



Associazione Italiana di Radioterapia Oncologica

Gruppo Regionale Tre Venezie



**TOSSICITA' E TERAPIE DI
SUPPORTO NEI TRATTAMENTI
DEI TUMORI DEL CAPO COLLO**

TREVISO 30 GENNAIO 2015

Il problema della tossicità
nei trattamenti combinati e
loro impatto sulla qualità di
vita dei pazienti.

Elvio G. Russi

Radioterapia Cuneo

DICHIARAZIONE

Relatore: Elvio G. Russi

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Merck Serono)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro



Main topics

- Patogenesi e gestione delle tossicità
- Misurazione delle tossicità
- Inferenza delle tossicità sulla QoL



Non-cancer related causes of Death

The main types of toxicity-related causes of death:

- ✓ **Acute toxicity**
- ✓ **Long term toxicity**
- ✓ **High rate of late mortality**
 - ✓ **(Intercurrent deaths)**



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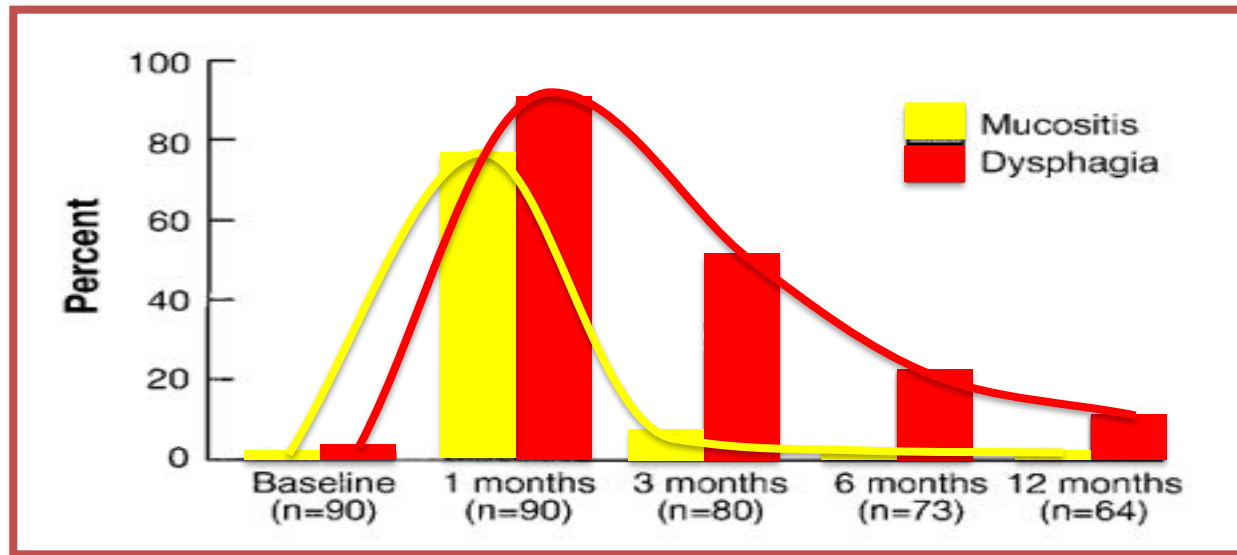
✓ **Long term toxicity**

✓ **High rate of late mortality**

✓ **(Intercurrent deaths)**



Dysphagia, mucositis



- ✓ Feeding-tube dependence
- ✓ Chronic aspiration

Long term Treatment-related Deaths

	N. Death	%
Late deaths (>6 months)	12	3.7%
Surgical complications	4	33%
Carotid "blow out"	2	17%
Endocarditis	1	8%
Pneumonia	1	8%
Laryngeal necrosis/pneumonia	1	8%
Renal failure	1	8%
Bleeding	1	8%
Unknown	1	8%

*Chronic inflammation
and
fibrosis*

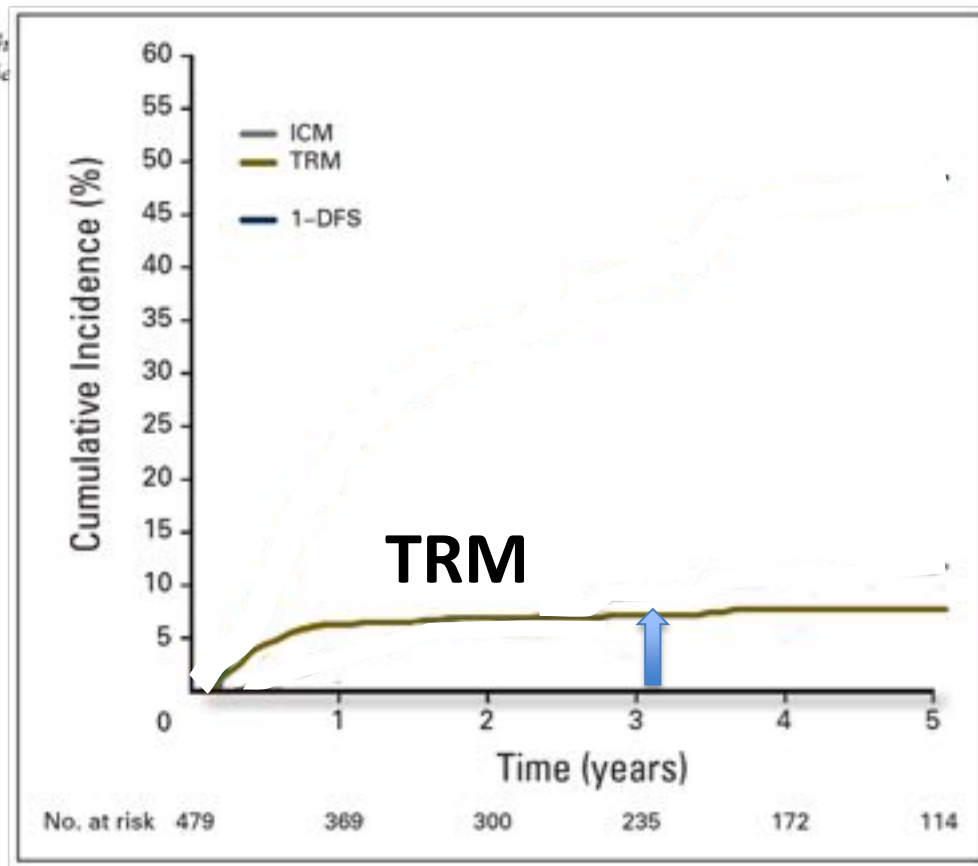


Predictors of Competing Mortality in Advanced Head and Neck Cancer

Loren K. Mell, James J. Dignam, Joseph
Amit D. Bhate, Mary Ellyn Witt, Daniel
and Ralph R. Weichselbaum

479 pts, HN stage III-IV

**Treatment-related
mortality (TRM)**



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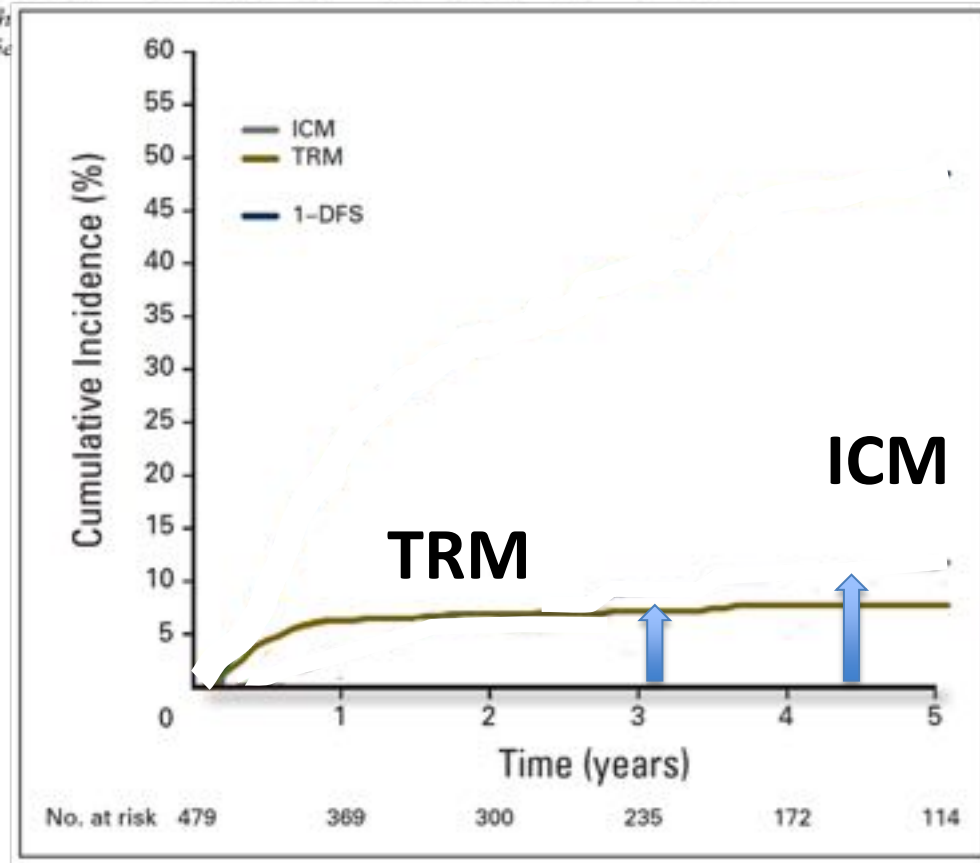
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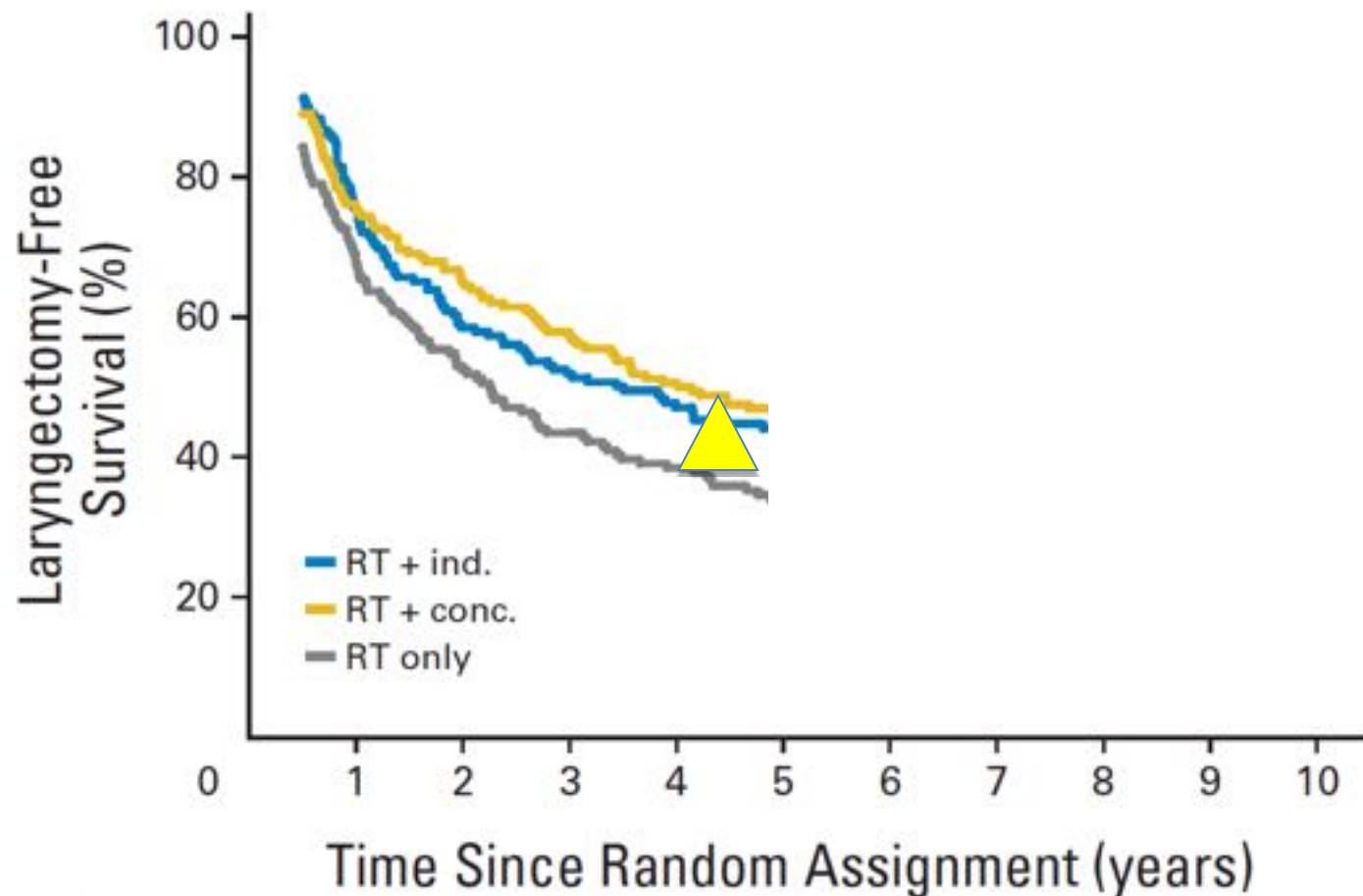
Treatment-related mortality (TRM)

Inter-Current Mortality



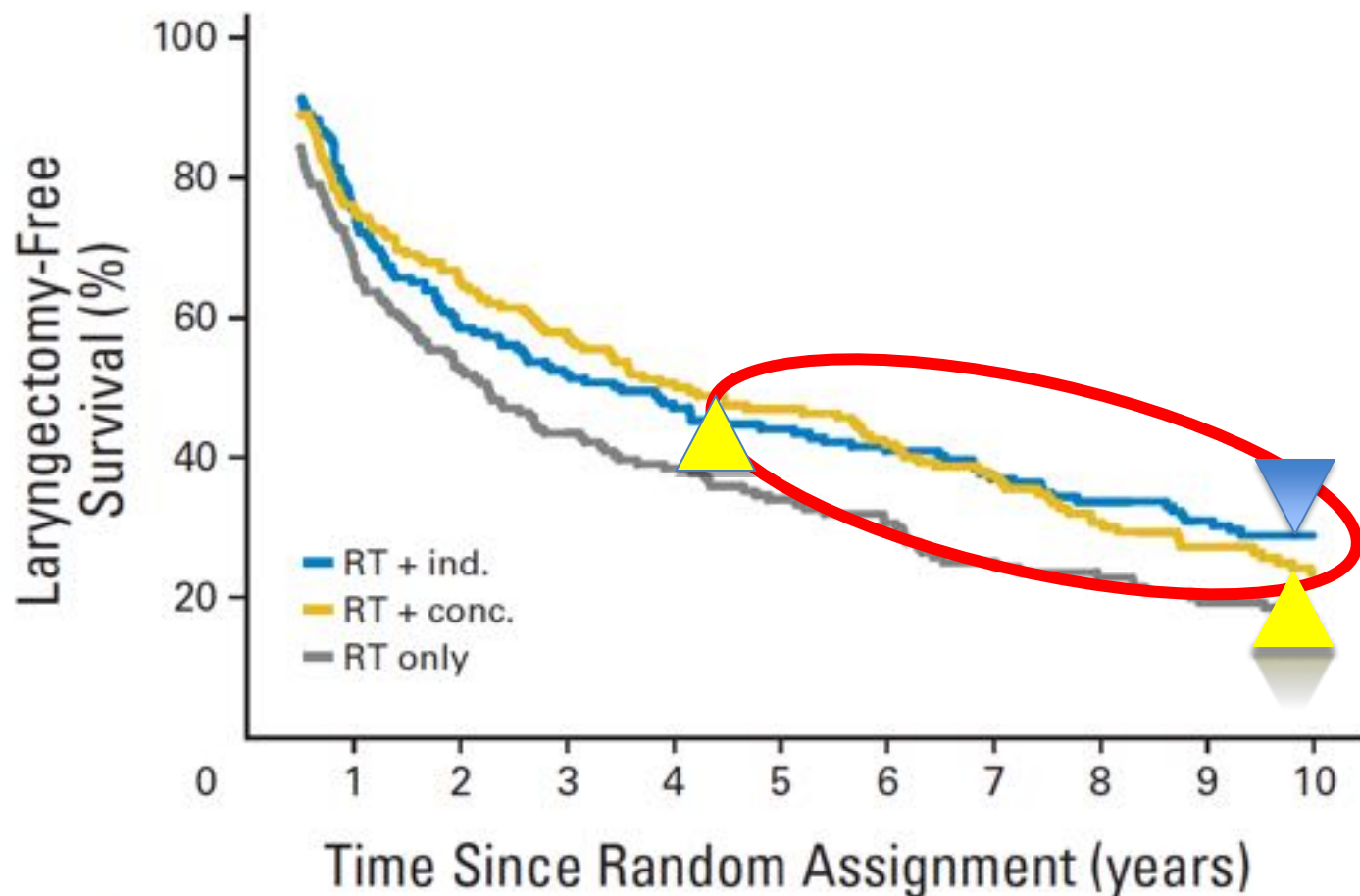
Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

Arlene A. Forastiere, Qiang Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak, William Morrison, Bonnie Glisson, Andy Trotti, John A. Ridge, Wade Thorstad, Henry Wagner, John F. Ensley, and Jay S. Cooper



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non-cancer related causes of Death

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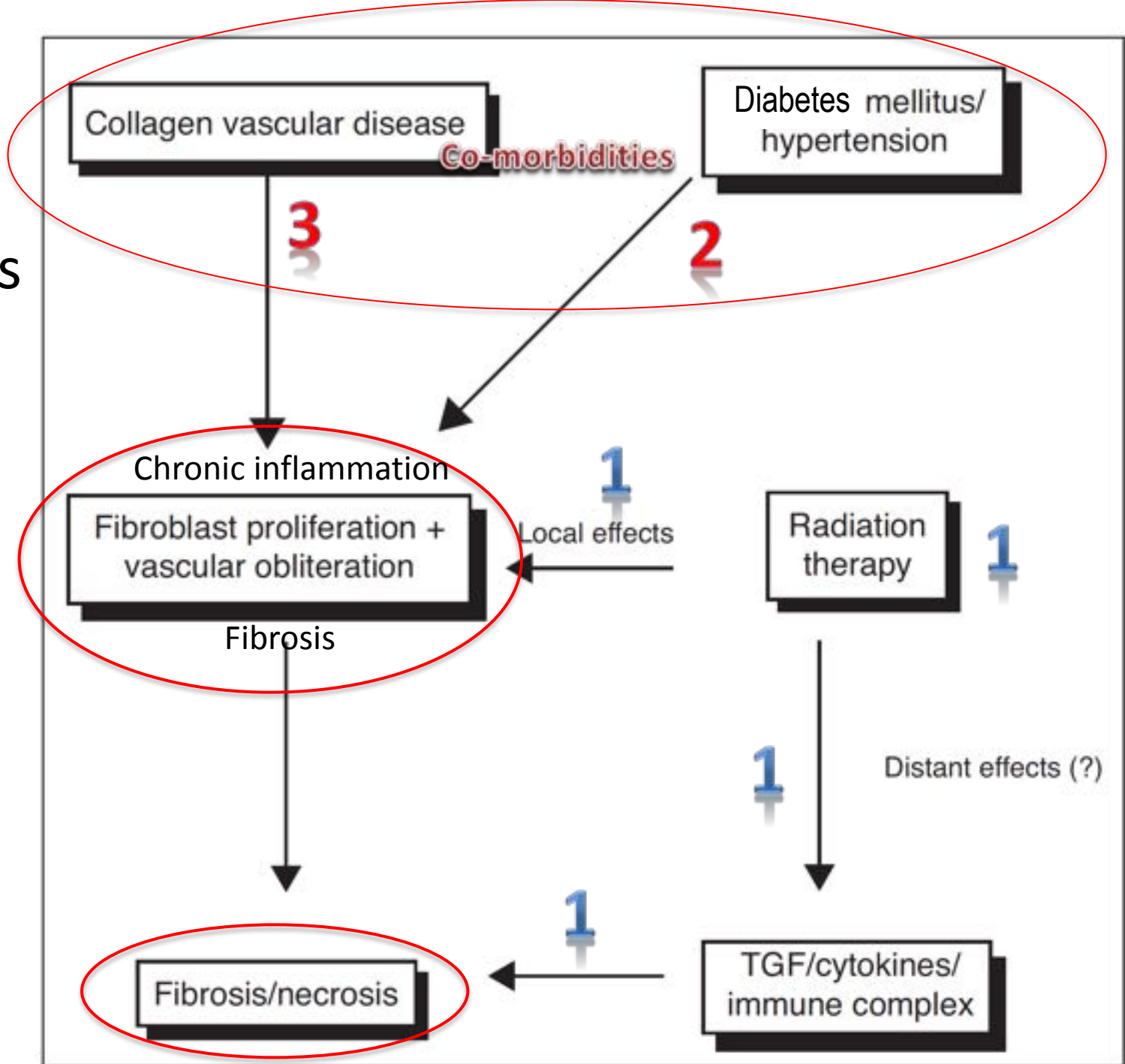
✓ **Long term toxicity**

✓ **High rate of late mortality**

→ (predisposing co-factors and/or co-morbidity?)



Co-Factors
and Late
damages



The Incidence and Impact of Comorbidity Diagnosed After the Onset of Head and Neck Cancer

Katherine C. Yung, MD; Jay F. Piccirillo, MD

Table 3. Prognostic Impact of Comorbidity Scores

Comorbidity Score at Diagnosis	Comorbidity Score at Last Follow-up		
	None	Mild	Moderate
None			
HR (95% CI)	1.0	1.4 (0.4-5.3)	1.7 (0.4-6.7)
No. (%)	30 (16.4)	8 (4.4)	7 (3.8)
Mild			
HR (95% CI)		2.6 (1.1-6.2)	2.7 (0.8-8.9)
No. (%)	0	38 (20.8)	6 (3.3)
Moderate			
HR (95% CI)		2.0 (0.4-9.4)	2.8 (1.2-6.8)
No. (%)	0	6 (3.3)	30 (16.4)
Severe			
HR (95% CI)			
No. (%)		0	
Total, No. (%)		52 (28.4)	

10.4%
at diagnosis

23.5%
at last follow up

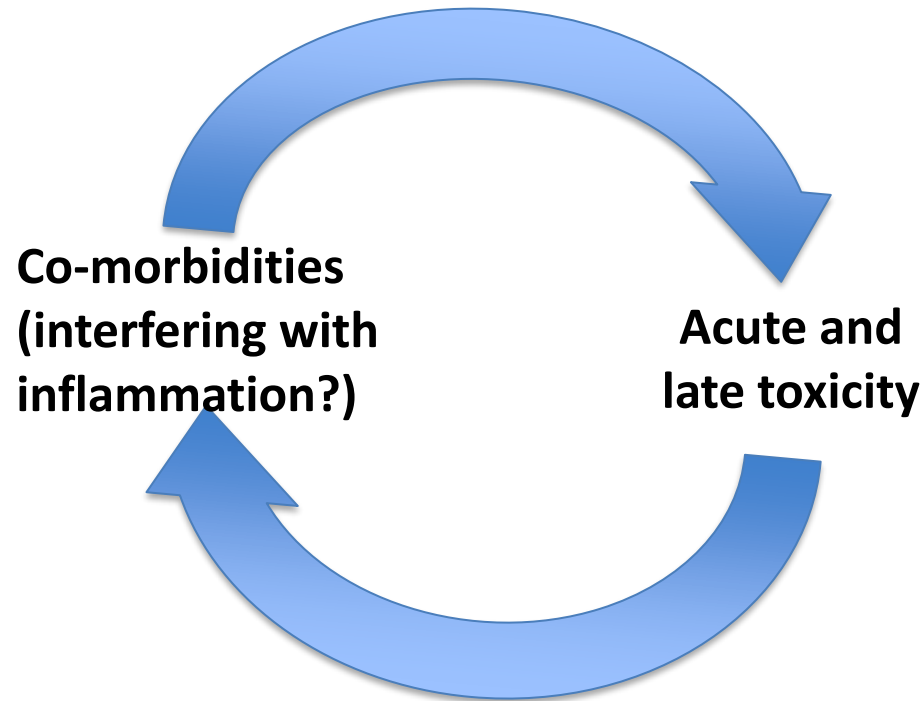
1. Co-morbidity at diagnosis is strongly correlated with prognosis

2 the increase of co-morbidity at last follow-up may be a result of treatment itself

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aBecause of rounding, percentages may not total 100.

“Vicious circle” between co-morbidities and toxicities



Dermatitis
Dysphagia

S.I.R.S

Renal Failure
Fatigue

Sepsis

Pneumonia
Weight-loss

Endocarditis

Aspiration
Mucositis

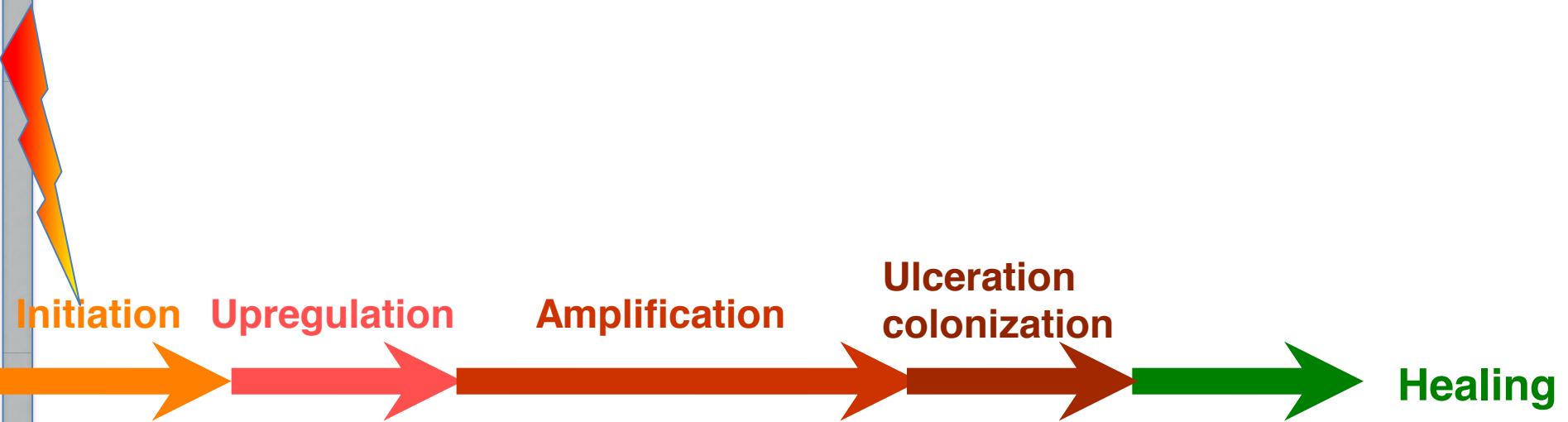
Comorbidity

They share the same pathogenetic basis:
e.g. Local and Systemic inflammation?

THE PATHOBIOLOGY OF MUCOSITIS

Stephen T. Sonis





Local effects

Intracellular or
Intercellular
signalling



Review Article

Local and Systemic Pathogenesis and Consequences of Regimen-Induced Inflammatory Responses in Patients with Head and Neck Cancer Receiving Chemoradiation

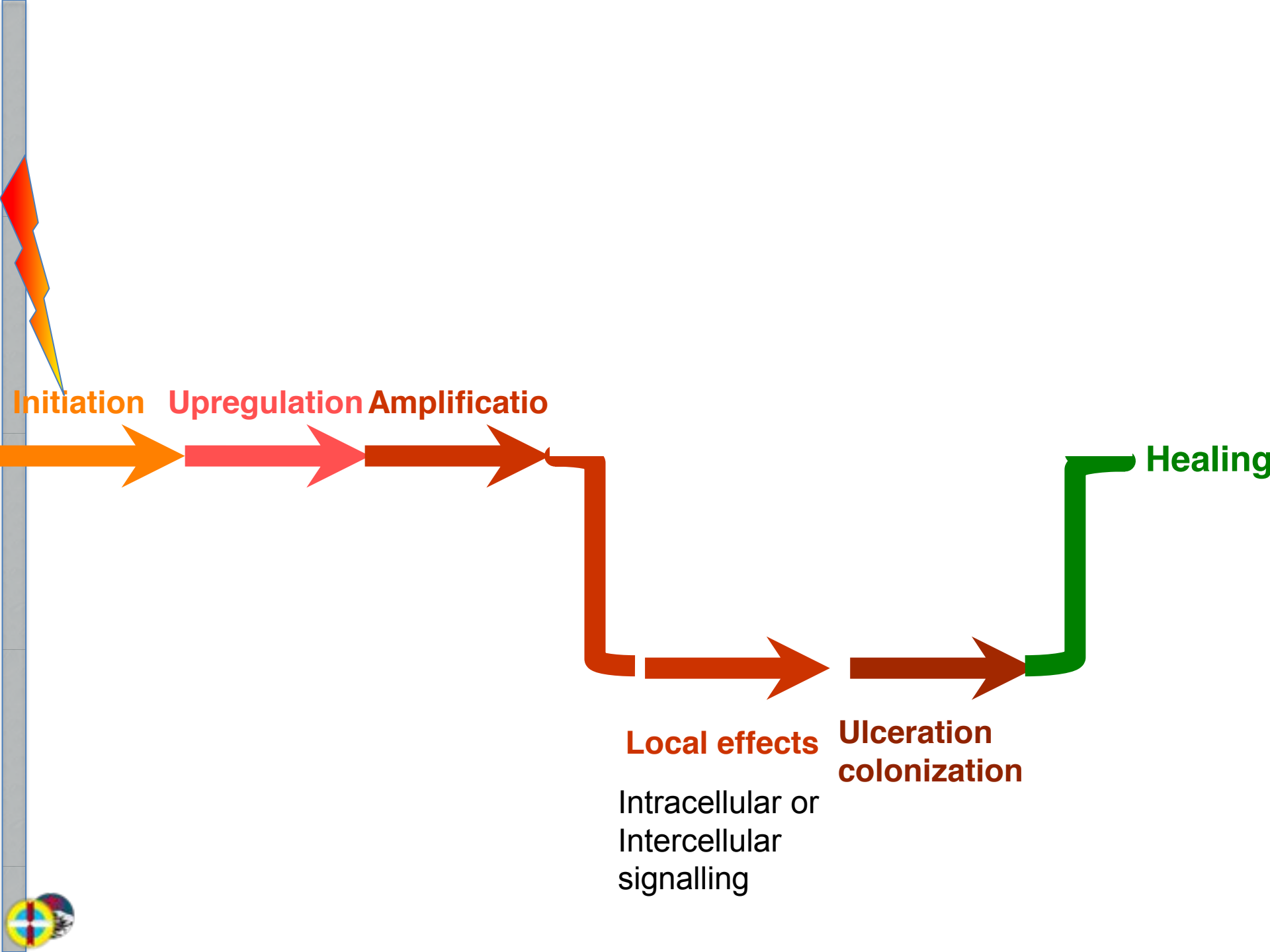
Elvio G. Russi,¹ Judith E. Raber-Durlacher,² and Stephen T. Sonis³

¹ *Department of Radiation Oncology, University Teaching Hospital A.O. "S. Croce e Carle", Via M. Coppino 26, 12100 Cuneo, Italy*

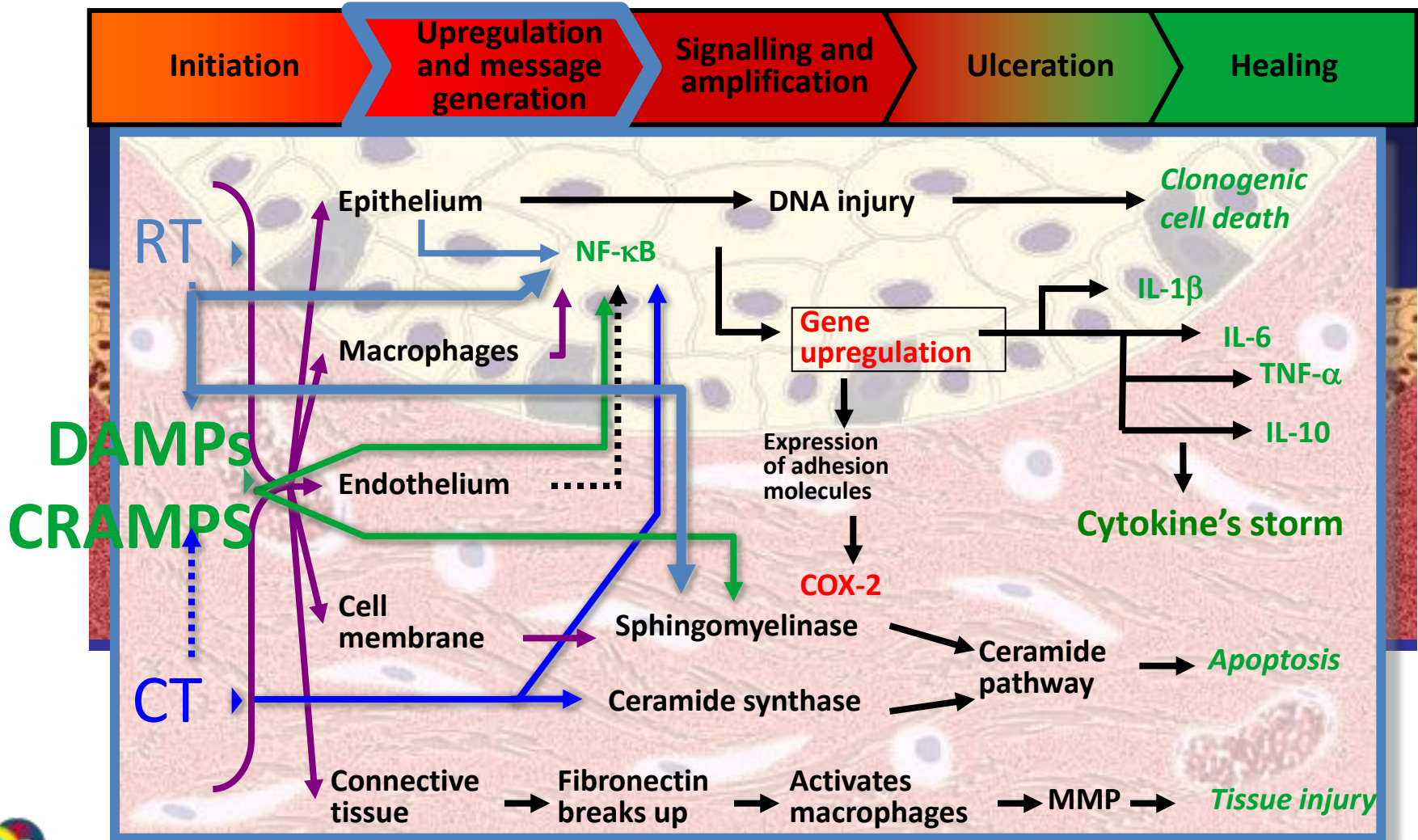
² *Department of Oral and Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Gustav Mahlerlaan 3004, 1081 LA Amsterdam, The Netherlands*

³ *Division of Oral Medicine, Brigham and Women's Hospital and the Dana-Farber Cancer Institute and Biomodels, LLC, 75 Francis Street, Boston, MA 02115, USA*

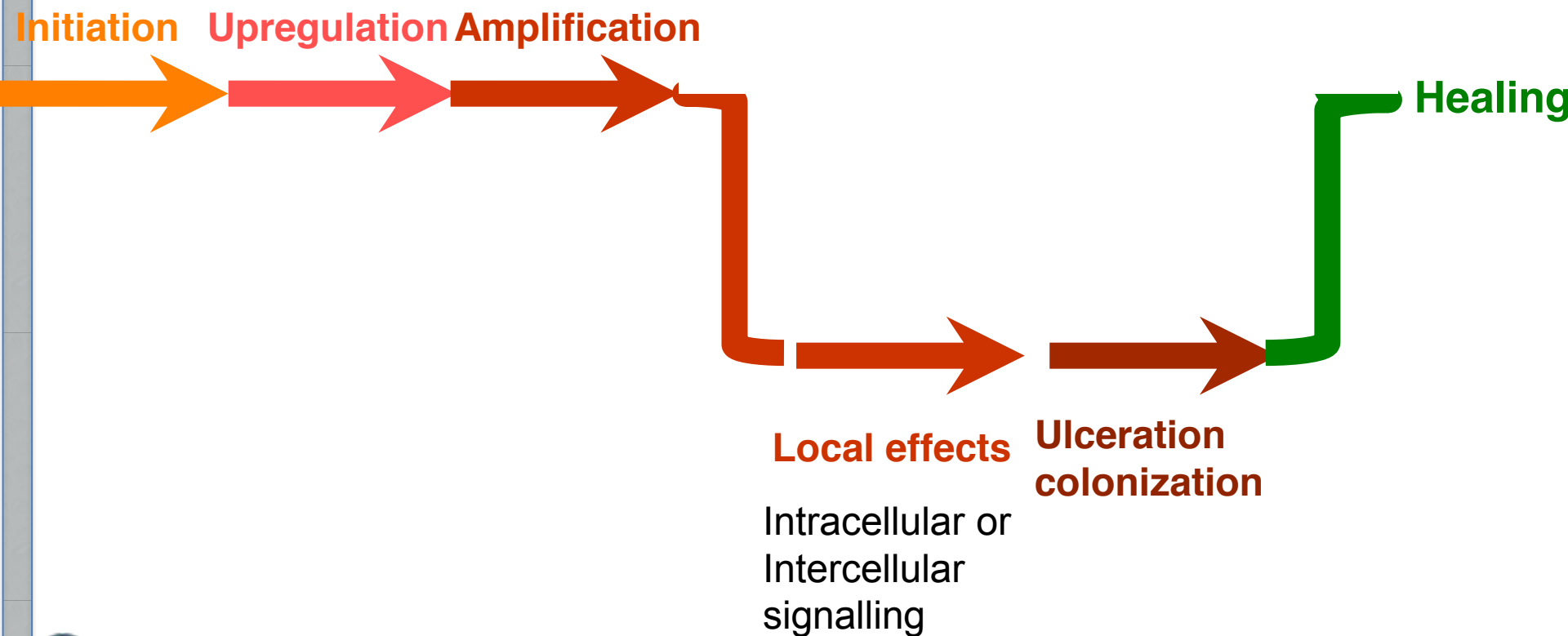
Correspondence should be addressed to Elvio G. Russi; elviorussi@gmail.com



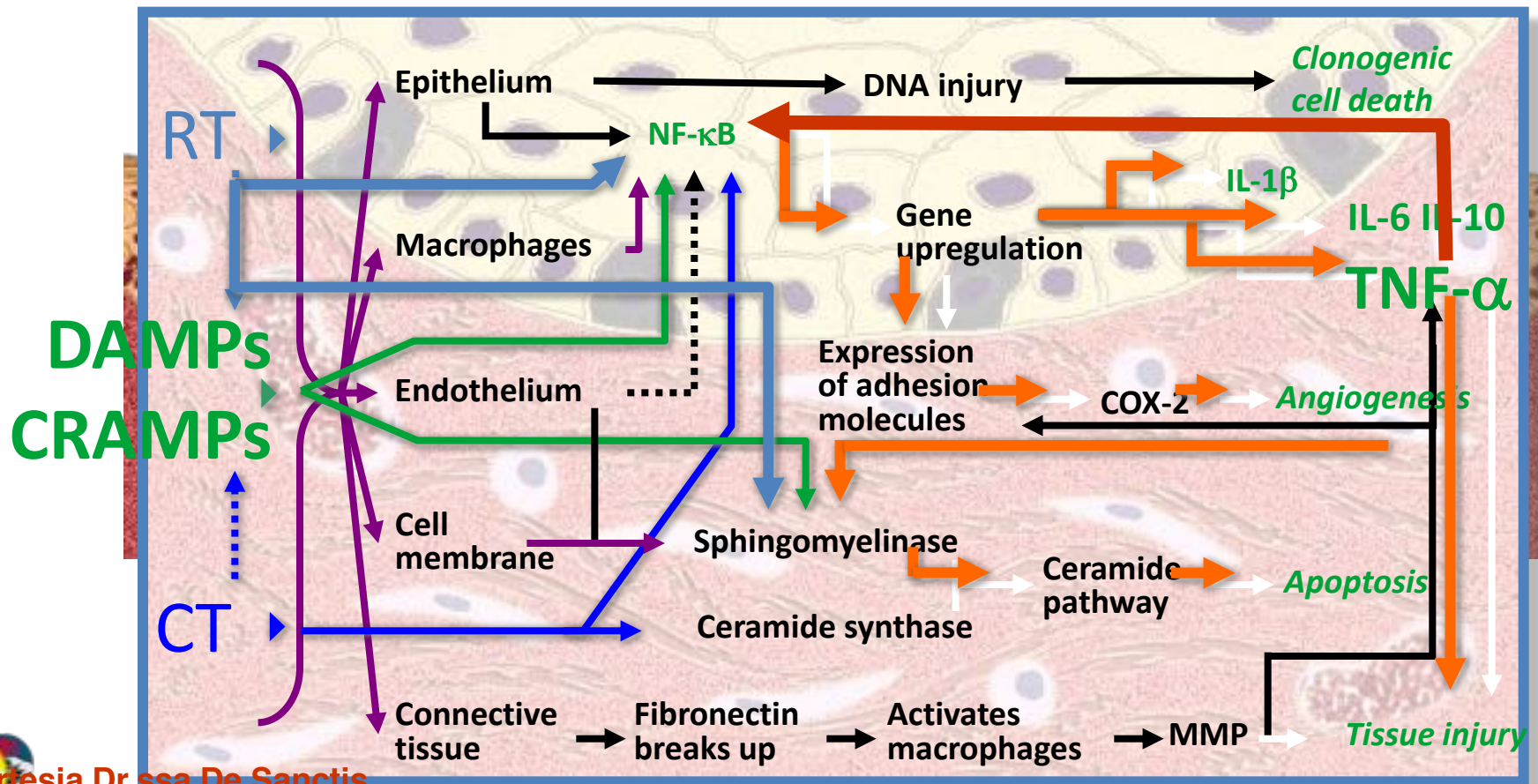
Simultaneous biological events in all tissues



MMP = matrix metalloproteinase; COX-2 = cyclo-oxygenase-2



Biological Cross-talk and signal amplification



Local toxicities

dermatitis

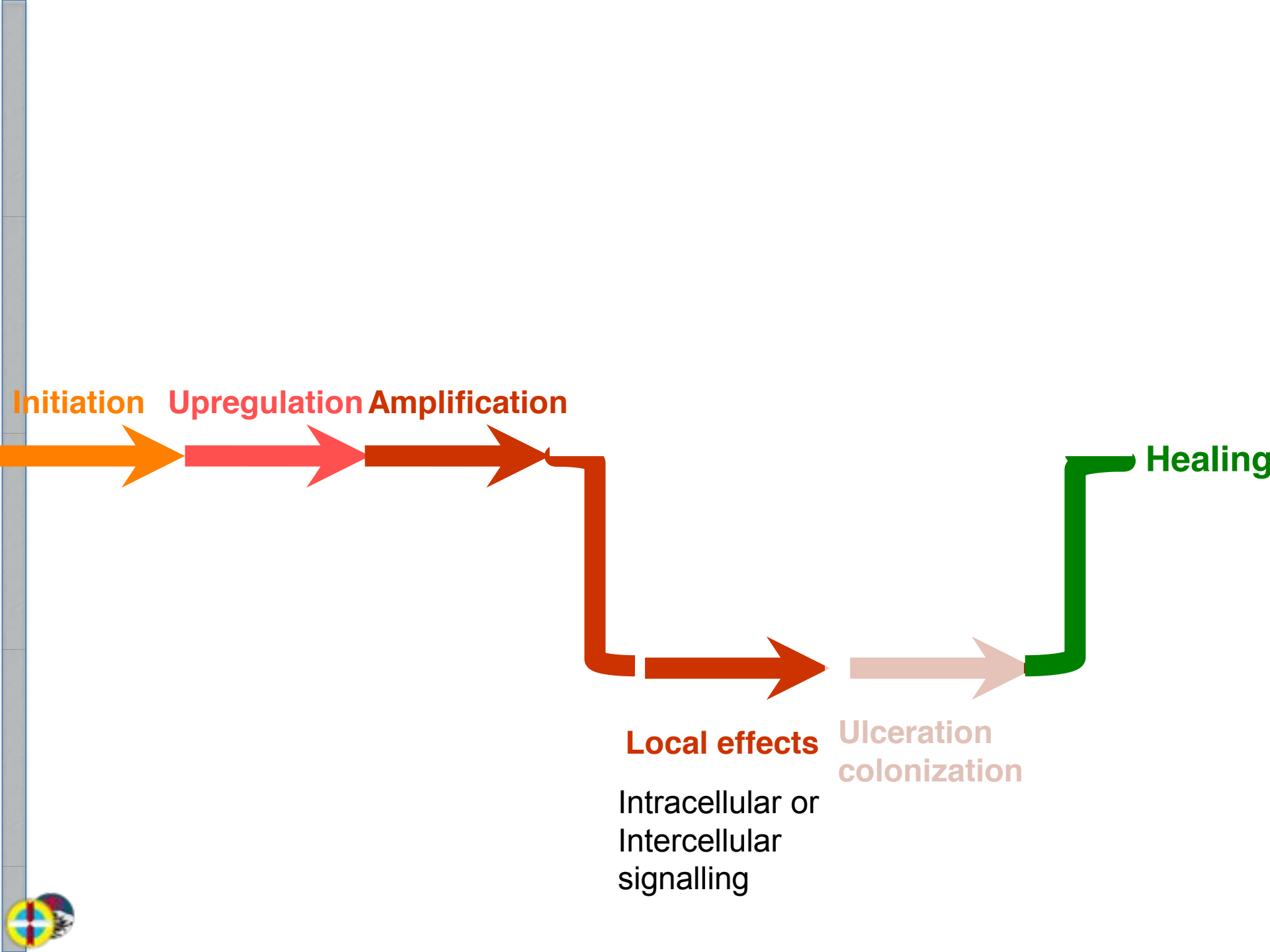
mucositis

xerostomia

pain

dysphagia





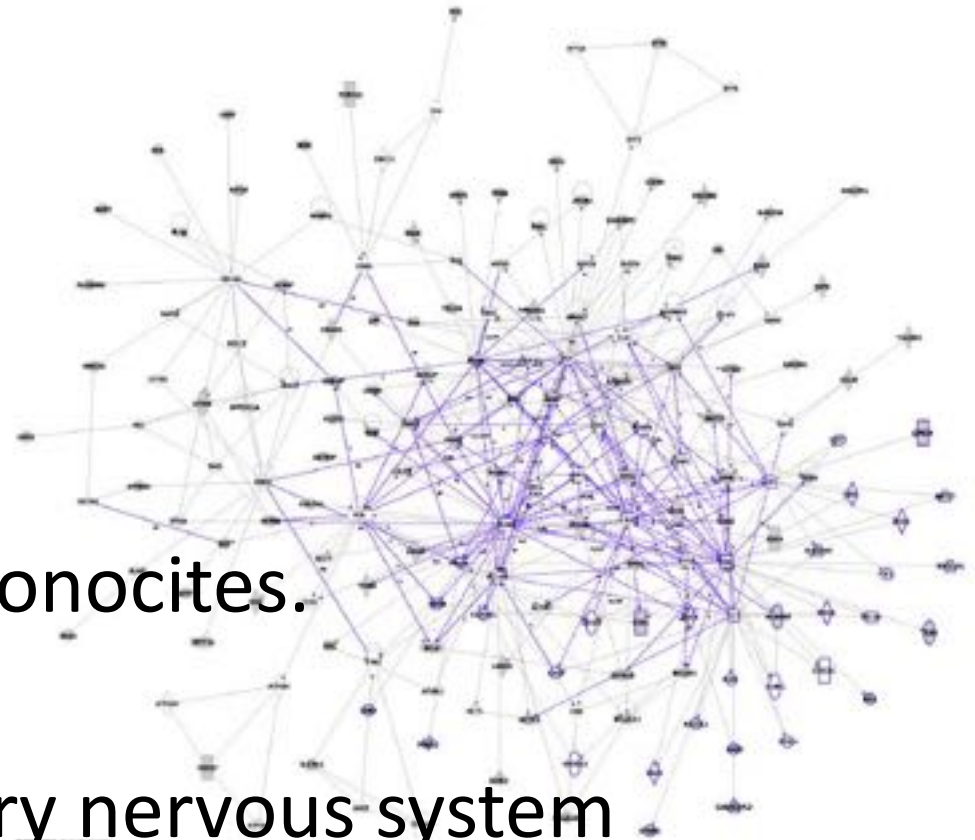
Signalling amplification endocrine-like effects

- NFkB, TNFa, IL-1b and IL-6

bloodstream level

- Genetic changes in
peripheral blood monocytes.

- Activation of sensory nervous system



Local toxicities

Systemic toxicities

dermatitis

mucositis

Fatigue

Cachexia

xerostomia

pain

dysphagia

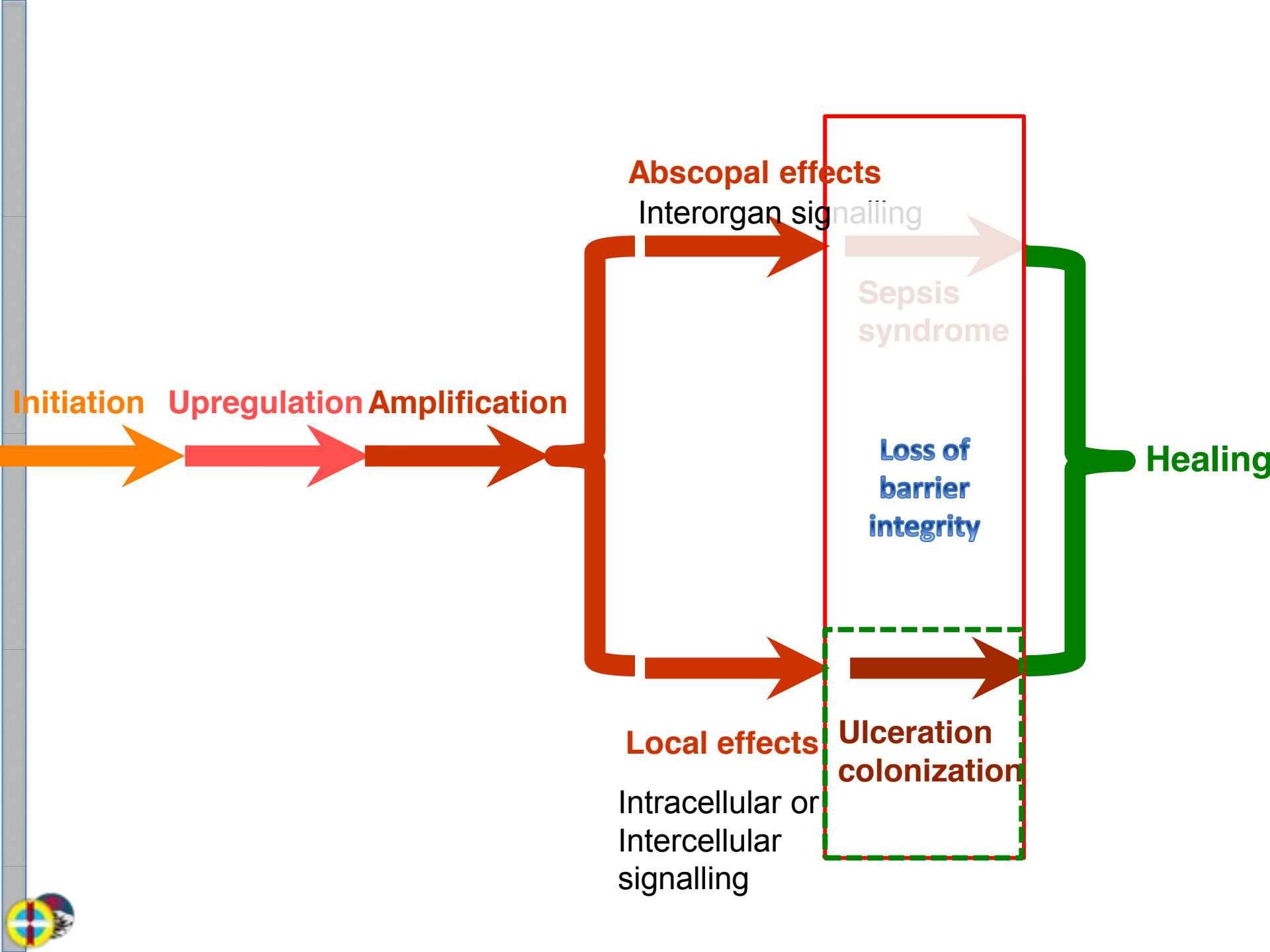


neutropenia

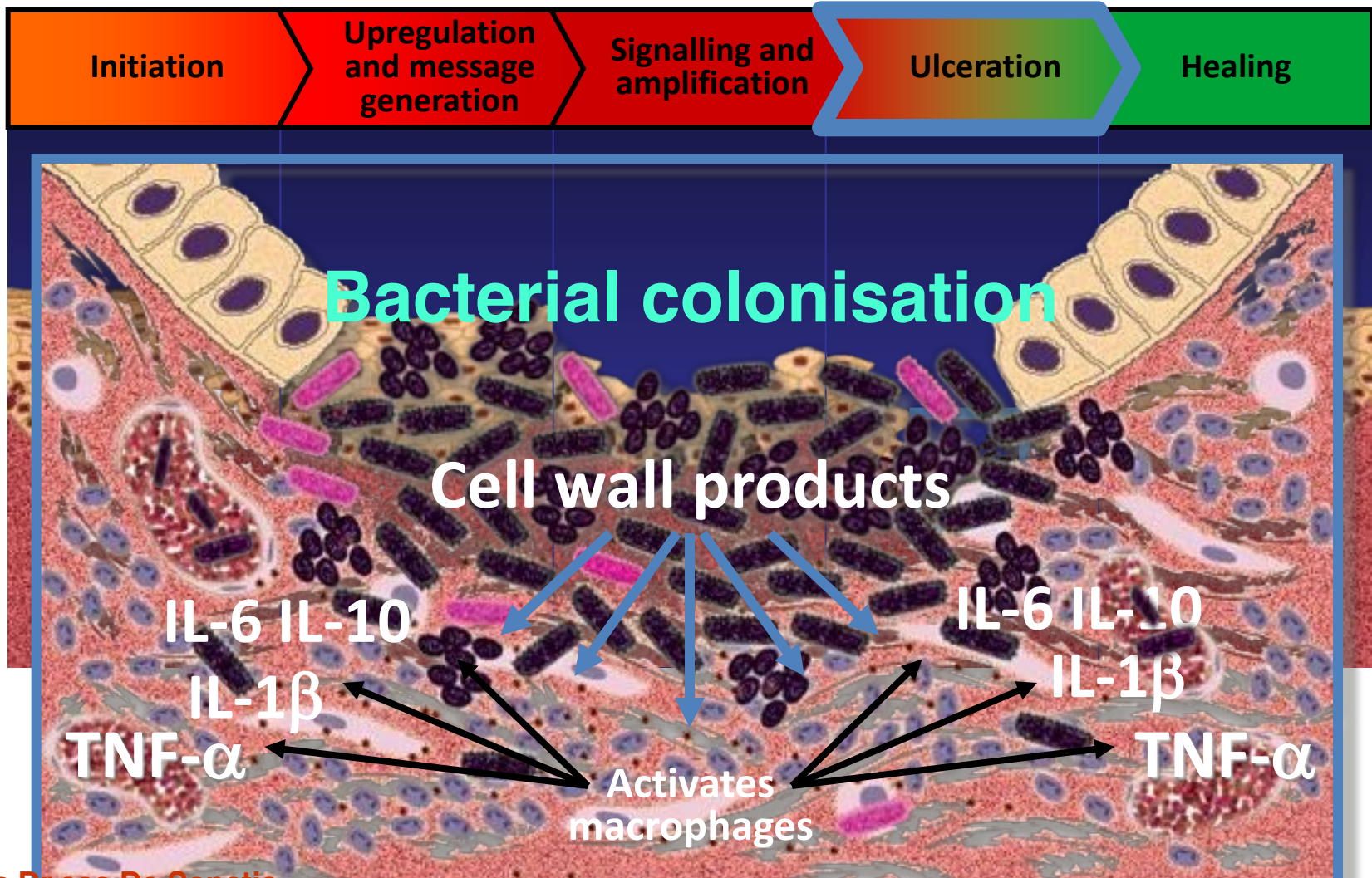
fever

SIRS





Loss of barrier integrity with sepsis risk and pain



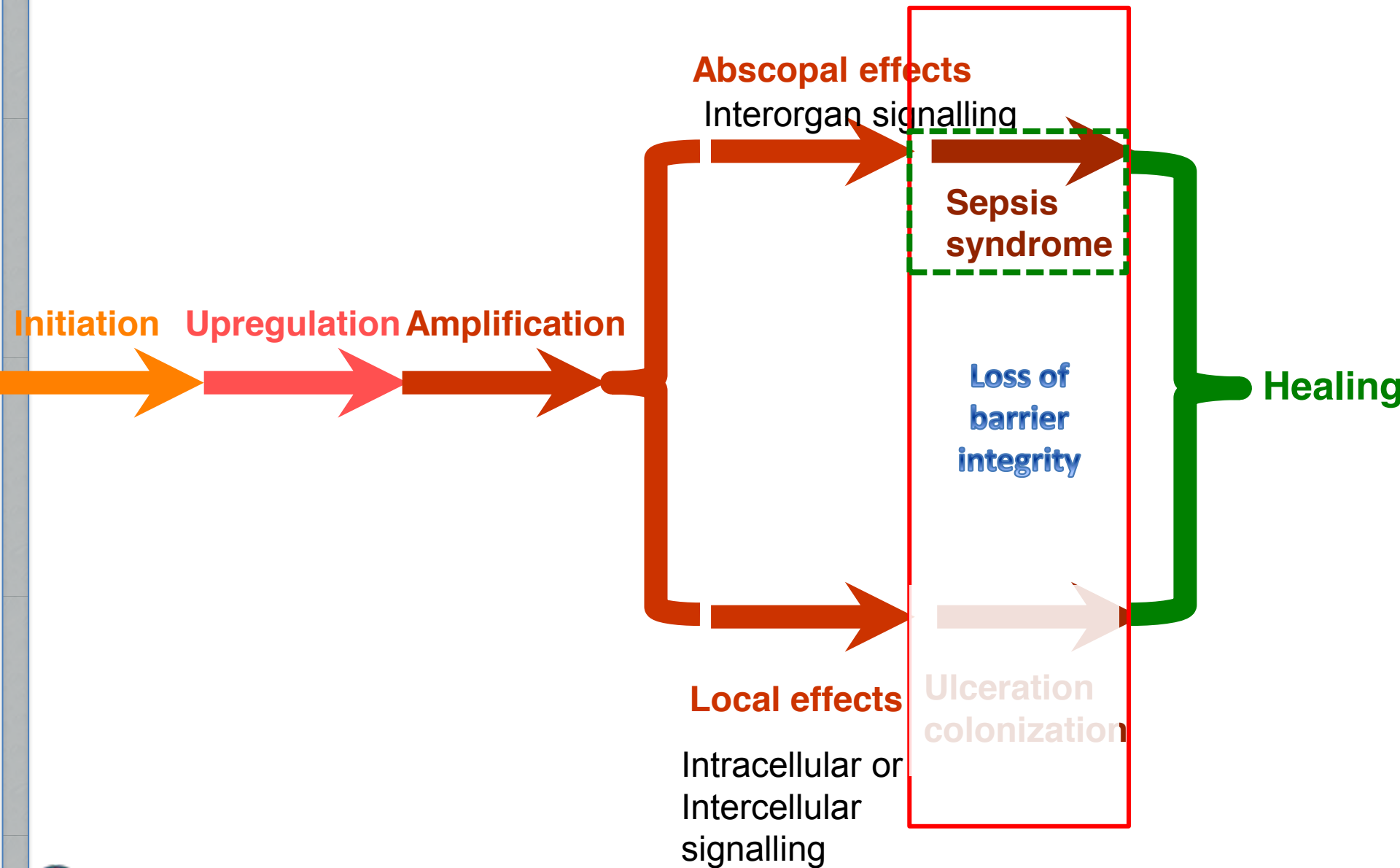


ceration Phases
complication



Colonization



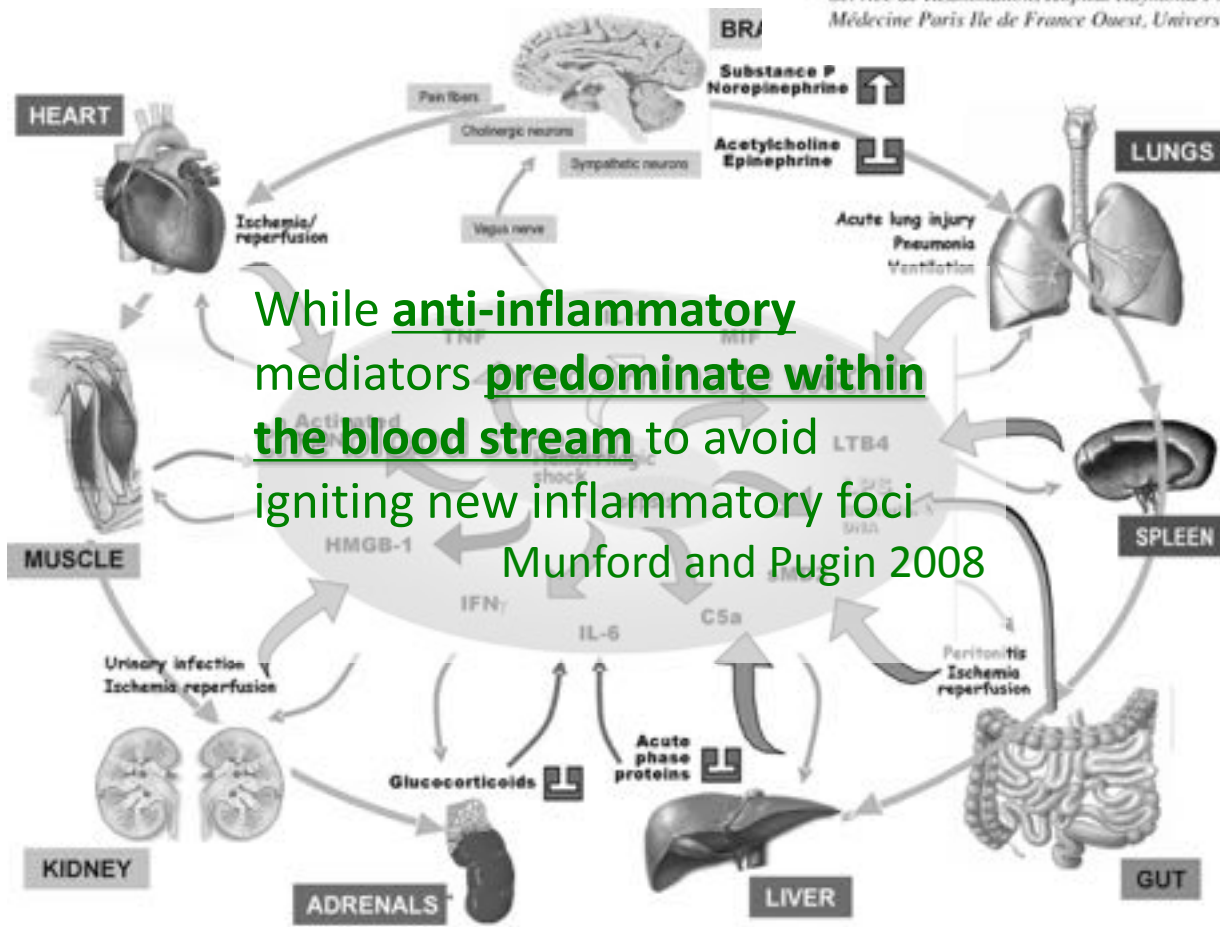


Compartmentalization of the inflammatory response in sepsis and SIRS

Jean-Marc Cavaillon¹, Djillali Annane²

¹Cytokines & Inflammation, Institut Pasteur, Paris, France

²Service de Réanimation, Hôpital Raymond Poincaré, Assistance Publique – Hôpitaux de Paris, Faculté de Médecine Paris Ile de France Ouest, Université de Versailles Saint-Quentin-en-Yvelines, Garches, France



While anti-inflammatory mediators predominate within the blood stream to avoid igniting new inflammatory foci
Munford and Pugin 2008

... their **presence within tissues** may not always be sufficient **to prevent the initiation of a deleterious inflammatory response** in the different compartments.



Local toxicities

Systemic toxicities

dermatitis

mucositis

Fatigue

Cachexia

xerostomia

pain

dysphagia



neutropenia

fever

SIRS



1. Blijlevens NMA, Logan RM, Netea MG: Mucositis: **from febrile neutropenia to febrile mucositis**. J Antimicrob Chemother 2009, 63(suppl 1):i36–i40.



Cluster di Eventi avversi associati

Sintomo o segno...

**es. Desquamazione umida, febbre,
odinofagia....**

**...espressione di un
effetto collaterale,**

es. stomatite o dermatite etc

ma anche **misura...**

**...dell'espressione di una
malattia sistemica a
genesi infiammatoria.**

**es. fatigue
cachexia
SIRS
Sepsi**



Finalità della gestione della tossicità

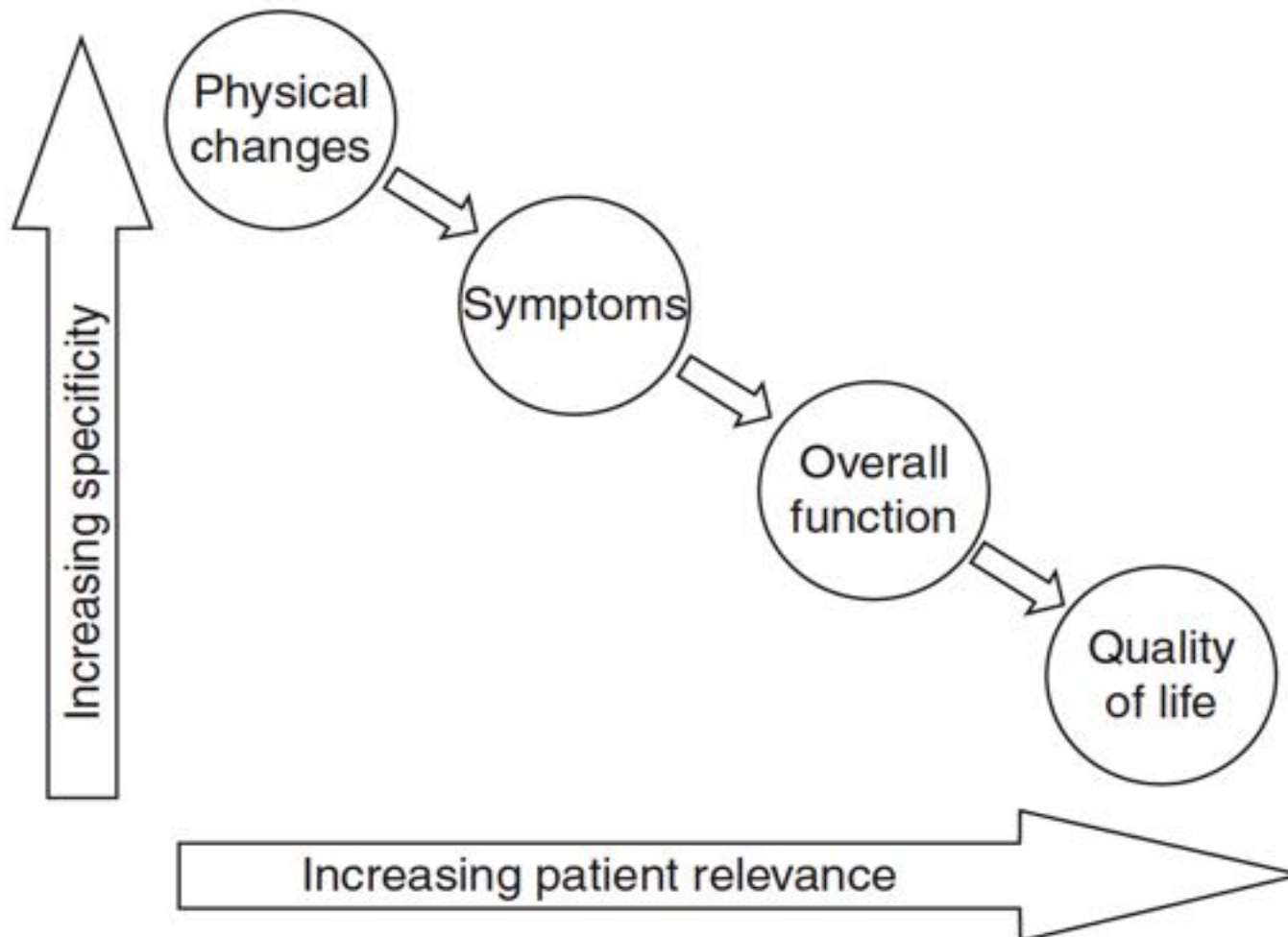
- **La gestione delle tossicità ha l'obiettivo di ridurre le mortalità**
- **...ma cosa sappiamo circa la gravità di questi effetti e la qualità della vita di questi pazienti?**
- **...come la misuriamo?**



Main topics

- Patogenesi e gestione delle tossicità
- Misurazione delle tossicità
- Inferenza delle tossicità sulla QoL

Illustration of the cause–effect chain and the trade-off between relevance and specificity of different measures of side effects.



Come sono stimati I sintomi in letteratura?

ORO: Observer-rated Outcome



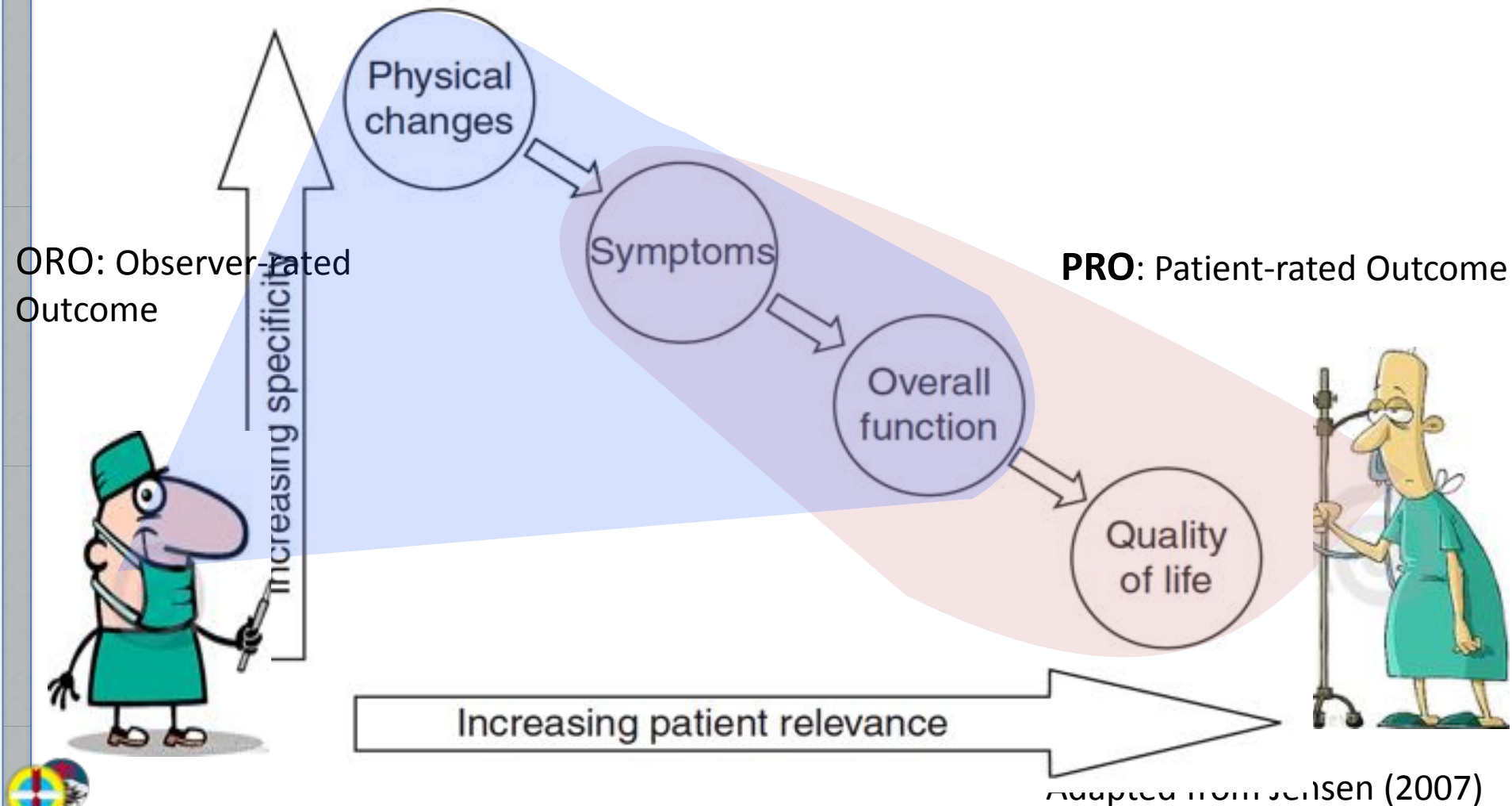
PRO: Patient-rated Outcome



Adapted from Jensen (2007)



Illustration of the cause-effect chain and the trade-off between relevance and specificity of different measures of side effects.

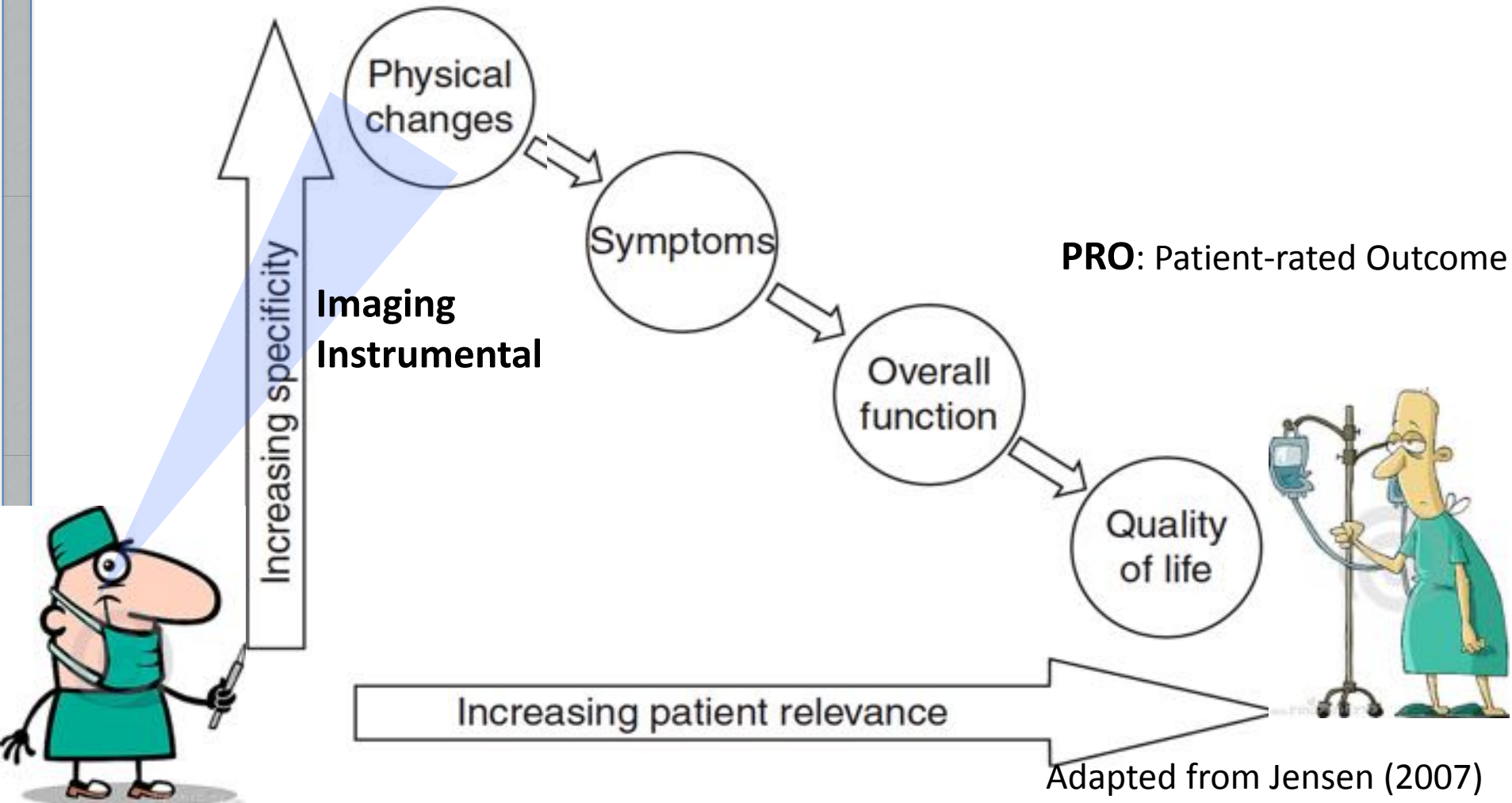


OBSERVER RATED

Biological and
Physiological
Variables



Valutazione analitica

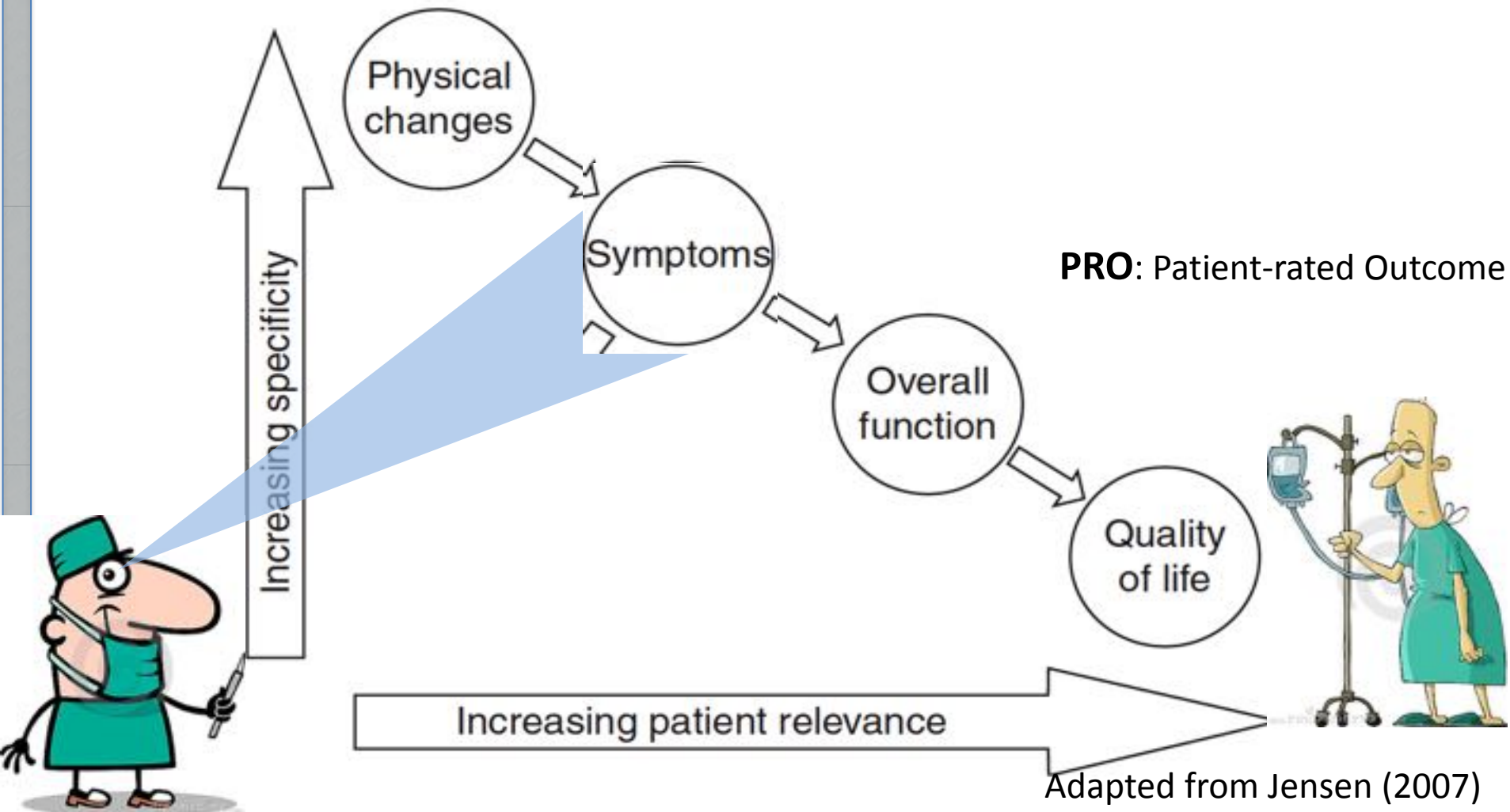


Valutazione analitica

- Alterato flusso salivare di base o sotto stimolo:
 - whole mouth flow (Navazesh 1982)
 - Gland-specific flow (Jones 1996)
- Valutazione funzionale della ghiandola salivare:
 - SPECT o PET (Buus 2006 Van Acker 2001)
- Disfagia:
 - VF: metodo quantitativo (residuo, aspirazione, penetrazione) Langmore 2003
 - FEES: metodo semiquantitativo (Aviv 2000; Wu 1997)
- Dimagrimento:
 - Peso,
 - quantità di cibo



Observer-rated Subjective symptoms



Observer-rated Subjective symptoms

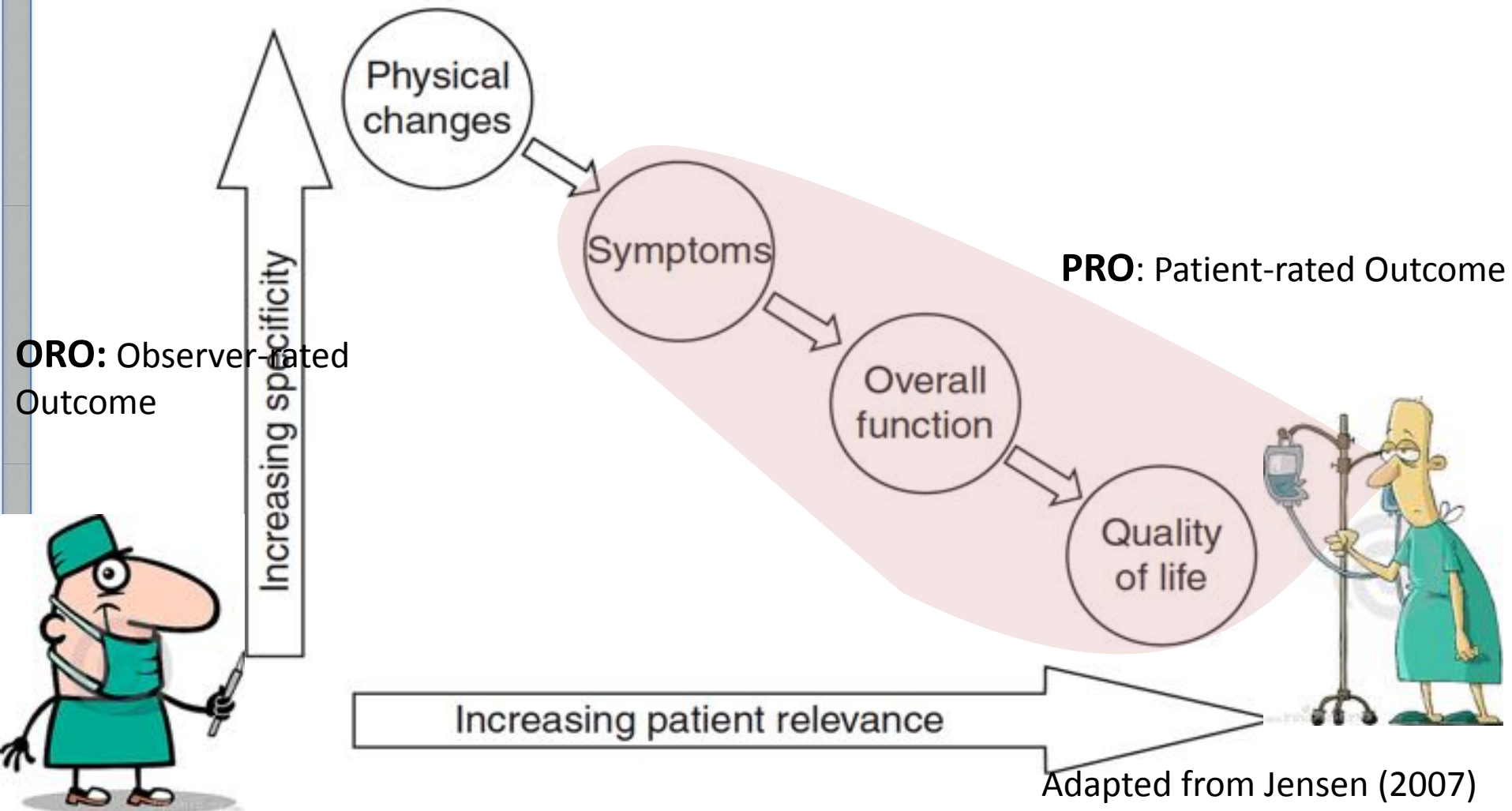
- NCI-CTCAE (Trotti 2003)
- WHO (Miller 1981)
- EORTC/RTOG (Cox 1995)
- SOMA-LENT (Rubin 1995)
- DAHANCA (Overgaard 2003)

Sensibili a individuare differenze in tossicità in base a:

- Volume (Jansen 2007)
- frazionamento (Dische 1997)
- accelerazione del trattamento (Skladowski 2006)
- chemioterapia concomitante (Denis 2003)



Illustration of the cause–effect chain and the trade-off between relevance and specificity of different measures of side effects.



OBSERVER RATED

Biological and
Physiological
Variables



Quali le PRO scale?



PRO definition

- PROs are defined as measures of “any aspect of a patient’s health **that comes directly from the patient** (i.e., without the interpretation of the patient’s responses by a physician or anyone else)”
 - FDA Guidance 2006



A Generic

Generic
eg MOS

Medical Outcome Study short Form
MOS-SF36

1)

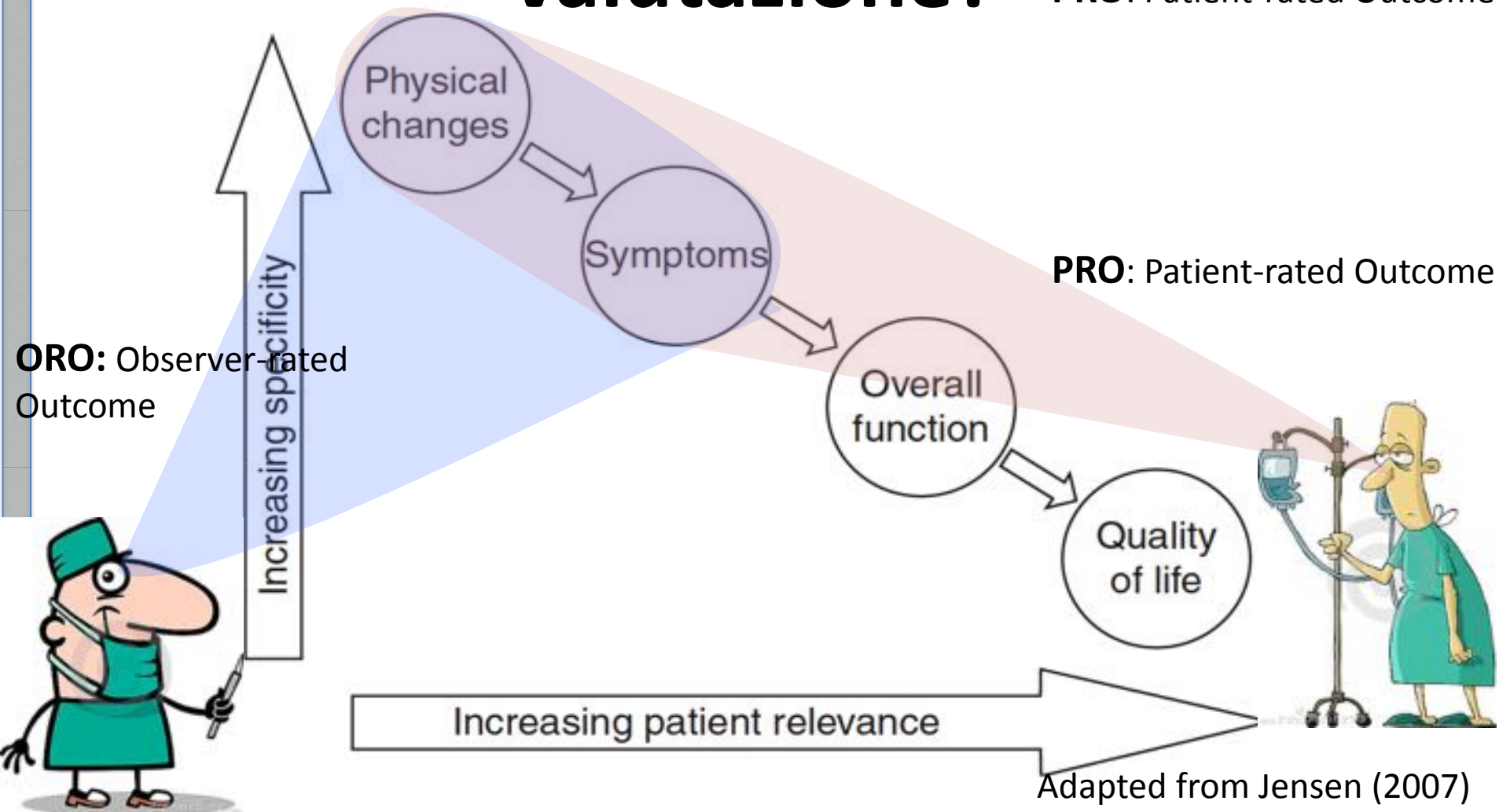
HR-QoL Scales

B Specific

PRO Tools

Quali le relazioni tra i due tipi di valutazione?

PRO: Patient-rated Outcome



PRO/ Analytically measured endpoint

Analytically measured endpoint and Objective finding

- Saliva flow measurements
- Swallowing assessment (FEES)
- Dental examination (orthopantomography)
- Trismus (opening mouth)
- CTCAE v.3.0/4.0

PRO

- EORTC C30
- H&N35

PRO



Warning:

Aspiration/Penetration & EORTC QLQ H&N35

- *Inadequate sensitivity, specificity, and predictive values of patient self-reporting with the EORTC QLQ-H&N35 scales* have been identified in comparisons to the objective findings **of aspiration or penetration in patients undergoing FEES evaluation of swallowing**

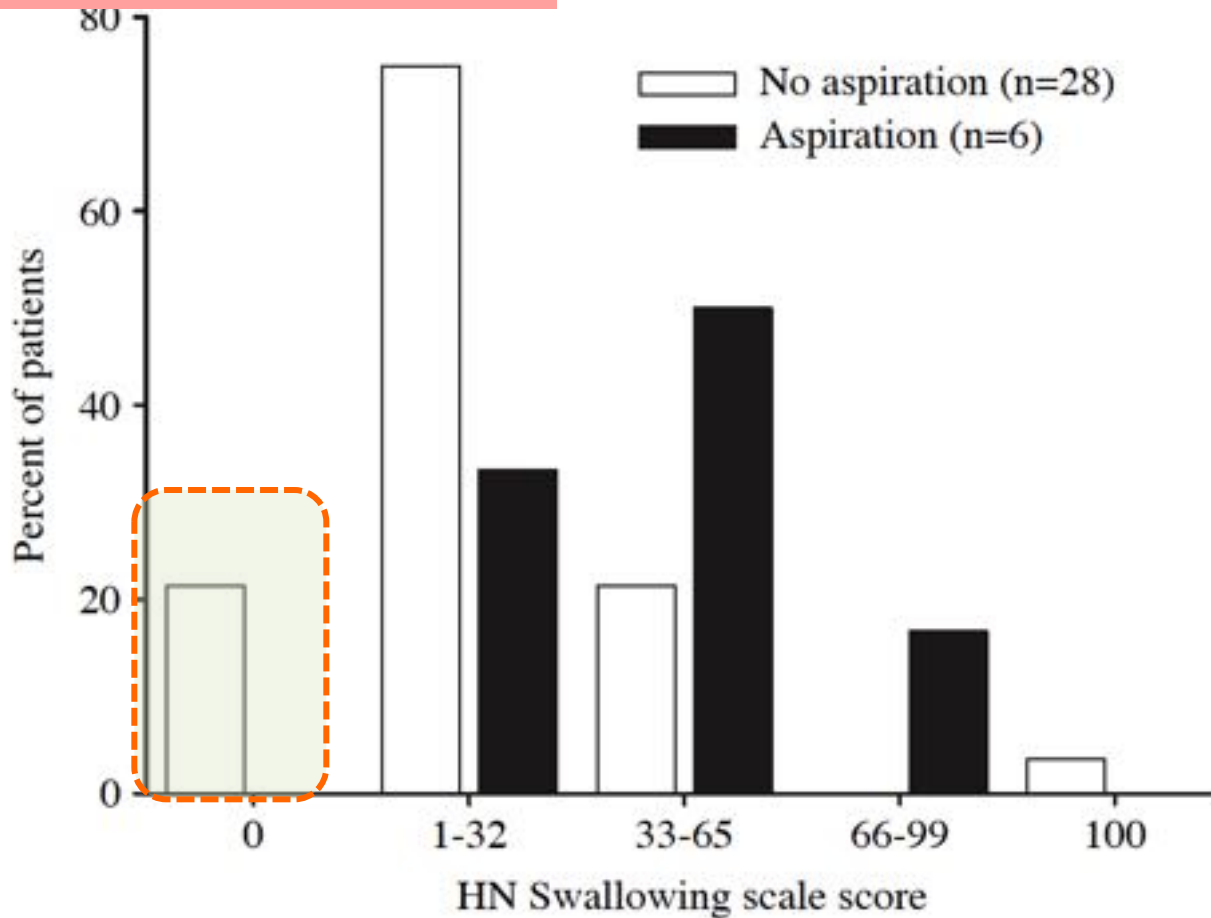
– (Jensen et al.2007).



ma.....

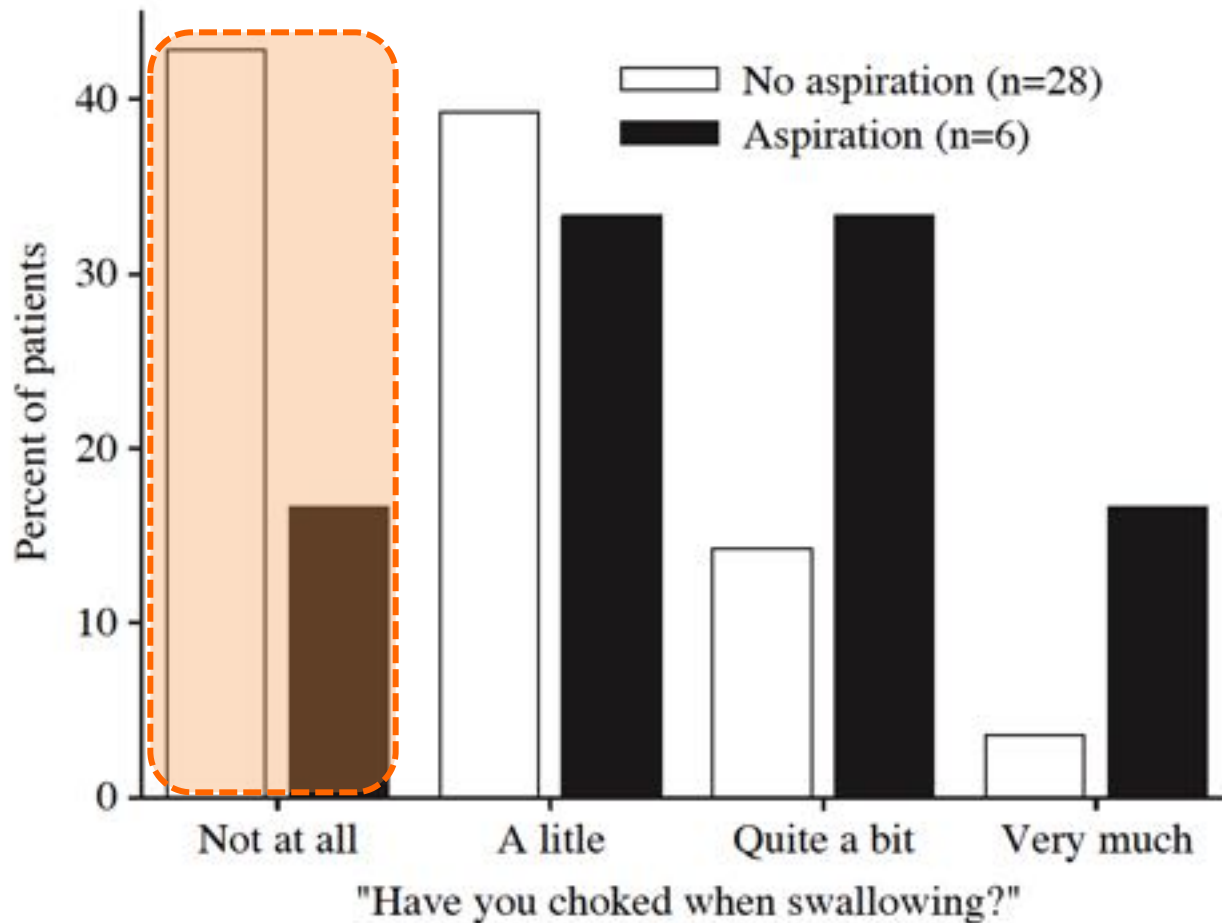
Valore predittivo negativo fra Disturbi di deglutizione/Aspirazione

0.94 (0.70; 1.0)



Valore predittivo negativo fra "Chocking"/Aspirazione

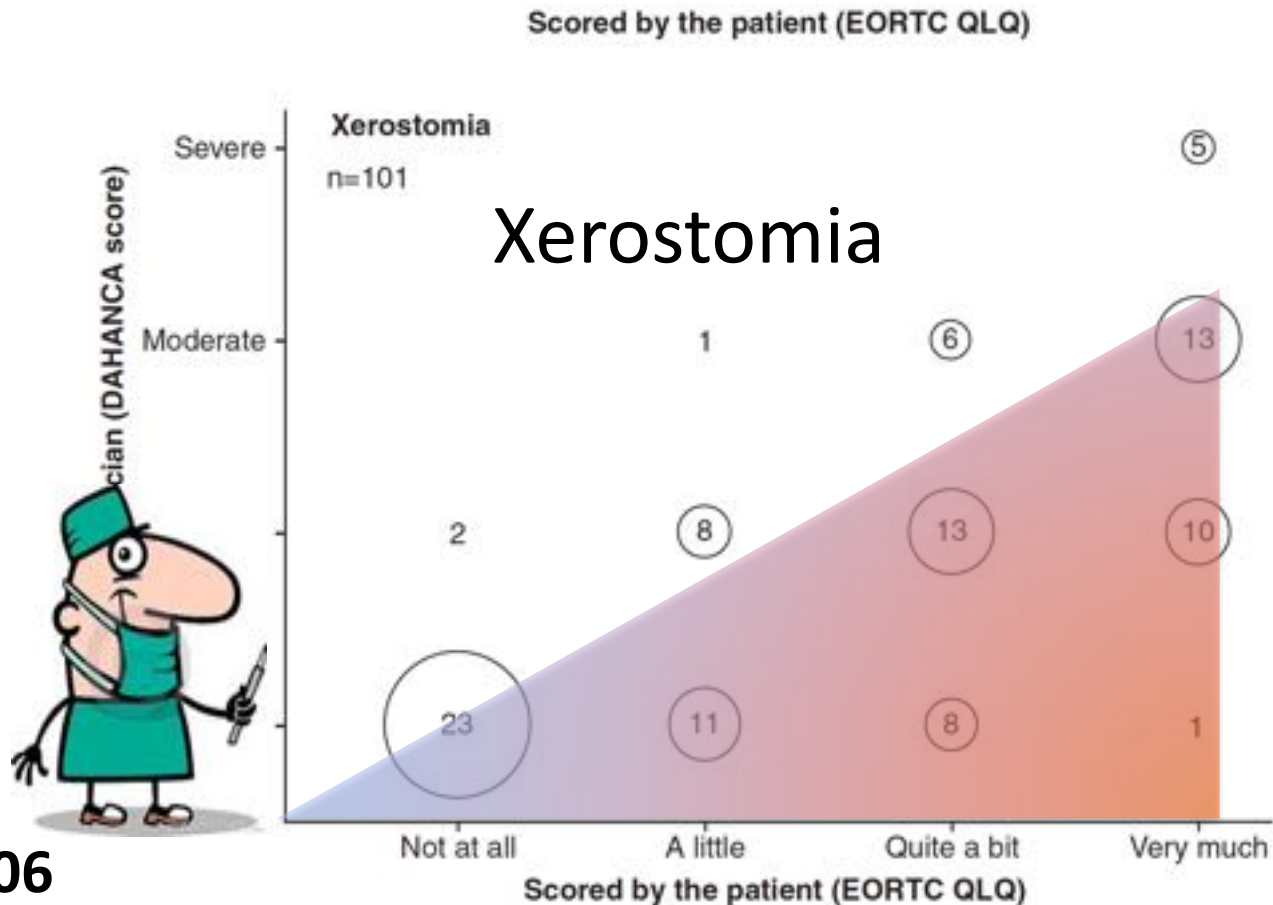
0.92 (0.64; 1.0)



PATIENT REPORTED OUTCOME e PHYSICIAN ASSESSED TOXICITIES

- Il Operatore sanitario tende a sottostimare la presenza e la severità dei sintomi rispetto a PRO

MEASUREMENT

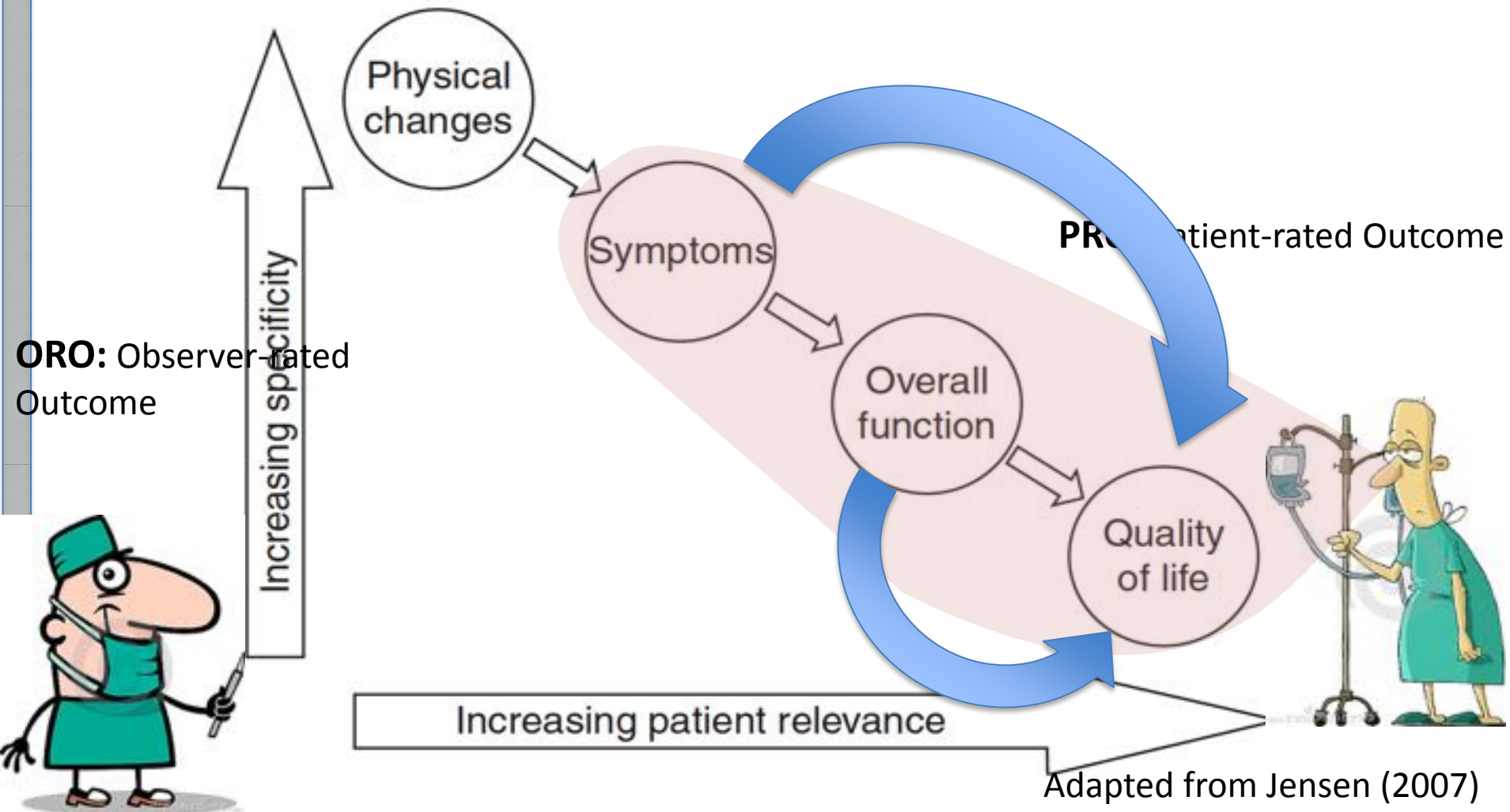


Main topics

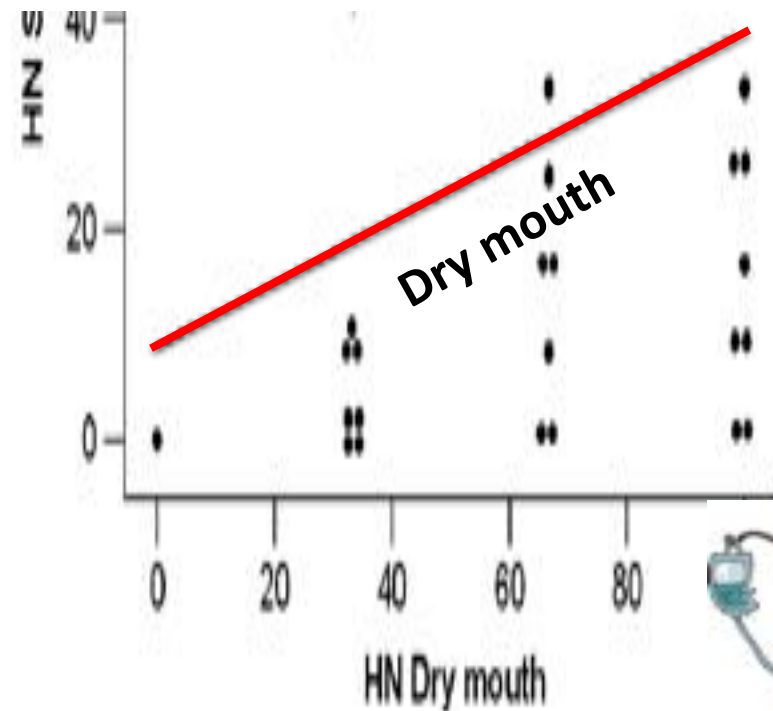
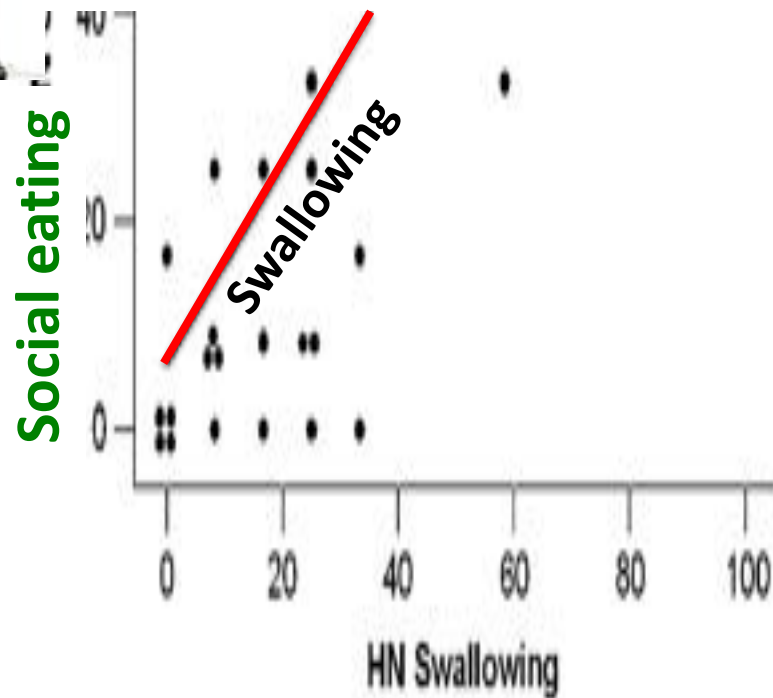
- Patogenesi delle tossicità
- Misurazione delle tossicità
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Relazione tra PRO-evaluated domains and HR-QoL



Swallowing dysfunction, dry mouth vs. HR-QoL



Swallowing had better correlation with overall QoL, physical function **and social eating** scale than all other H&N specific symptoms, e.g. xerostomia

Conclusion

- Ogni AE deve essere trattato come tossicità per sé, ma anche valutato come espressione di Tossicità Sistemica (clusters).
- La misurazione ORO è utile per correlare le tossicità tra loro e tra operatori.
 - Non può misurare la HR-QoL.
- La misurazione PRO è utile per correlare lo stato della QoL dello stesso paziente nel tempo.
 - L'assenza di una misurazione può inficiarne l'utilità.



- Cancer Treatments must:
“...not only add years to life
but life to years....”

GRAZIE

- Burckhardt CS, Anderson KL. The quality of life scale (QOLS): reliability, validity, and utilization. Health Qual Life Outcomes 2003;1:60

