

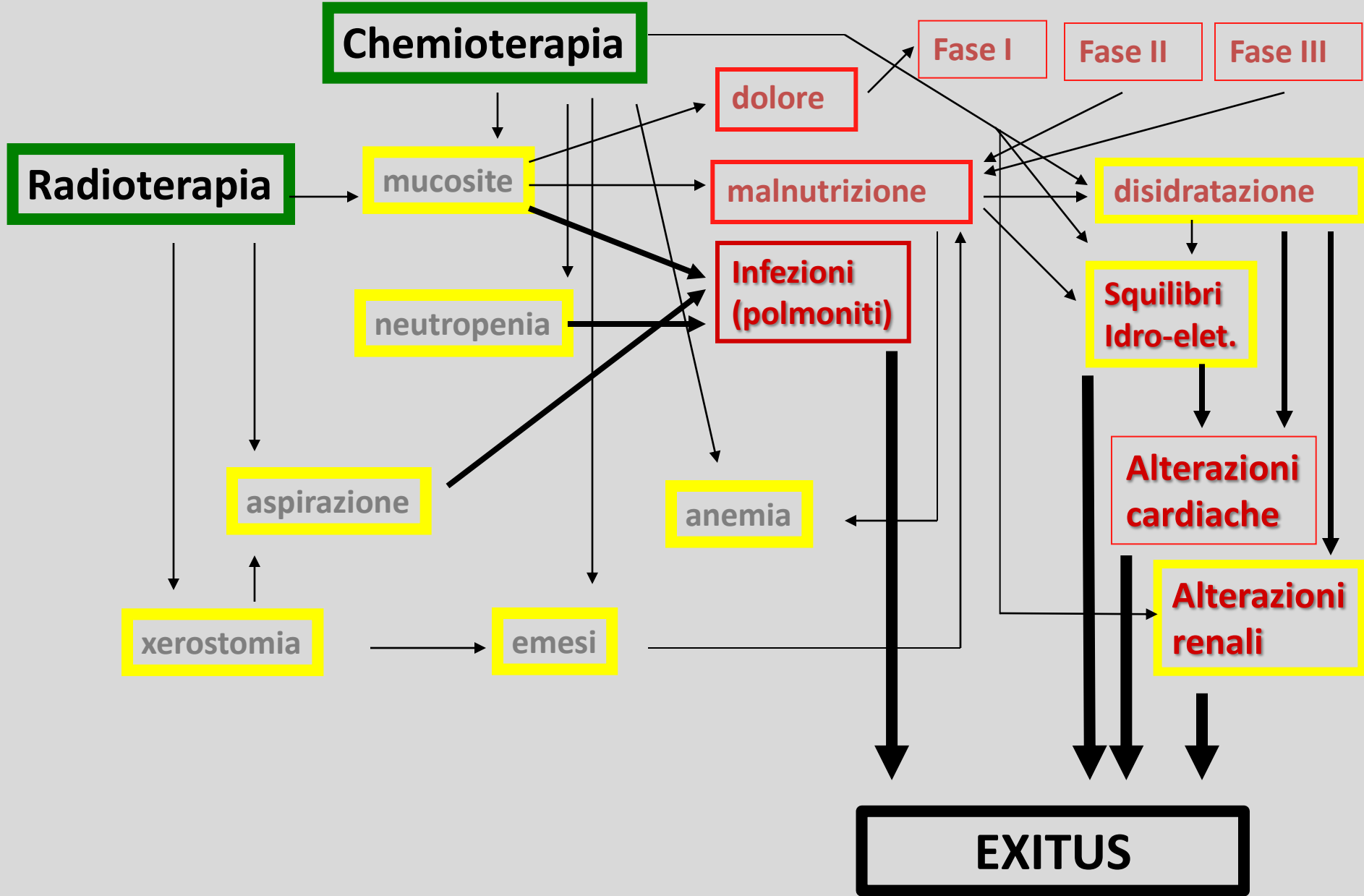
**Attualità nella terapia integrata locoregionale
delle neoplasie delle vie aeree digestive superiori
Taranto 12-14 gennaio 2012**

Attualità in Oncologia Medica

La gestione della tossicità

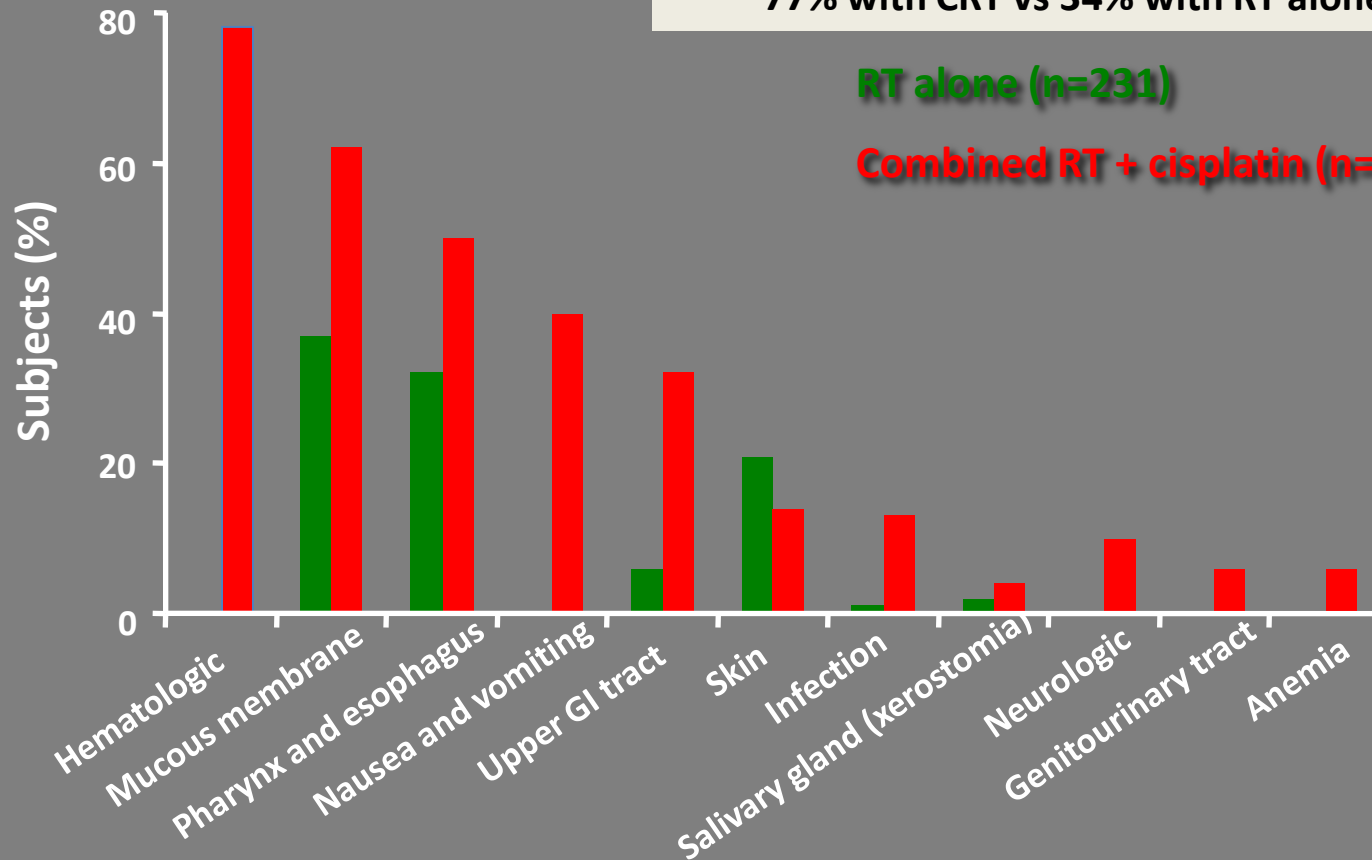
Marco Merlano

ASO S. Croce e Carle



Chemoradiation significantly increases acute toxicity

Acute adverse effects: grade 3 or higher
77% with CRT vs 34% with RT alone (p<0.001)

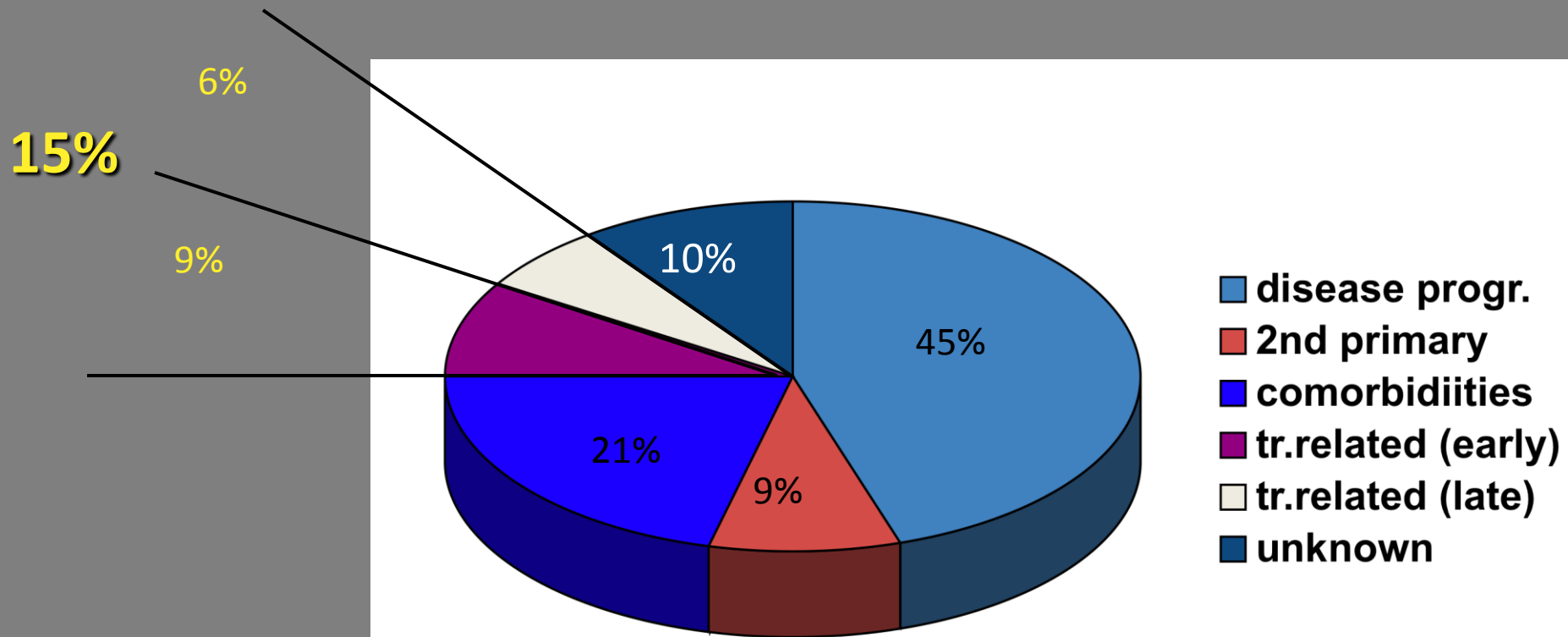


Adelstein DJ et al; J. Clin. Oncol. 2003;21:92-98

The Intergroup trial	Standard radiotherapy	Standard radiotherapy + cisplatin 100mg/m² q 3 wks
All grade III-V toxicities	50%*	90%*
Toxic deaths	2%	4.5%

* = P<0.0001

Chemoradiation: percentage of treatment-related deaths after primary treatment

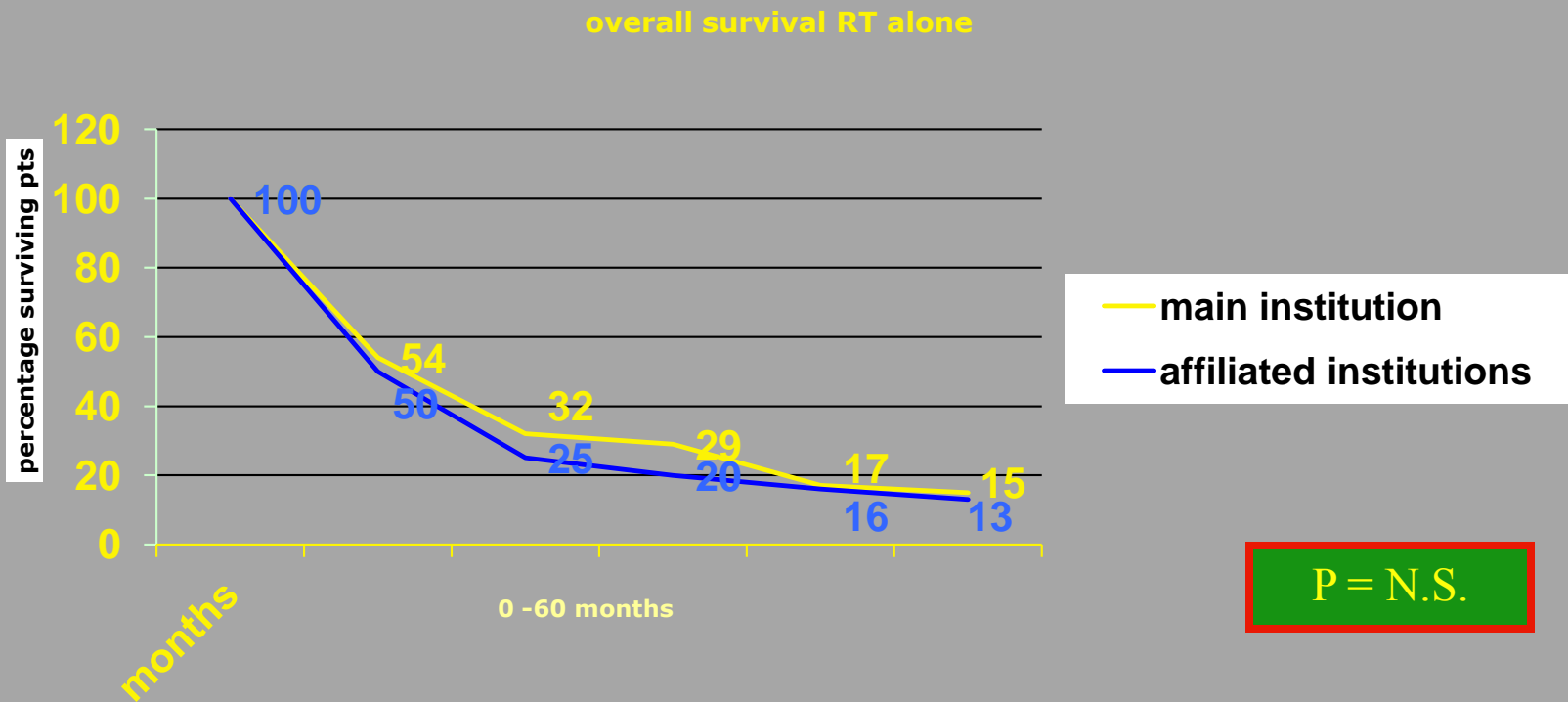


Management of toxicity



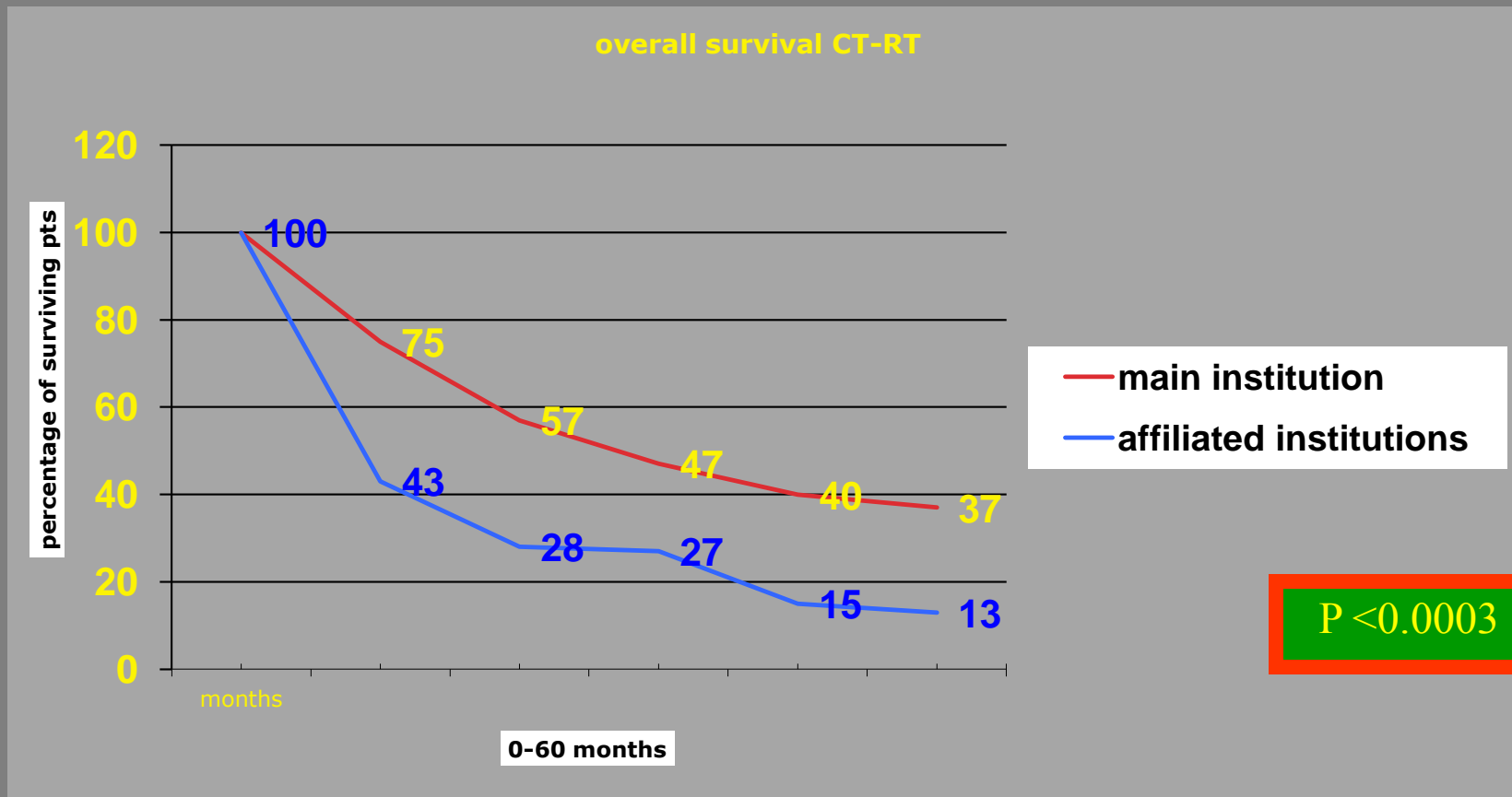
"Impact of the treating institution on the survival of patients with HNC treated with concomitant alternating chemotherapy and radiotherapy"

Benasso M et al: Eur J Cancer 2003;39:1895-1898



"Impact of the treating institution on the survival of patients with HNC treated with concomitant alternating chemotherapy and radiotherapy"

Benasso M et al: Eur J Cancer 2003;39:1895-1898



...and in the daily clinical practice?



Adverse Events Associated with concurrent chemoradiation therapy in patients with head and neck cancer

Givens DJ, Karnell LH, Gupta AK et al

Arch Otolaryngol Head Neck Surg 2009;135:1209-17

104 pts
treated between 2/2000 and 3/2007
< 65 yo 83.7%
≥ 65 yo 16.4%

Oropharynx 69.2%
Larynx 16.3%
Hypopharynx 3.8%

Stage IV 75.0%
Stage III 22.1%

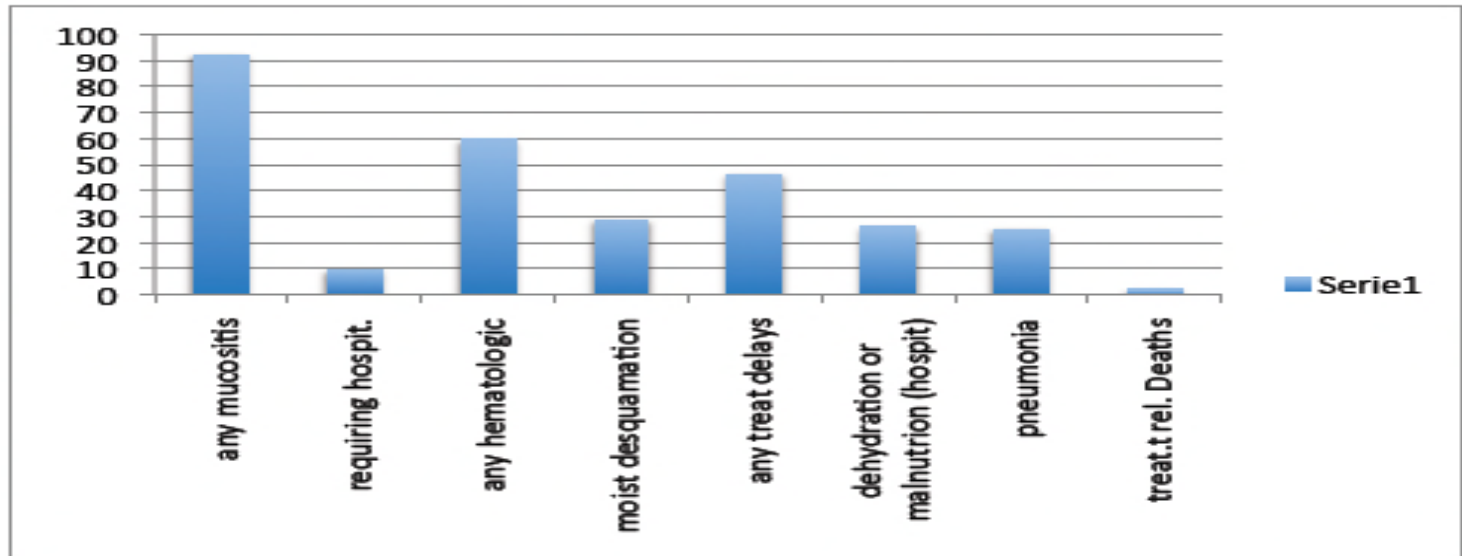
IMRT	85.6%
2D	14.4%
CisPT q 21	60.6%
CisPT weekly	33.7%
Other	5.8%

Adverse Events Associated with concurrent chemoradiation therapy in patients with head and neck cancer

Givens DJ, Karnell LH, Gupta AK et al

Arch Otolaryngol Head Neck Surg 2009;135:1209-17

any mucositis	92,3
requiring hospit.	9,6
any hematologic	59,6
moist desquamatio	28,8
any treat delays	46,2
dehydration or mal	26
pneumonia	25
treat.t rel. Deaths	1,9



The S. Croce General Hospital Experience

317 pts
treated between 11/1997 and 11/2008
< 65 yo 71%
≥ 65 yo 29%

Oropharynx 33.4%
Larynx 19.9%
Hypopharynx 24.6%
Oral cavity 12.6%

T 3-4 68.1%
N 2-3 74.5%

Adjuvant CRT 6.9%
NA-CT -> CRT 10.1%
Bio-RT 8.2%
Altern. CRT 74.8%

HPV-pos 14%
HPV-neg 84%
EGFR 3+ 61.8%
EGFR 0-2+ 38.2%

The S. Croce General Hospital Experience

Safety	Y	O	All pts	P-value
Stomatitis G3	87 (38.8%)	31 (33.3%)	118 (37.2%)	0.356 a
Stomatitis G4	57 (25.4%)	30 (32.3%)	87 (27.4%)	0.216 a
Diarrhoea >G1	7 (3.1%)	4 (4.3%)	11 (3.5%)	0.736 b
Thrombosis	4 (1.8%)	2 (2.2%)	6 (1.9%)	0.567 b
B.W. Loss	7.61% (SD±5.56)	6.66 (SD±4.51)		0.12 c
TPN	71 (31.7%)	38 (40.9%)	109 (34.4%)	0.11 a
PN/EN	8 (3.6%)	1 (1.1%)	9 (2.8%)	0.291 b
Neutropenia G3	45 (20.1%)	21 (22.56%)	66 (20.8%)	0.617 a
Neutropenia G4	23 (10.3%)	9 (9.7%)	32 (10.1%)	0.862 a
Anemia G3	29 (12.9%)	18 (19.4%)	47 (14.8%)	0.143a
Anemia G4	1 (0.4%)	0 (0%)	1 (0.3%)	0.707 b
Infections	35 (15.6%)	26 (28.0%)	61 (19.2%)	0.011 a
Pneumonia	5 (2.2%)	10 (10.8%)	15 (4.7%)	0.002 b
On-treatment deaths	8 (3.6%)	6 (6.5%)	14 (4.4%)	0.366 b

Y, young (age < 65 years); O, old (age ≥ 65 years); TPN, total parenteral nutrition; PN/EN, parenteral and enteral nutrition.

a. Chi square Test; b. Fisher's Test; c. Student's T test

The S. Croce General Hospital Experience

Toxic Death.

Cause	All pts	Y	O
Bleeding	1	1	0
Sepsis	2	1	1
Pneumonia	7	3	4
Sudden Death	4	3	1

p = NS

Y, young (age < 65 years); O, old (age ≥ 65 years)

The S. Croce General Hospital Experience

Treatments Compliance.

Parameter	Y	O	All pts	P-value
Treatment delays \geq 1 week	66 (29.5%)	21 (22.6%)	87 (27.4%)	0.21 a
Not completed treatment	9 (4.0%)	6 (6.5%)	15 (4.7%)	0.38 b
Not completed treatment (including on treatment deaths)	17 (7.6%)	12 (12.9%)	29 (9.1%)	0.20 a

Good treatment compliance:

Yong = 58.9%

Elderly = 61 %

Overall = 58.8%

Bonner 2006

Table 4. Adverse Events.*

Adverse Event	Radiotherapy Alone (N=212)		Radiotherapy plus Cetuximab (N=208)		P Value†	
	All Grades	Grades 3–5	All Grades	Grades 3–5	All Grades	Grades 3–5
	<i>percent of patients</i>					
Mucositis	94	52	93	56	0.84	0.44
Acneiform rash	10	1	87	17	<0.001	<0.001
Radiation dermatitis	90	18	86	23	0.24	0.27
Weight loss	72	7	84	11	0.005	0.12
Xerostomia	71	3	72	5	0.83	0.32
Dysphagia	63	30	65	26	0.68	0.45
Asthenia	49	5	56	4	0.17	0.64
Nausea	37	2	49	2	0.02	1.00
Constipation	30	5	35	5	0.35	1.00
Taste perversion	28	0	29	0	0.83	—
Vomiting	23	4	29	2	0.18	0.42
Pain	28	7	28	6	1.00	0.84
Anorexia	23	2	27	2	0.26	1.00
Fever	13	1	26	1	0.001	1.00
Pharyngitis	19	4	26	3	0.10	0.80
Dehydration	19	8	25	6	0.16	0.57
Oral candidiasis	22	0	20	0	0.63	—
Coughing	19	0	20	<1	1.00	0.50
Voice alteration	22	0	19	2	0.47	0.06
Diarrhea	13	1	19	2	0.11	0.50
Headache	8	<1	19	<1	0.001	1.00
Pruritus	4	0	16	0	<0.001	—
Infusion reaction	2	0	15	3	<0.001	0.01
Insomnia	14	0	15	0	0.89	—
Dyspepsia	9	1	14	0	0.13	0.50
Increased sputum	15	1	13	<1	0.78	0.62
Infection	9	1	13	1	0.28	1.00
Anxiety	9	1	11	<1	0.75	1.00
Chills	5	0	11	0	0.03	—
Anemia	13	6	3	1	<0.001	0.006

* Adverse events that occurred in at least 10 percent of patients in either treatment group are shown, regardless of cause.

† P values were determined with the use of Fisher's exact test.

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Acneiform rash	10	1	87	17	<0.001	<0.001
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b Budach W NEJM 2007



International Journal of Radiation
Oncology*Biology*Physics

Volume 69, Issue 2, 1 October 2007, Pages 638–639



Letters to the Editor

Ultrathin Hydrocolloid Dressing in Skin Damaged From Alternating Radiotherapy and Chemotherapy Plus Cetuximab in Advanced Head and Neck Cancer (G.O.N.O. AlterRCC Italian Trial): In Regard to Macmillan *et al.* (*Int J Radiat Oncol Biol Phys* 2007;68:864–872)

Elvio G. Russi, M.D.

Gruppo Oncologico Nord Ovest, Department of Radiotherapy, General Hospital "S. Croce e Carle", Cuneo, Italy

Marco C. Merlano, M.D.

Gruppo Oncologico Nord Ovest, Department of Oncology, General Hospital "S. Croce e Carle", Cuneo, Italy

Alberto Comino, M.D.

Department of Pathologic Anatomy, General Hospital "S. Croce e Carle", Cuneo, Italy

Gianmauro Numico, M.D.

Gruppo Oncologico Nord Ovest, Department of Radiotherapy, General Hospital "S. Croce e Carle", Cuneo, Italy

Available online 14 September 2007.

Bonner 2010

	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94.3%)	45 (21.2%)	3 (1.4%)	204 (98.1%)	73 (35.1%)	4 (1.9%)
Mucositis/stomatitis†	199 (93.9%)	110 (51.9%)	9 (4.2%)	194 (93.3%)	116 (55.8%)	13 (6.3%)
Dysphagia	134 (63.2%)	63 (29.7%)	3 (1.4%)	136 (65.4%)	54 (26.0%)	1 (0.5%)
Xerostomia‡	150 (70.8%)	6 (2.8%)	0 (0%)	150 (72.1%)	10 (4.8%)	0 (0%)
Acneiform rash§	21 (9.9%)	3 (1.4%)	0 (0%)	174 (83.7%)	35(16.8%)	1 (0.5%)
Infusion reaction¶	4 (1.9%)	0 (0%)	0 (0%)	32 (15.4%)	6 (2.9%)	2 (1.0%)

*Skin reaction includes all Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terms in the Skin and Appendages body system. †Mucositis/stomatitis includes COSTART terms aphthous stomatitis; gingivitis; glossitis; mouth ulceration; mucous membrane disorder; stomatitis; and ulcerative stomatitis. ‡Xerostomia is COSTART term dry mouth. §Acneiform rash includes COSTART terms acne; rash; maculopapular rash; exfoliative dermatitis. ¶Infusion reaction includes COSTART terms allergic reaction; anaphylactoid reaction; and/or fever; chills; or dyspnoea on the first day of treatment. ||Statistically significant ($p < 0.05$) difference between the treatment groups; Fisher's exact test.

Table 2: Most common adverse events

Radiation induced skin toxicity

Pathogenesis:

Ionising Radiation damages mitotic ability of clonogenic cells within the basal layer, thus preventing repopulation and weakening skin integrity.

Moist desquamation occurs when basal layer becomes unable to repopulate in time to replace the damage tissue.

This effect is evident at a cumulative dose of 20-25 Gy and the maximum depletion is observed at 50 Gy.

Factors influencing severity, onset and duration of skin reactions¹

Areas of the body containing skinfolds (such as the neck)

Intrinsic factors

General skin condition (photoaging)

Nutritional status

Age (chronoaging)

Comorbid disease

Ethnicity

Extrinsic factors

Dose

Energy

Fractionation regimen

Combination with chemotherapy

Doxorubicin, MTX, 5Fu, Hyd, BLM, Taxanes
(i.e. those able to induce radiation recall)

EGFr

EGFr activation is the first response to skin injury:

- It is involved in wound healing of the skin**
- Acute disruption of permeability barrier stimulate epidermal proliferation via amphiregulin EGFr activation**
- Sustained EGFr activation is a well established event in response to UVB exposure, and plays a crucial role in UVB induced epidermal hyperplasia**

EGFr plays a role in repair of radiation induced skin damage

“There is clear evidence that EGFR expression increases after RT, and it possibly plays a role as a mechanism for repopulating irradiated areas”

**Application of specific inhibitor of EGFr ligand
greatly retards
re-epithelization by inhibition of keratinocyte migration**

**BLOCKADE OF EGFR SIGNALING DOES NOT INDUCE KERATINOCYTE
CELL DEATH, RATHER, IT ENHANCES SUSCEPTIBILITY TO CELL
DEATH INDUCTION**

**Exacerbates effects of other factors:
Microtrauma, UVB exposition, radiotherapy**

Pastore S et al: The epidermal growth factor receptor system in skin
Repair and inflammation. J. Investigative Dermatol. 2008;128:1365-74

**So, it makes sense that EGFr inhibitors
can exacerbate radiation-induced skin
toxicity interfering with its repair**

But, up to which extent?



Original article

High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: Results of a survey in EORTC institutes

Christian Giro^a, Bernhard Berger^b, Edwin Bölke^a, I. Frank Ciernik^c, Frederic Duprez^d, Laura Locati^e, Sophie Maillard^f, Mahmut Ozsahin^g, Raphael Pfeffer^h, A. Gerry Robertsonⁱ, Johannes A. Langendijk^j, Wilfried Budach^{a,*}

^a Department of Radiation Oncology, University Hospital Düsseldorf, Germany

^b Department of Radiation Oncology, University Hospital Tübingen, Germany

^c Department of Radiation Oncology, Istituto Oncologico della Svizzera Italiana, Switzerland

^d Department of Radiation Oncology, University Hospital Gent, Belgium

^e Department of Medical Oncology, Head and Neck Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

^f Department of Radiation Oncology, Institut Jean Godinot Reims, France

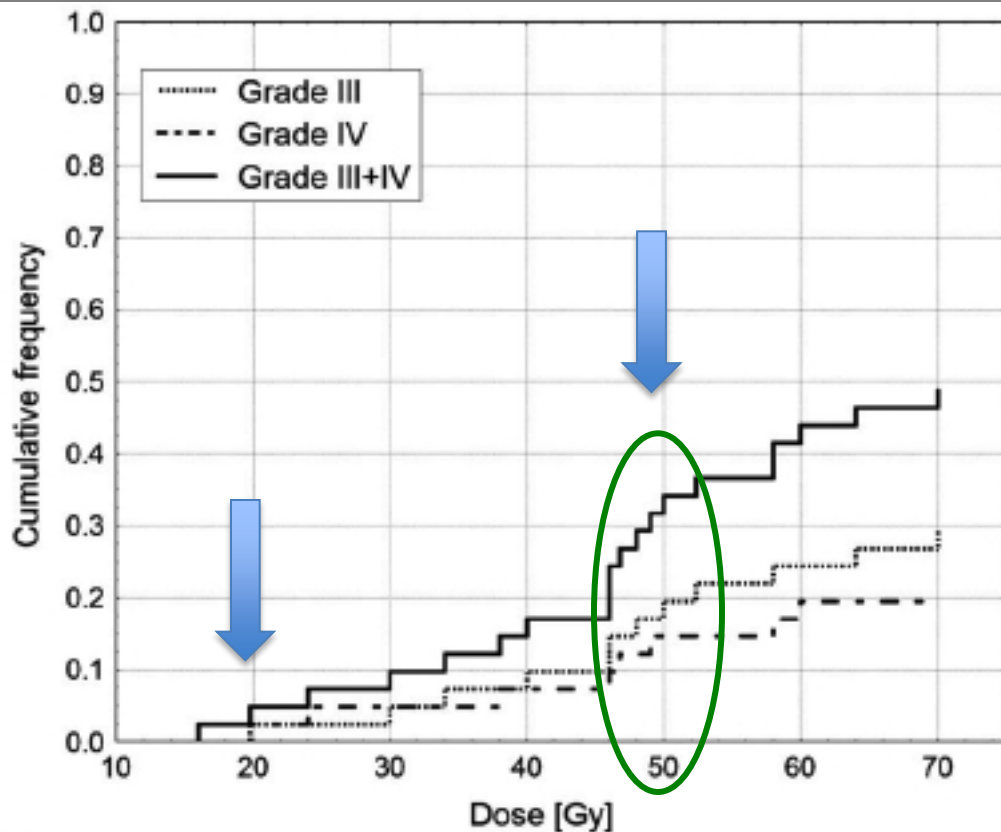
^g Department of Radiation Oncology, University Hospital Lausanne, Switzerland

^h Department of Radiation Oncology, The Chaim Sheba Medical Center, Israel

ⁱ Department of Radiation Oncology, University Hospital North Glasgow, UK

^j Department of Radiation Oncology, University Medical Center Groningen, The Netherlands

**Grade 3/4
incidence:
≈ 49%**





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^a Department of Radiation Oncology, University Hospital Düsseldorf, Germany

^b Department of Radiation Oncology, University Hospital Erlangen, Germany

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^h Department of Radiation Oncology, The Chaim Sheba Medical Center, Israel

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Radiation + cetuximab induced skin toxicity

The lowest total dose at which G 3/4 reactions were observed, were 16 and 20 Gy respectively. The steepest incline was seen between 46 and 54 Gy.

Radiation induced skin toxicity

This effect is evident at a cumulative dose of 20-25 Gy and the maximum depletion is observed at 50 Gy.

Enhanced toxicity with concurrent cetuximab and radiotherapy

In head and neck cancer

David I. Prior, Sandro V. Porceddu, Bryan H. Burmeister et al

Dept Radiation Oncology

Princess Alexandra Hospital

Australia

Radiotherapy Oncology 2008

13 pts: 77% G 3/4 skin reactions

All received standard fractionation RT

6 pts > 70 y.o.

12 pts skin actinic damage

13 unsuitable for CT/RT

AGE

GENERAL SKIN CONDITIONS

CO-MORBIDITIES

Factors influencing severity, onset and duration of skin reactions¹

Areas of the body containing skinfolds (such as head and neck)

Intrinsic factors

General skin condition (photoaging)

Nutritional status

Age (chronoaging)

Comorbid disease

Ethnicity

Extrinsic factors

Dose

Energy

Fractionation regimen

Combination with chemotherapy

Doxorubicin, MTX, 5Fu, Hyd, BLM, Taxanes
(i.e. those able to induce radiation recall)

Increased Risk of High-Grade Dermatologic Toxicities With Radiation Plus Epidermal Growth Factor Receptor Inhibitor Therapy

Ajay Tejwani, MD¹, Shenhong Wu, MD², Yuxia Jia, MD², Mark Agulnik, MD⁴, Laura Millender, MD³, and Mario E. Lacouture, MD⁵

Cancer 2009

site	G 3/4 radio dermatitis	Tot n. of pts	cetuximab	erlotinib	gefitinib	panitumu mab
HNC	98	616	569	29	10	8
Non HNC	0	309	261	48	0	0

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Merlano et al tested cetuximab in combination with alternating chemoradiation in HNSCC in a phase II trial... Eighteen of twenty patients developed a grade III/IV radiation dermatitis during the second course of radiotherapy (22-40 Gy).
...indicates that chemotherapy may further aggravate radiation induced skin toxicity.

Cisplatin-based chemoradiation plus cetuximab in locally advanced head and neck cancer: a phase II clinical study

M. Merlano^{1*}, E. Russi², M. Benasso³, R. Corvò⁴, I. Colantonio¹, R. Vigna-Taglianti², V. Vigo³, A. Bacigalupo⁴, G. Numico⁵, N. Crosetto^{1†}, M. Gasco^{1‡}, C. Lo Nigro^{1‡}, R. Vitiello⁶, S. Violante⁷ & O. Garrone¹

Departments of ¹Medical Oncology; ²Radiation Therapy, S. Croce General Hospital, Cuneo; ³Department of Medical Oncology, La Spezia General Hospital, La Spezia; ⁴Department of Radiation Therapy, National Institute for Cancer Research, Genoa; ⁵Department of Medical Oncology, Aosta General Hospital, Aosta; ⁶Department of Otorhinolaryngology; ⁷Clinical Trials Office, Department of Medical Oncology, S. Croce General Hospital, Cuneo, Italy

Received 2 December 2009; revised 11 March 2010; revised 7 May 2010; accepted 21 June 2010

Table 2. Treatment responses and toxicities

Response	45 evaluable patients					
Objective response rate, %	91.1%					
CR, <i>n</i> (%)	32 (71.1)					
PR, <i>n</i> (%)	9 (20)					
Failures, <i>n</i> (%)	4 (8.9)					
Grade	0	1	2	3	4	Total
Relative frequencies of observed acute toxic effects						
Haematological toxic effects, <i>n</i> (%)						
Leukopenia	12 (27)	1 (2)	14 (31)	17 (38)	1 (2)	45
Neutropenia	12 (27)	1 (2)	14 (31)	15 (33)	3 (7)	45
Grade 3–4 with fever				8	8	
Anaemia	13 (29)	12 (27)	16 (35)	4 (9)	0	45
Thrombocytopenia	26 (58)	5 (11)	7 (16)	6 (13)	1 (2)	45
Non-haematological toxic effects, <i>n</i> (%)						
Stomatitis	2 (4)	3 (7)	11 (24)	13 (29)	16 (36)	45
Dysphagia	38 (84)	0	4 (9)	3 (7)	0	45
Radiodermatitis	0	1 (2)	11 (24)	33 (74)	0	45
C225-induced rash	37 (82)	3 (7)	2 (4)	3 (7)	0	45
Diarrhoea	34 (76)	4 (9)	3 (7)	4 (9)	0	45
Alopecia	30 (67)	10 (22)	4 (9)	1 (2)	0	45
Peripheral neuropathy	44 (98)	1 (2)	0	0	0	45
Fatigue	6 (13)	18 (40)	20 (44)	1 (2)	0	45
Worse non-haematological toxicity					Stomatitis	
Worse overall toxicity					Stomatitis	

METHODS

TREATMENT

RAPIDLY ALTERNATING CT/RT⁽¹⁾ COMBINED WITH C-mab

Weeks	1	2	3	4	5	6	7	8	9	10	
Chemotherapy	↑↑↑↑↑	-----	-----	-----	↑↑↑↑↑	-----	-----	-----	↑↑↑↑↑	-----	-----
Radiotherapy	-----	↑↑↑↑↑	↑↑↑↑↑	-----	-----	↑↑↑↑↑	↑↑↑↑↑	-----	-----	↑↑↑↑↑	↑↑↑↑↑
C-mab	↑-----	↑-----	↑-----	↑-----	↑-----	↑-----	↑-----	↑-----	↑-----	↑-----	↑-----

Chemotherapy: cisplatin, 20 mg/m²/die, days 1 to 5; fluorouracil bolus i.v., 200 mg/m²/die, days 1 to 5

Radiation: 200 cGy/die, 1 fraction per day, 5 fractions per week

C-mab: day 1 of each treatment week; 400mg/m² followed by 250mg/m² weekly during the whole treatment

(1): Merlano M. et al, J.Natl.Cancer Inst. 1996



MAJOR TOXICITIES - LOCAL SKIN TOXICITY



At 36 Gy



At 52 Gy



1 wk after
Treatment end



7 wks after
Treatment end

CONCLUSIONS

- *The combination of c-mab and alternating CT/RT adds an UNEXPECTED SKIN TOXICITY IN THE IRRADIATED FIELD (LOCAL SKIN TOXICITY) which is different from the c-mab induced skin rash*
- **THE LOCAL SKIN TOXICITY COMPLETELY RECOVERS AT THE END OF THE TREATMENT, CAN BE EFFICACIOUSLY MANAGED AND DOES NOT SIGNIFICANTLY IMPACT WITH TREATMENT FEASIBILITY⁽¹⁾**
- *A possible negative interaction among RADIATION, FLUOROURACIL AND C-mab AT SKIN LEVEL, could account for the observed local skin toxicity.*
- *ACTIVITY: the response rate achieved, overcomes the statistical hypothesis (32 instead of 26 CRs required).*

1) Russi EG et al: Ultrathin hydrocolloid dressing in skin damaged from Alternating Radiotherapy and Chemotherapy plus Cetuximab in advanced head and neck cancer (G.O.N.O. AlteRCC italian trial). Int. J. Radiat. Oncol. Biol. Phys.2007 [letter]



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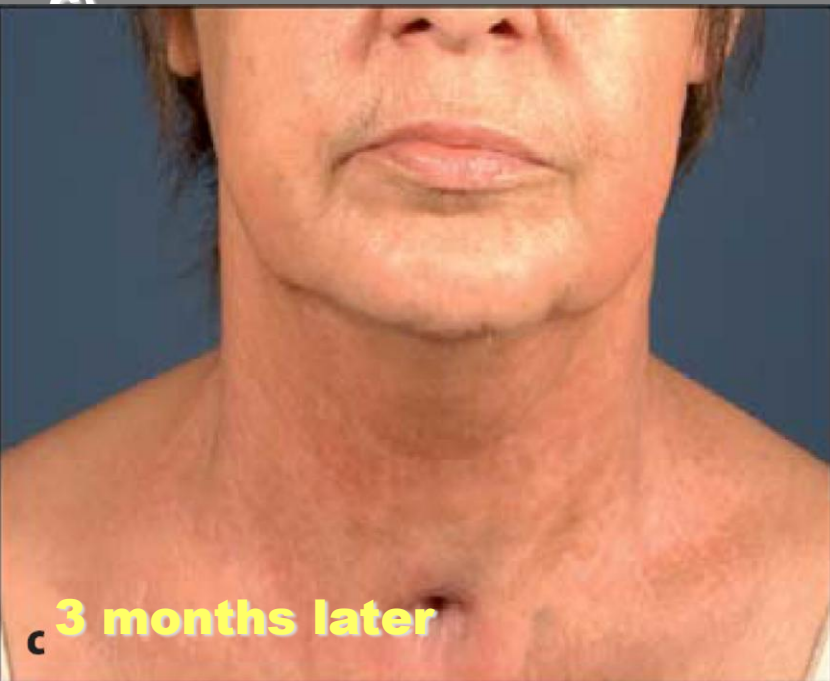
CT- CAE v3.0

Radiotherapy and chemoradiation skin toxicity grading

3	4
<p>Moist desquamation other than skin folds and creases; <u>bleeding induced by minor trauma</u> or abrasion</p>	<p>Skin necrosis or ulceration of <u>full thickness dermis</u>; <u>spontaneous bleeding</u> from involved site</p>



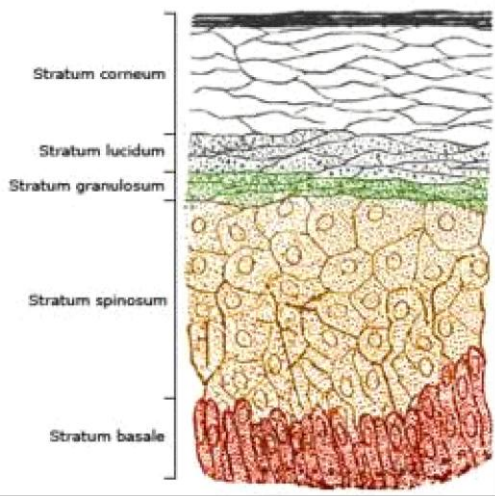
A completely healed skin without disfiguring scars in the damaged area.



A completely healed skin without disfiguring scars in the damaged area.

**SHOCKING ASPECT
AND G 4 SKIN TOXICITY
ARE NOT THE SAME**

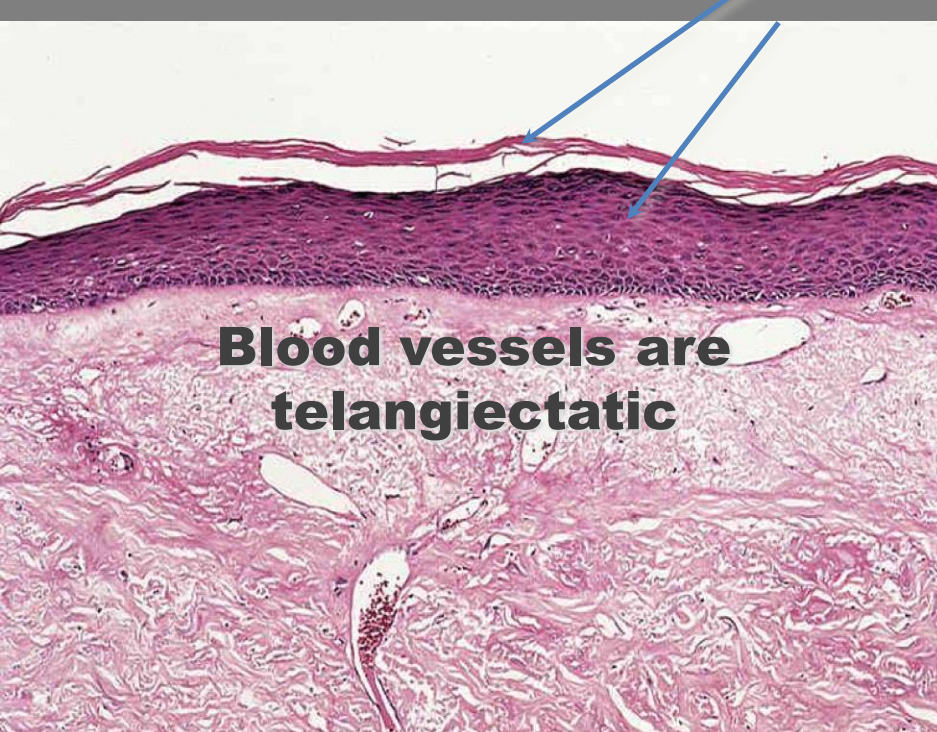
Histopathology



Normal epidermis

Loss of stratum corneum
Thinning of the epidermis

Interruption of the epidermis for limited necrosis of the epidermis



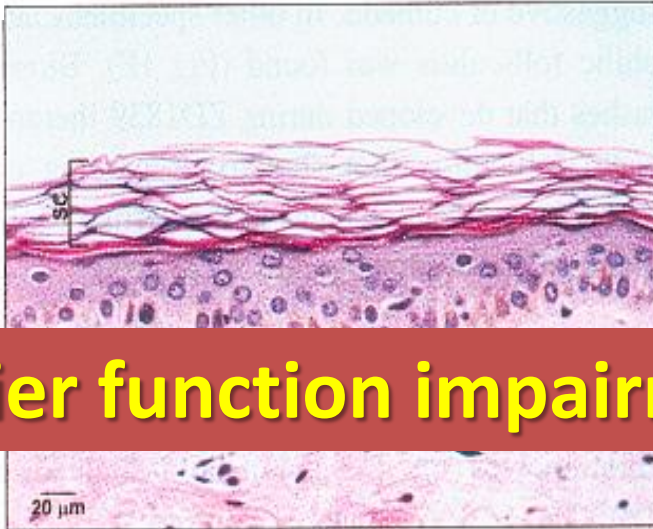
Traditional radio-dermatitis



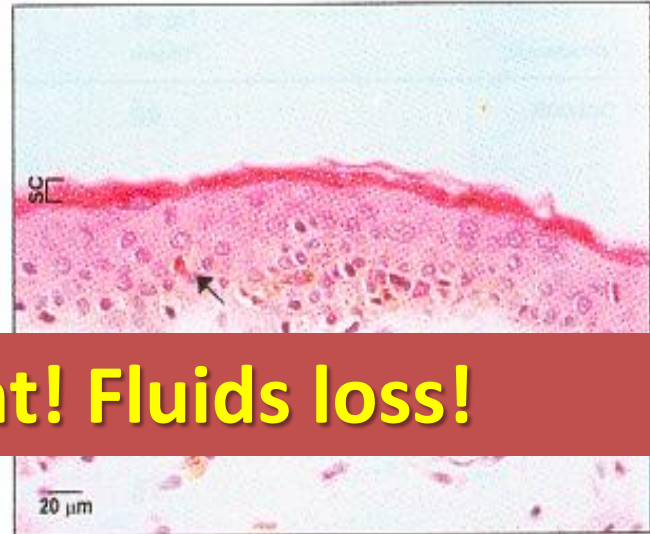
radio-dermatitis (AlteRCC)

Cellules apoptiques

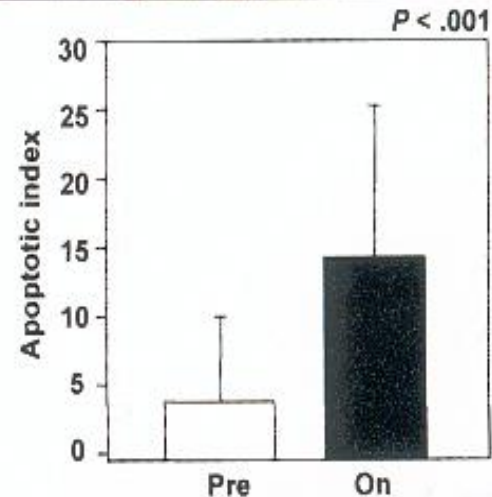
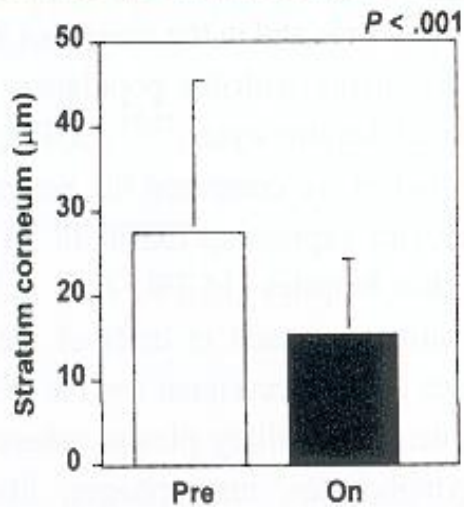
Pre-ZD1839



On-ZD1839



Barrier function impairment! Fluids loss!



(Albanell, 2002)

MANAGEMENT
Holy Cross Gen Hosp
experience

Prevent xerosis and continuous rubbing



- Since first radiotherapy fractions
 - reduce skin trauma, protecting the neck from continuous rubbing with soft linen or cotton
 - use non-perfumed emollients on the xerotic intact skin

When crusty exudates appear



- Debridement using hydrogel,



The effects on pain and activity of daily living caused by crusted exudation in patients with head and neck cancer treated with cetuximab and radiotherapy

**Elvio G. Russi • Marco C. Merlano • Gianmauro Numico • Renzo Corvò •
Marco Benasso • Riccardo Vigna-Taglianti • Antonella Melano • Nerina Denaro •
Stefano Pergolizzi • Ida Colantonio • Francesco Lucio • Rodolfo Brizio •
Umberto Ricardi**

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When crusty exudates appear



- ...protect injured cutis with Hydrocolloid or Hydrofibers

Protect injured cutis with Hydrocolloid or Hydrofibers



Medications with advanced dressings

- **Hydrocolloid**

- carboxymethylcellulose in self-adhesive, biocompatible and hydratable polymeric matrix

- **Hydrofibers**

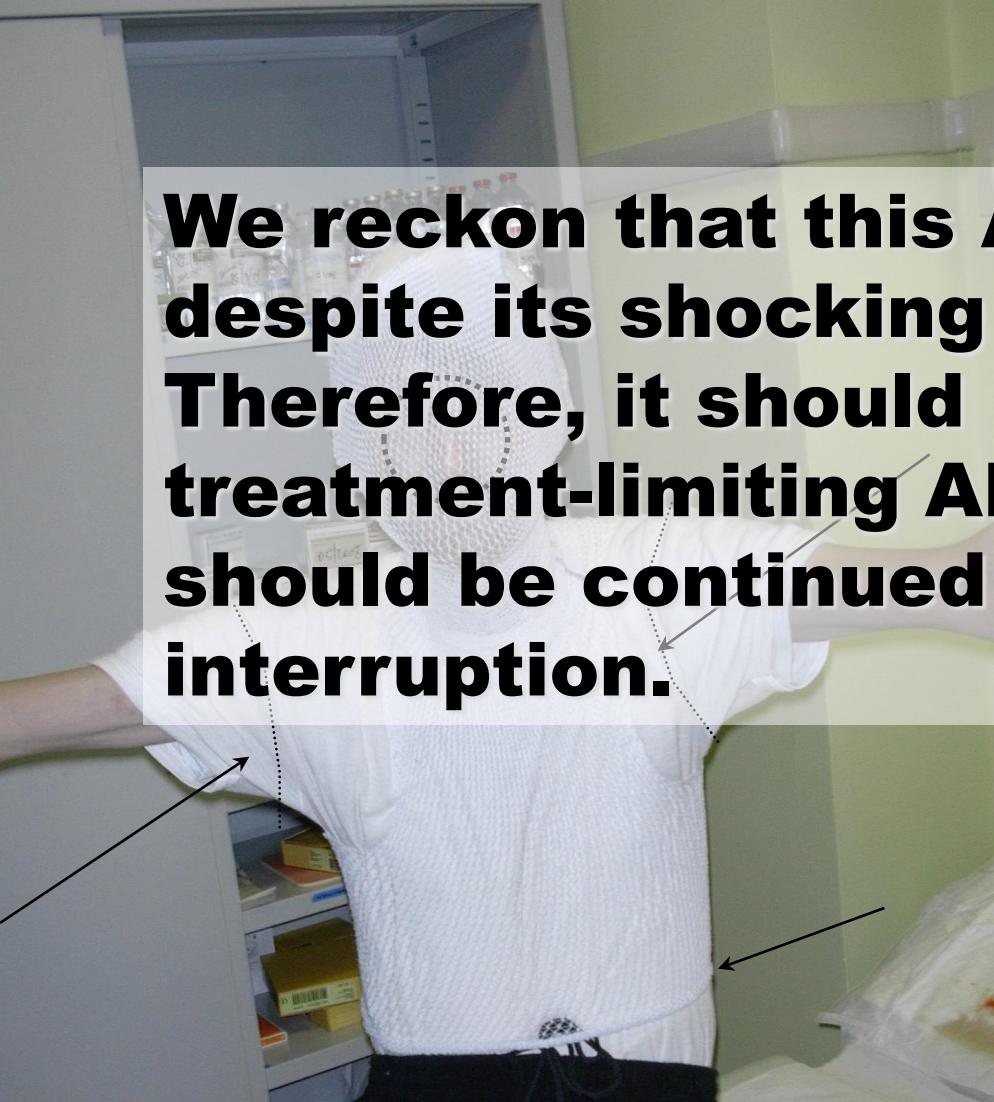
- carboxymethylcellulose



The transformation in gel of carboxymethylcellulose reduces the rubbing and the pain from cutaneous fold movements in the neck.

Avoid the use of patches

We reckon that this AE is manageable, despite its shocking aspect. Therefore, it should not be a treatment-limiting AE and therapies should be continued without interruption.



Thank you

