival With the Addition of Erbitux to Radiation in Patients With Locoregionally Advanced Head and Neck Cancer (SCCHN): Five-Year Results From a Randomized Trial

J. A. Bonner, P. M. Harari, J. Giralt, R. B. Cohen, C. Jones, R. K. Sur, D. Raben, J. Zhu, H. Youssoufian, K. K. Ang

ASTRO 2008

COMPLIANCE ALL'INTEGRAZIONE

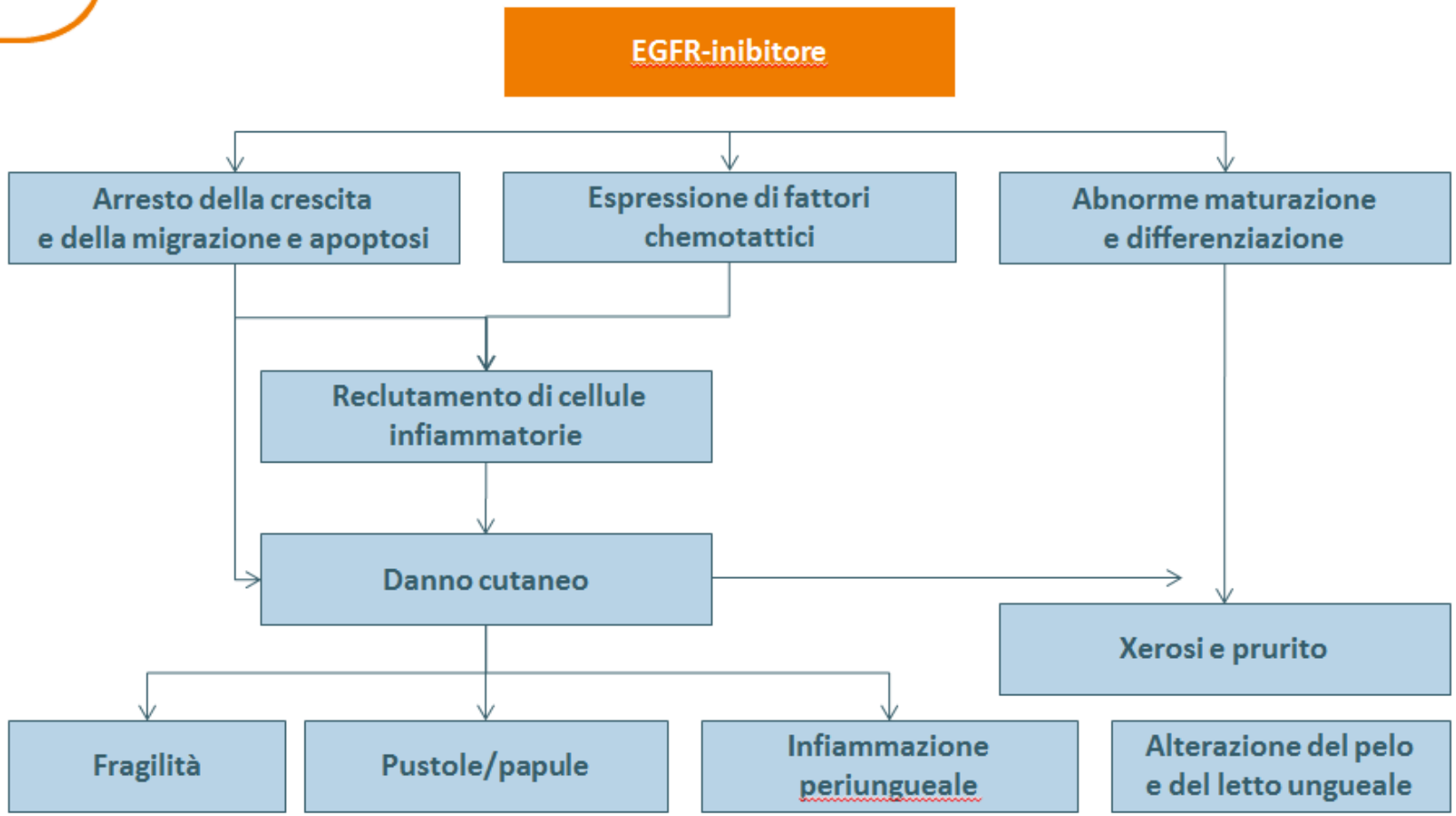


FA, folinic acid; 5-FU, 5-fluorouracil. [1]Huguenin *et al.* [21]; [2]Calais *et al.* [18];[3] Wendt *et al.* [19]. □ first cycle; □ second cycle; ■ third cycle.

Bonner : 90% dei pz. RT-Cetux hanno ricevuto tutte le dosi programmate

Jacques Bernier : A multidisciplinary approach to squamous cell carcinomas of the head and neck: an update Current Opinion in Oncology 2008, 20:249–255

Reazioni cutanee indotte dagli inibitori anti-EGFR



Lacouture, Nature Rewiews, 2006

OXFORD JOURNALS

Annals of Oncology

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRE

Oxford Journals > Medicine > Annals of Oncology > Advance Access > 10.1093/annonc/mdr139

Management of radiation dermatitis in patients receiving cetuximab and radiotherapy for locally advanced squamous cell carcinoma of the head and neck: proposals for a revised grading system and consensus management guidelines

J. Bernier[1,*], E. G. Russi[2], B. Homey[3], M. C. Merlano[4], R. Mesía[5], F. Peyrade[6] and W. Budach[7]

+ Author Affiliations

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The Oncologist®

Symptom Management and Supportive Care

Management of Skin Toxicity Associated with Cetuximab Treatment in Combination with Chemotherapy or Radiotherapy

CARMINE PINTO,[a] CARLO ANTONIO BARONE,[b] GIAMPIERO GIROLOMONI,[c] ELVIO GRAZIOSO RUSSI,[d] MARCO CARLO MERLANO,[e] DARIS FERRARI,[f] EVARISTO MAIELLO[g]

[a]Medical Oncology Unit, S.Orsola-Malpighi Hospital, Bologna, Italy; [b]Medical Oncology Unit, Gemelli Hospital, Rome, Italy; [c]Dermatology Unit, University of Verona, Verona, Italy; [d]Radiotherapy Unit and [e]Oncology Unit, Santa Croce and Carle Hospital, Cuneo, Italy; [f]Oncology Unit, San Paolo Hospital, Milan, Italy; [g]Oncology Unit, Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo (FG), Italy

Key Words. Cetuximab • EGFR • Italian Expert Opinions • Skin rash • Skin toxicity

Disclosures: Carmine Pinto: None; **Carlo Antonio Barone:** *Consultant/advisory role*: Merck; **Giampiero Girolomoni:** None; **Elvio Grazioso Russi:** None; **Marco Carlo Merlano:** *Consultant/advisory role*: Merck; *Expert testimony*: Merck; **Daris Ferrari:** None; **Evaristo Maiello:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

Trattamento del rash cutaneo di grado 3

Trattamento sistemico

Paziente fortemente sintomatico/ non responsivo

Retinoidi:

- isotretinoina os 0,3-0,5 mg pro *Kg (Aisoskin 10 mg capsule; Isoriac 10 mg capsule; Isotretinoina Difa Coper 10 mg; Roaccutan 10 mg capsule)*

Corticosteroidi ev:

- metilprednisolone (*Urbason 20 mg/ml fiale, 40 mg/ml fiale; Depo-Medrol 40 mg/ml flacone; Solu-Medrol 40 mg/ml, 125 mg/2 ml)*;
- desametasone (*Capital 4 mg/ml fiale; Decadron 4 mg/ml fiale, 8 mg/2 ml fiale; Desametasone Fosfato Hospira 4 mg/ml fiale, 8 ng/2 ml fiale; Megacort 4 mg/ml fiale; Soldesam 4 mg/ml fiale, 8 mg/2 ml fiale)*

Antiistaminici im/ev:

- clorfenamina *(Trimeton 10 mg/ml fiale)*

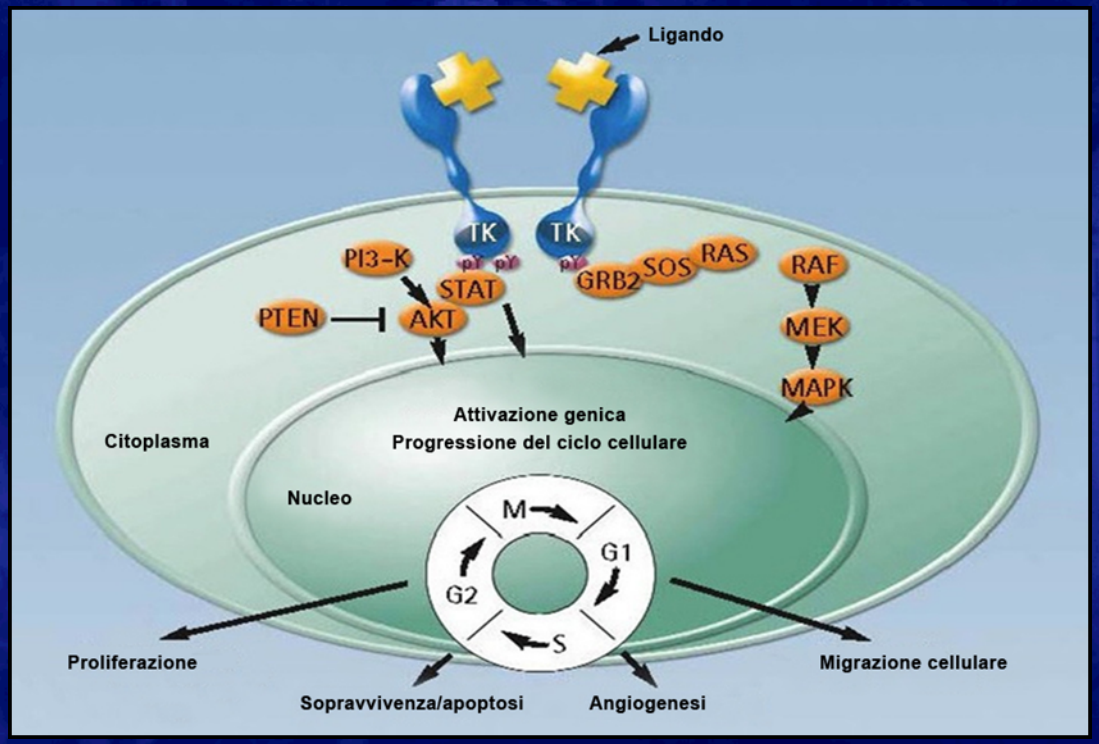
Antibiotici ev:

- amoxicillina/acido clavulanico *(Amoxicillina + Acido clavulanico Ibigen 1000 mg + 200 mg/20 ml flacone, 2000 mg + 200 mg/20 ml flacone; Augmentin 1000 mg + 200 mg/20 ml flacone, 2000 mg + 200 mg/20 ml flacone);*
- gentamicina *(Gentalyn 80 mg/ 2 ml fiale, 120 mg/1,5ml fiale, 160 mg/2 ml fiale, Gentamicina Solfato FisioPharma 80 mg/2 ml fiale, Gentomil 80 mg/2 ml fiale, 160 mg/2 ml fiale)*

Idratazione ev

RUOLO EGFR NELLA FISIOPATOLOGIA DELLA CUTE

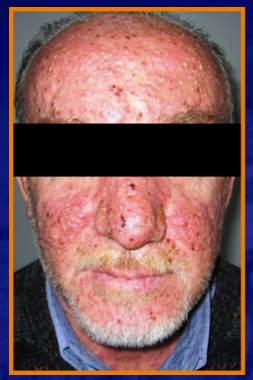
1. **Stimolazione della crescita dell'epidermide: sopravvivenza e proliferazione cellulare**
2. **Stimolazione della migrazione dei cheratinociti**
3. **Accelerazione della guarigione delle ferite**

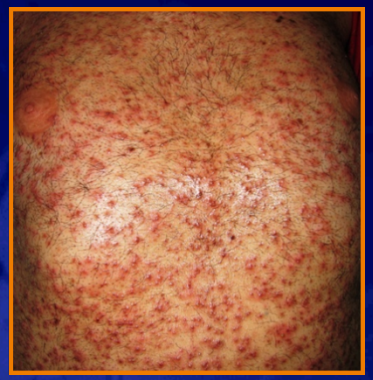


NOVITA' 3° MILLENNIO

3 NOVITA' PIU' RECENTI
NEL TRATTAMENTO NON CHIRURGICO DEI TUMORI DEL CAPO-COLLO

1. CT-RT CONCOMITANTE > SEQUENZIALE
2. TPF NEOADIUVANTE > PF NEOADIUVANTE
3. CETUXIMAB + RT > RT ESCLUSIVA





TRATTAMENTO DEL RASH CUTANEO DI GRADO 4

Lesioni cutanee e sintomi	Rash generalizzato; sintomi gravi che richiedono un trattamento urgente
Modifiche dose cetuximab	Interrompere immediatamente e definitivamente
Trattamento topico	*Antibiotici: clindamicina 1% gel; eritromicina 3% gel/crema; metronidazolo 0,75-1% crema/gel 2 volte al giorno fino a regressione a grado 1* *Manifestazioni del cuoio capelluto: eritromicina 2% lozione*
Trattamento sistemico	*Retinoidi os, Corticosteroidi ev, antiistaminici im/ev: clorfenamina* *Antibiotici ev: amoxicillina/acido clavulanico; gentamicina* *Ev Ospedalizzazione*