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)**
- Titolarietà 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

XXIV CONGRESSO NAZIONALE
AIRO2014
Associazione Italiana Radioterapia Oncologica
Padova, 8-11 novembre

Neoplasie del rinofaringe

Gestione delle tossicità e qualità di vita

Elvio G. Russi
Radioterapia
AO. S. Croce e Carle
Cuneo

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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- ✓**High rate of late mortality**
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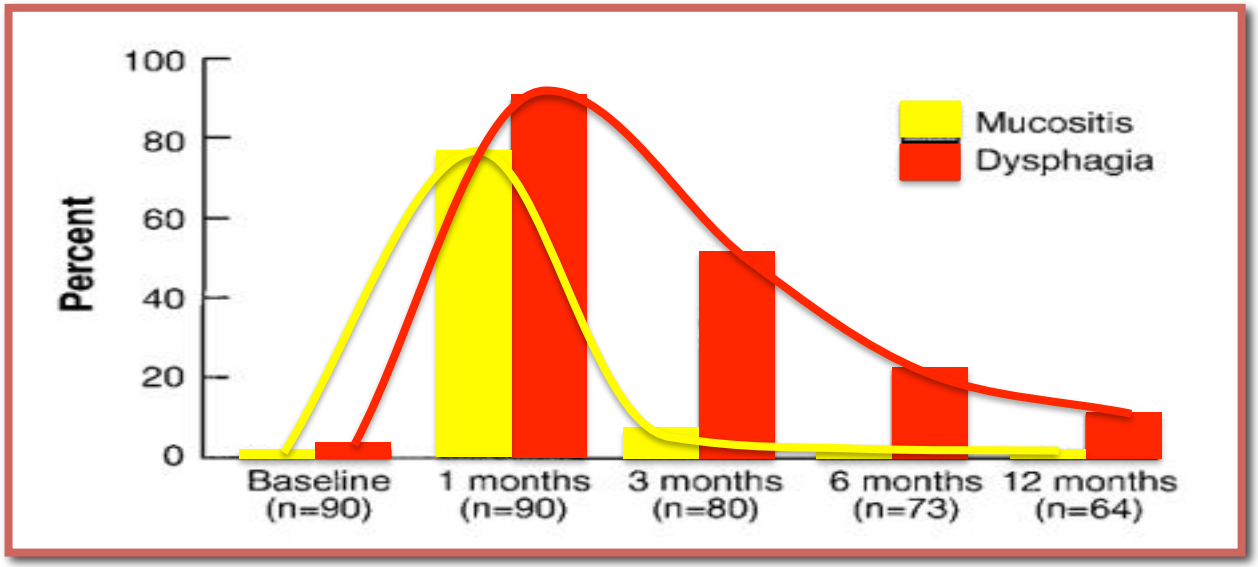
Dysphagia, mucositis ….



- ✓Feeding-tube dependence
- ✓Chronic aspiration

TM Mekhail, Cancer 2001

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

Argiris, Clin Cancer Res 2004

VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

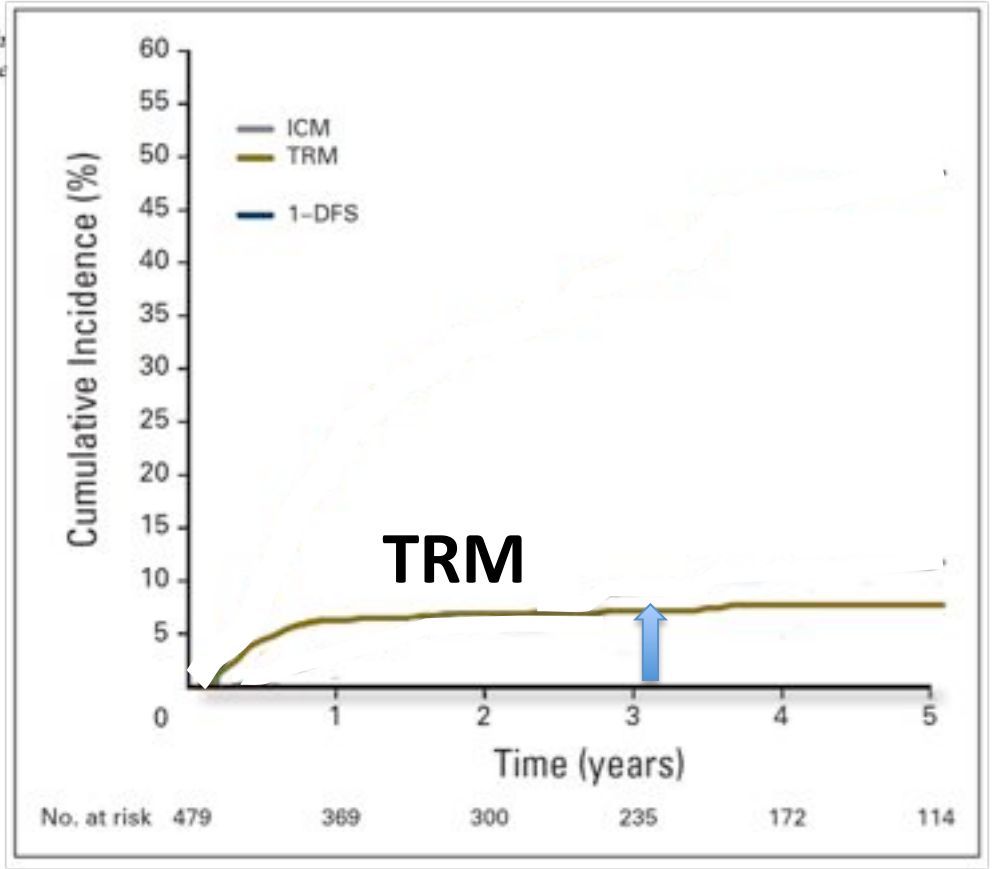
ORIGINAL REPORT

Predictors of Competing Mortality in Advanced Head and Neck Cancer

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

479 pts, HN stage III-IV

Treatment-related mortality (TRM)



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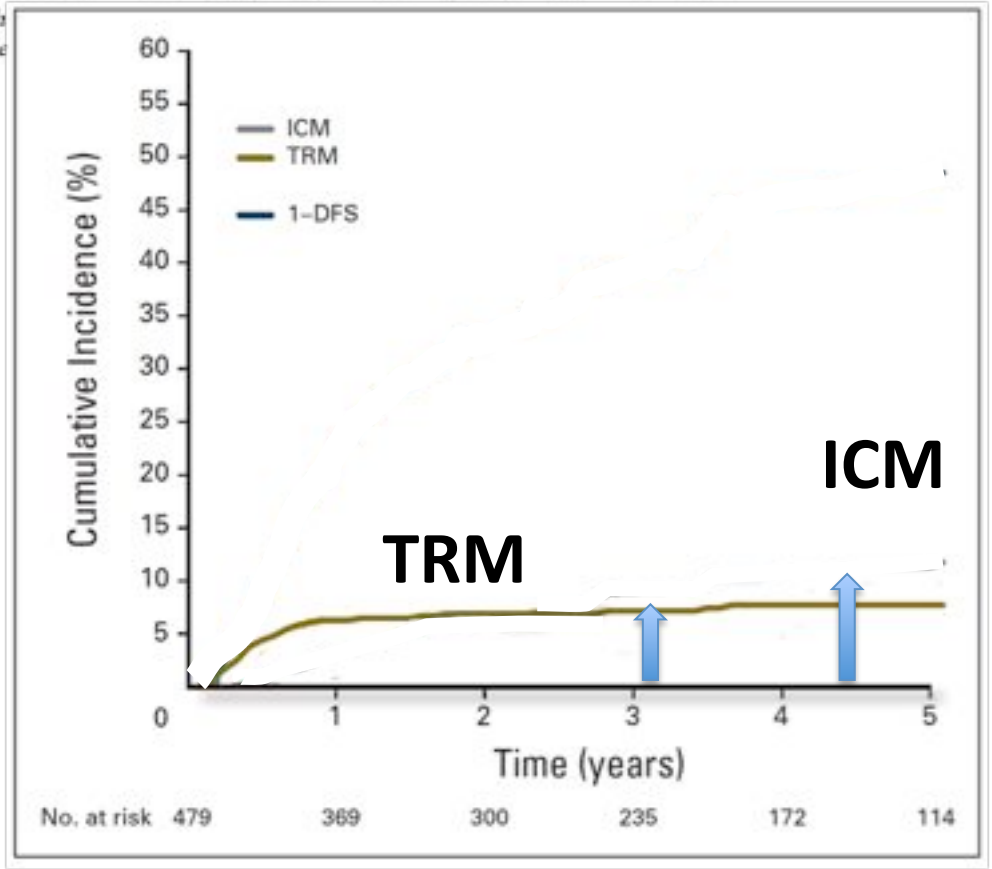
Inter-Current Mortality



VOLUME 31 · NUMBER 7 · MARCH 1 2013

JOURNAL OF CLINICAL ONCOLOGY

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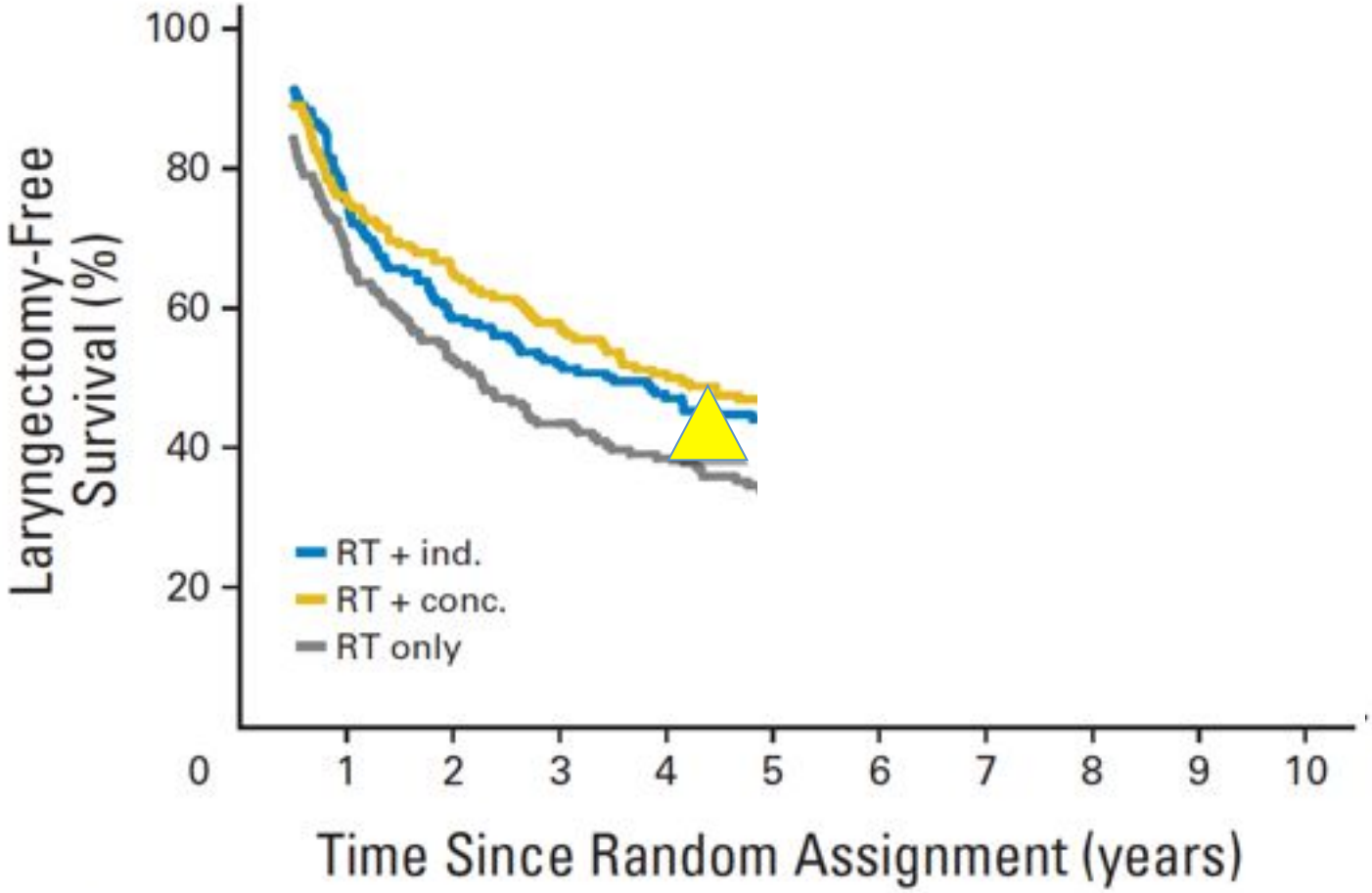
Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

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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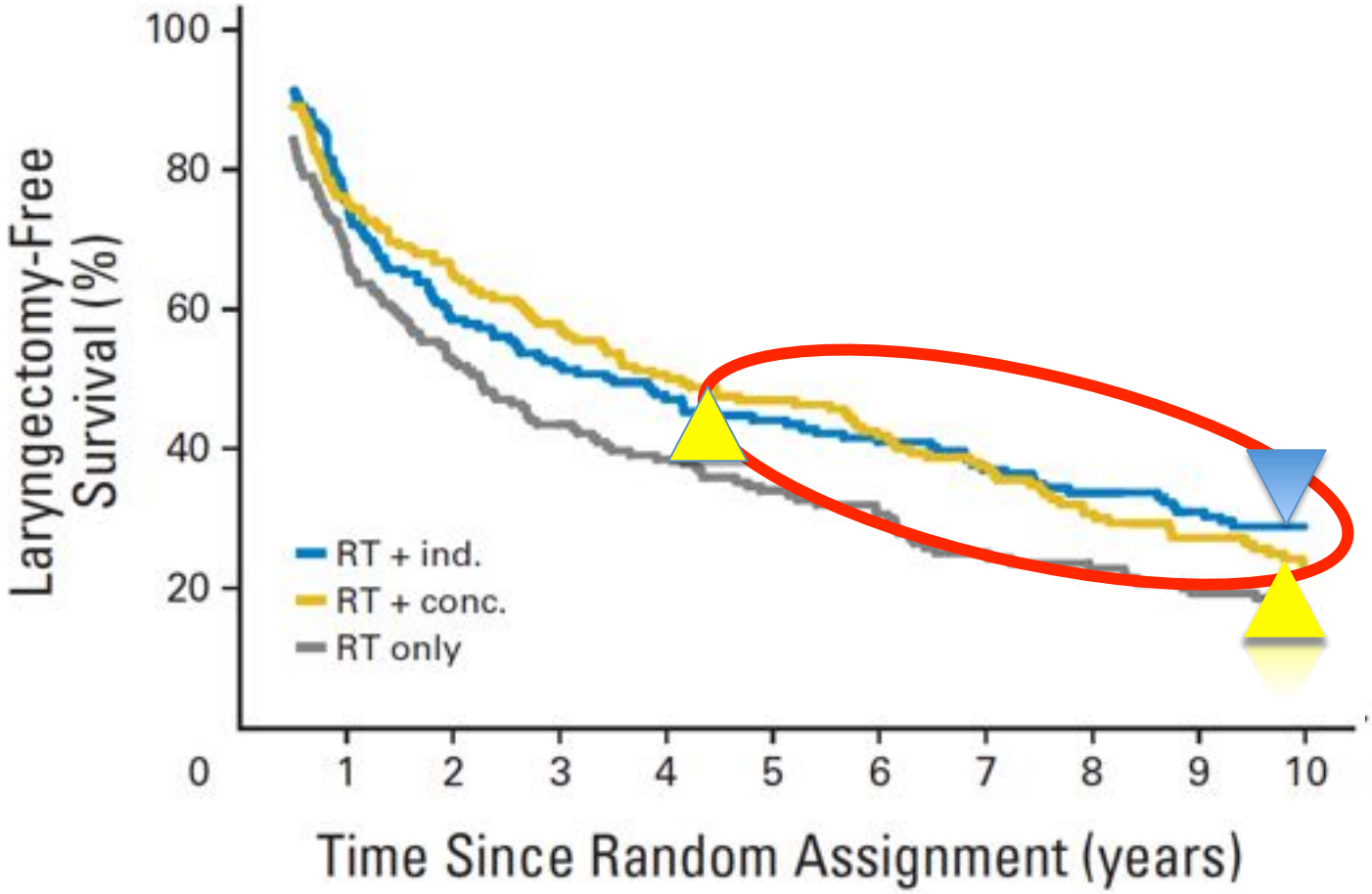


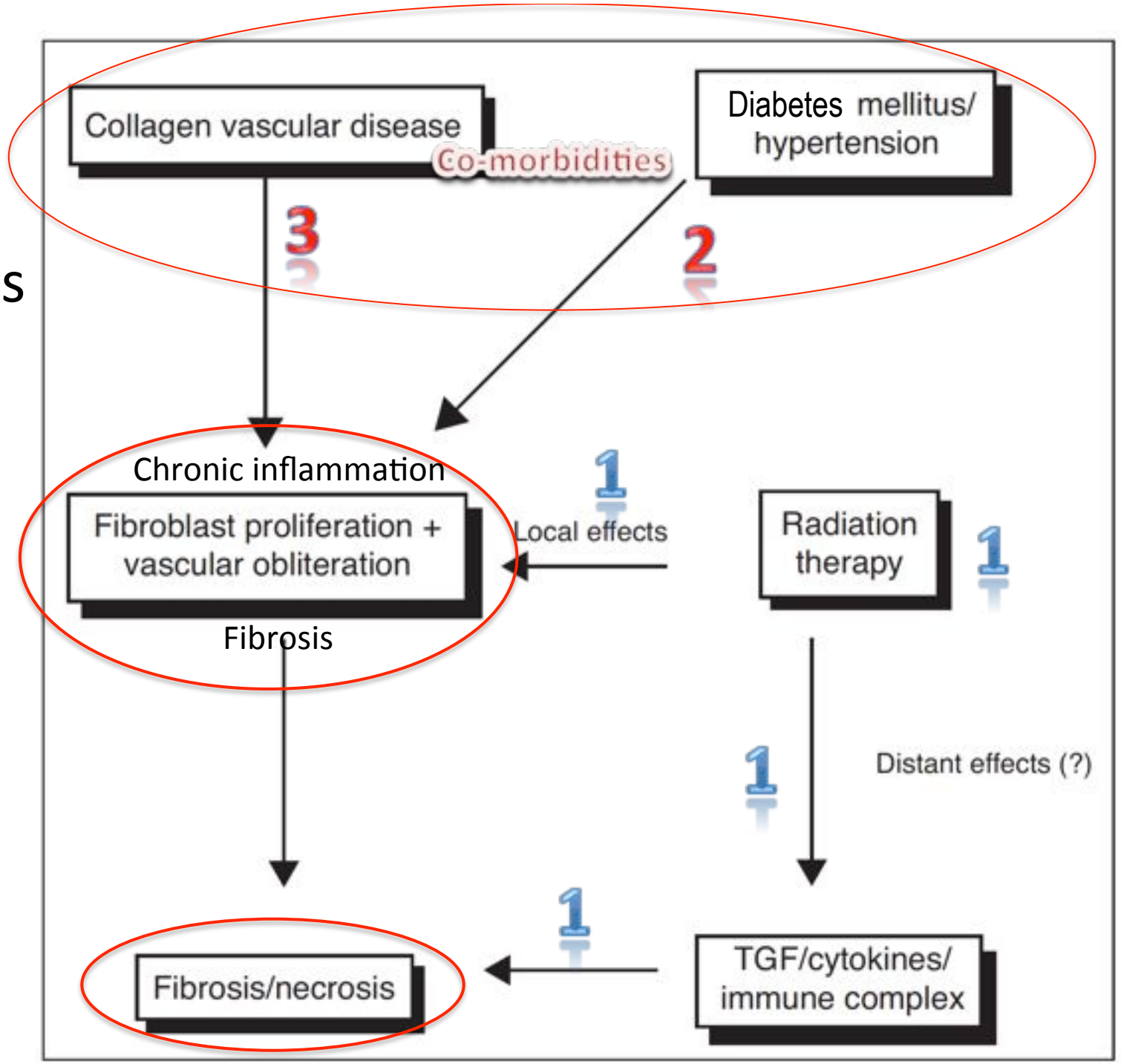
non-cancer related causes of Death

- ✓Acute toxicity
- ✓Long term toxicity
- ✓High rate of late mortality
  - ✓(predisposing co-factors and/or co-morbidity?)

Co-Factors

and Late

damages



Chon et al. 2002

ORIGINAL ARTICLE

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-u None	Mild	Moderate
None				
HR (95% CI)	53 (29.0)	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)	58 (31.7)		2.6 (1.1-6.2)	2.7 (0.8-8.9)
No. (%)		0	38 (20.8)	6 (3.3)
Moderate				
HR (95% CI)	53 (29.0)		2.0 (0.4-9.4)	2.8 (1.2-6.8)
No. (%)		0	6 (3.3)	30 (16.4)
Severe				
HR (95%				
No. (%)			0	
Total, No. (%			52 (28.4)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Because of rounding, percentages may not total 100.

10.4%
at diagnosis

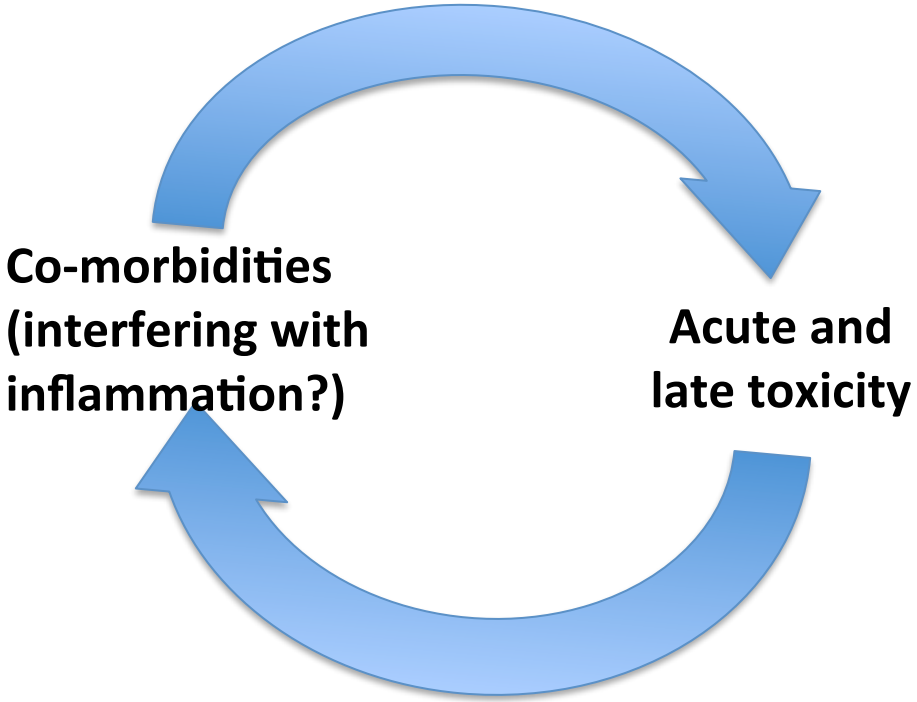
31.7%
at last follow up

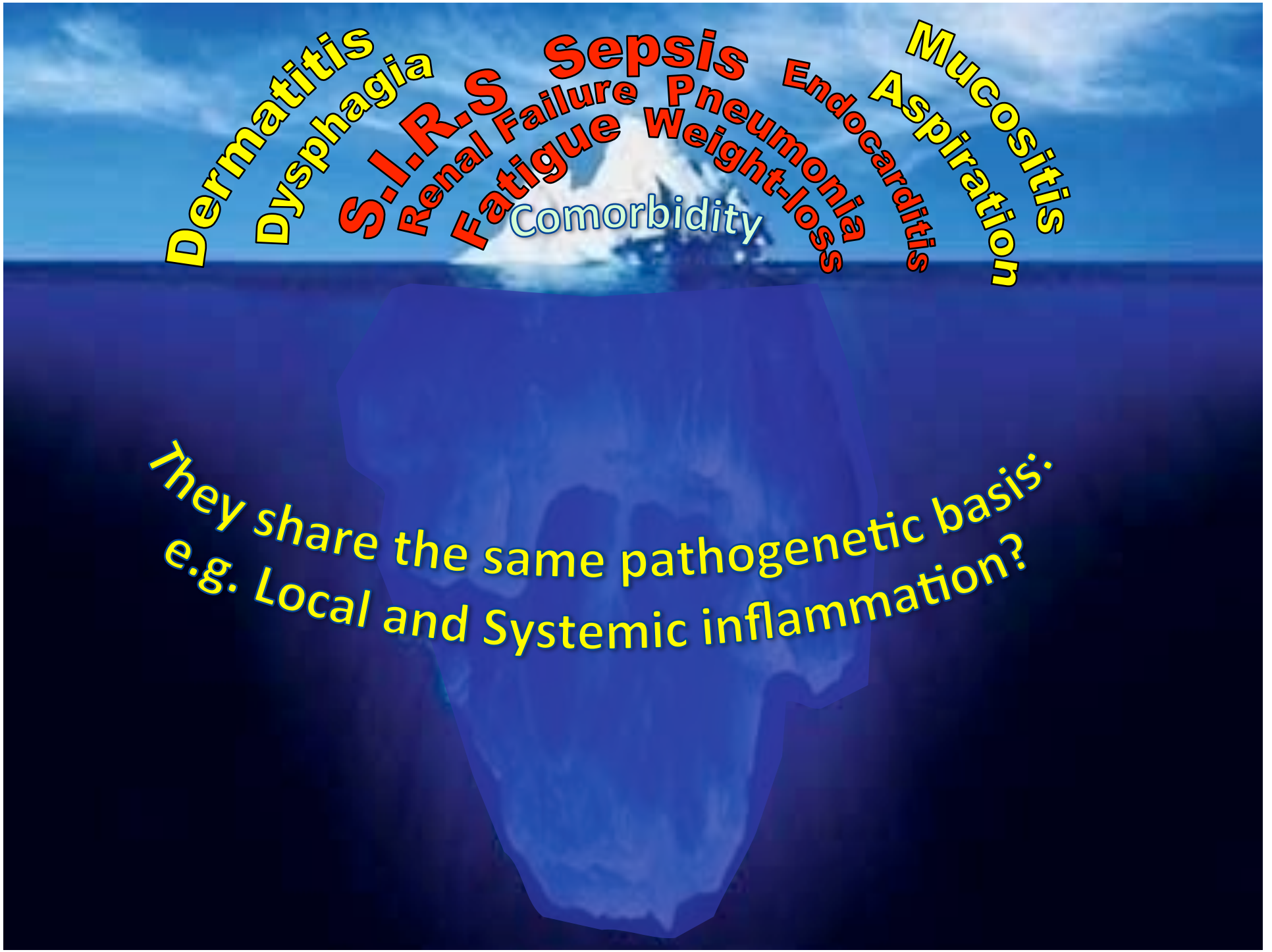
1. Co-morbidity at diagnosis is strongly correlated with prognosis

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

Piccirillo JF et al 2013

“Vicious circle” between co-morbidities and toxicities



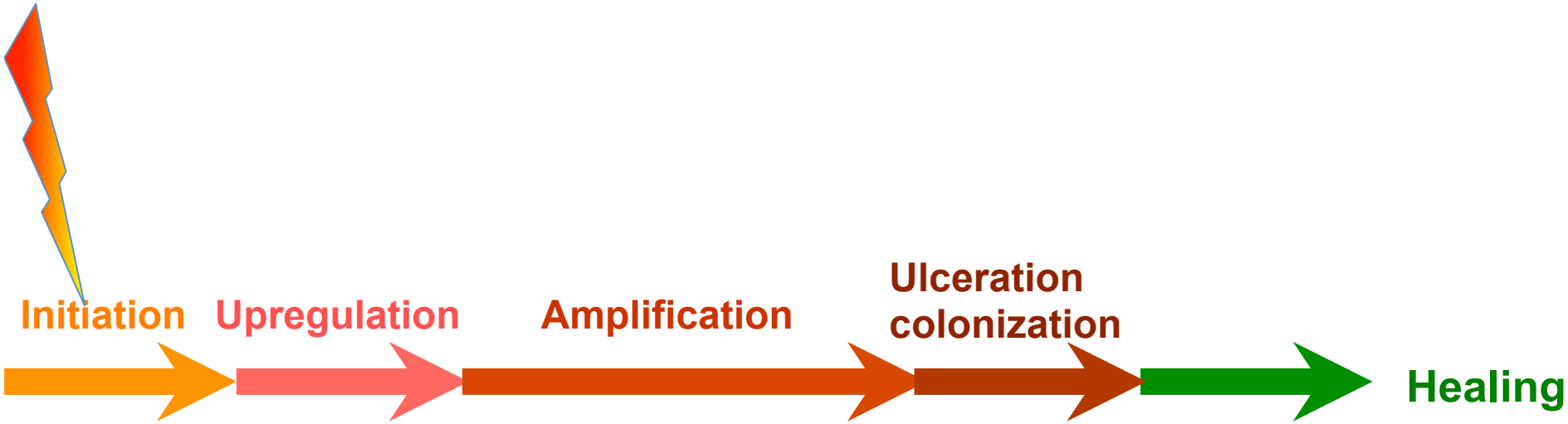

Dermatitis
Dysphagia
S.I.R.S
Renal Failure
Fatigue
Sepsis
Pneumonia
Weight-loss
Endocarditis
Aspiration
Mucositis
Comorbidity
They share the same pathogenetic basis:
e.g. Local and Systemic inflammation?

nature REVIEWS CANCER

Nature Reviews Cancer homepage

THE PATHOBIOLOGY OF MUCOSITIS

Stephen T. Sonis



Local effects

Intracellular or
Intercellular
signalling

Hindawi Publishing Corporation
Mediators of Inflammation
Volume 2014, Article ID 518261, 14 pages
http://dx.doi.org/10.1155/2014/518261

Mediators Inflamm 2014, **2014**:518-261

Hindawi

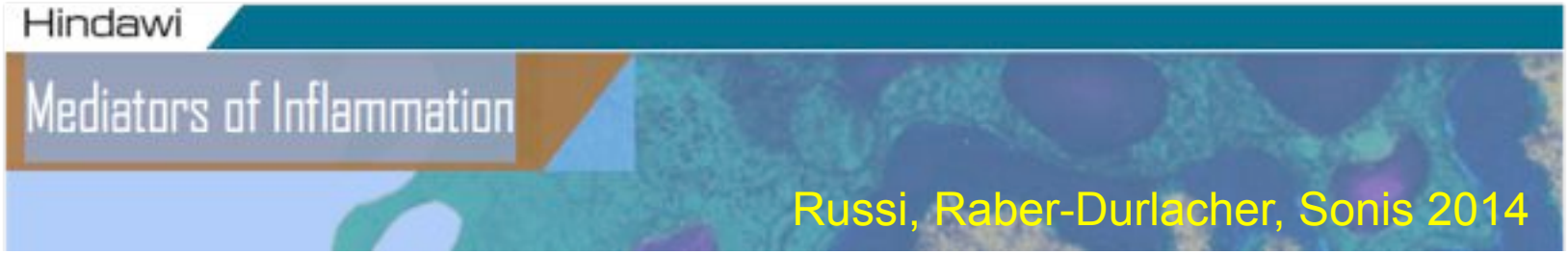
Review Article

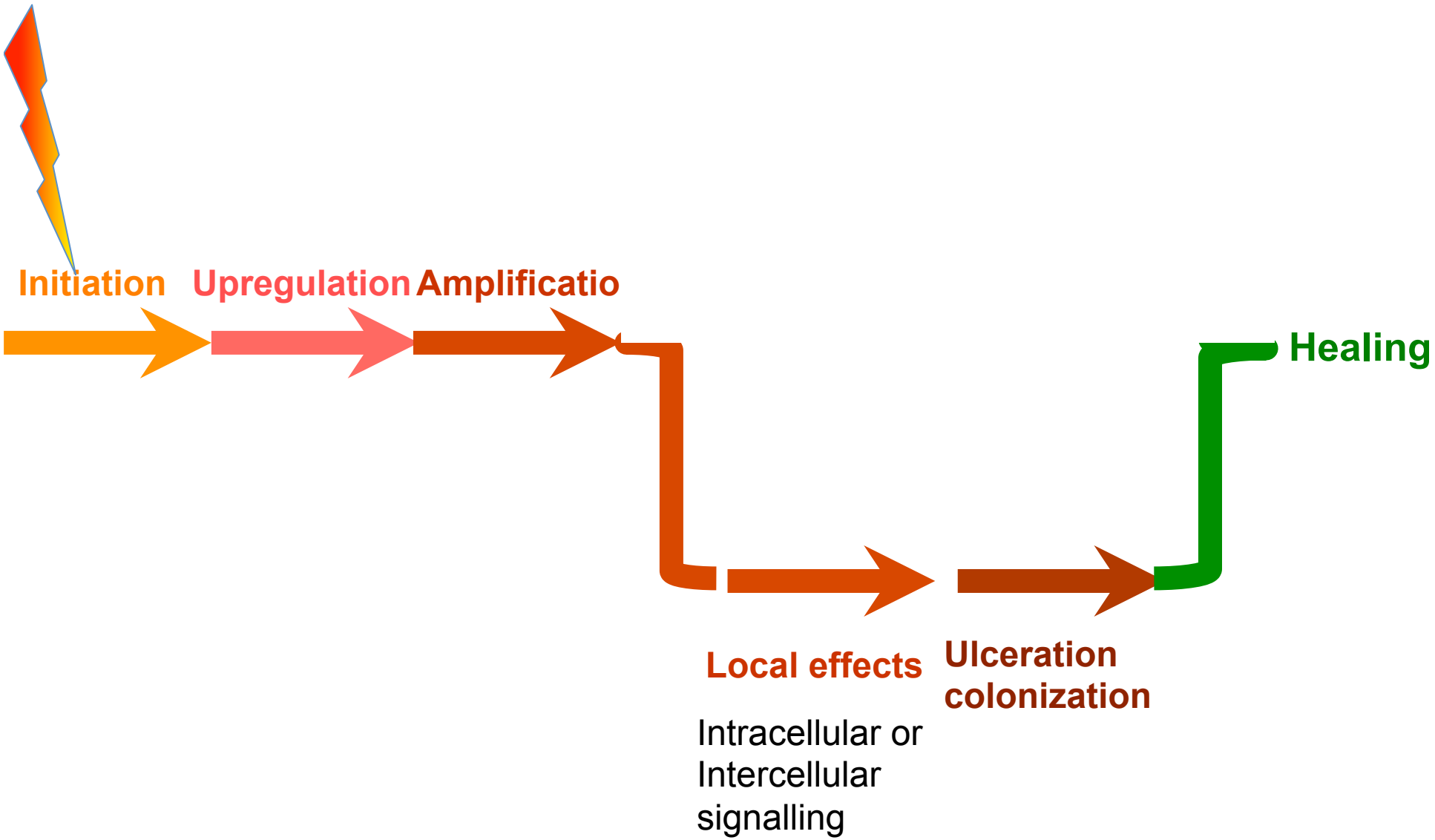
Local and Systemic Pathogenesis and Consequences of Regimen-Induced Inflammatory Responses in Patients with Head and Neck Cancer Receiving Chemoradiation

Elvio G. Russi,[1] Judith E. Raber-Durlacher,[2] and Stephen T. Sonis[3]

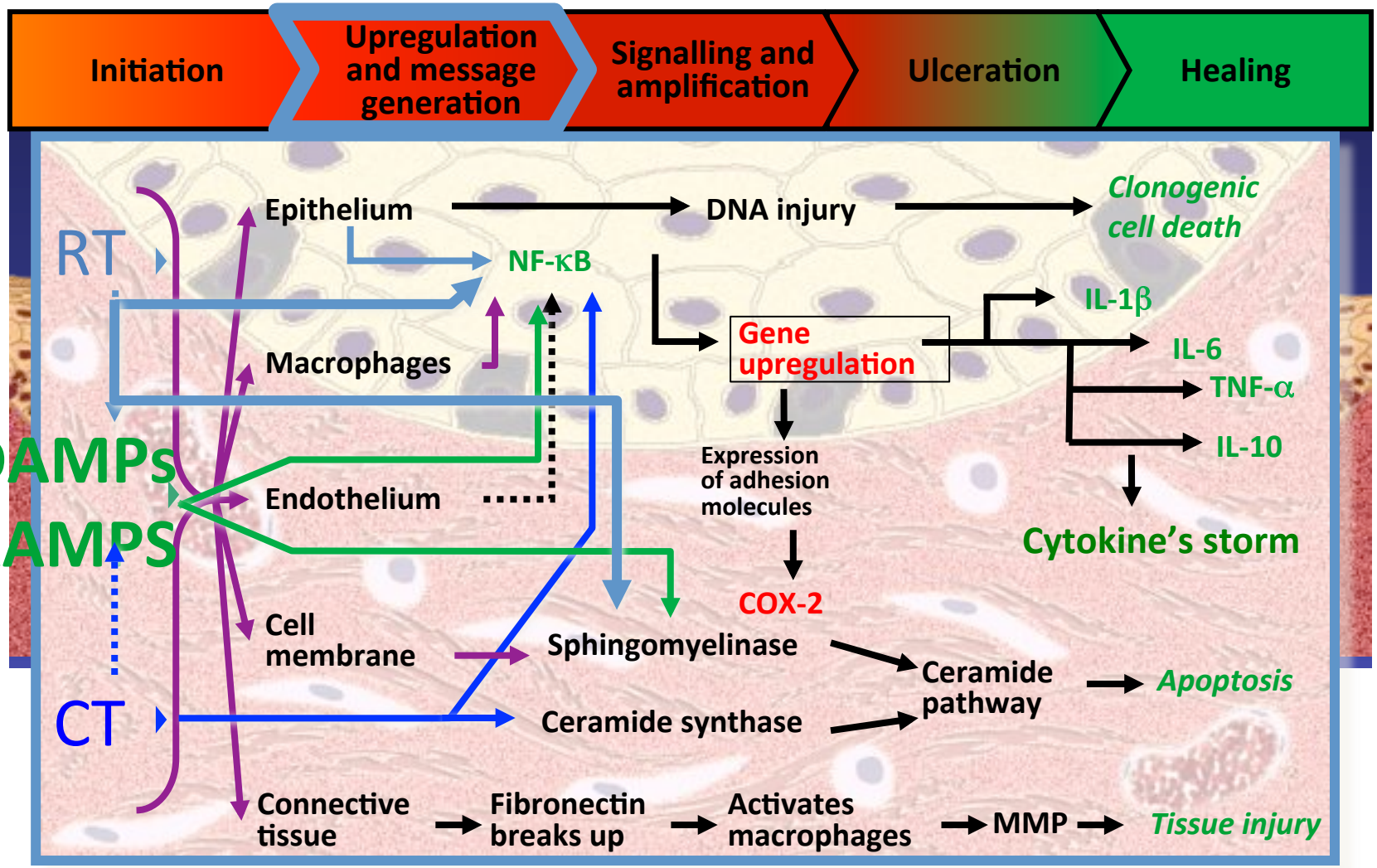
[1] *Department of Radiation Oncology, University Teaching Hospital A.O. "S. Croce e Carle", Via M. Coppino 26, 12100 Cuneo, Italy*
[2] *Department of Oral and Maxillofacial Surgery, Academic Medical Center, University of Amsterdam, Gustav Mahlerlaan 3004, 1081 LA Amsterdam, The Netherlands*
[3] *Division 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

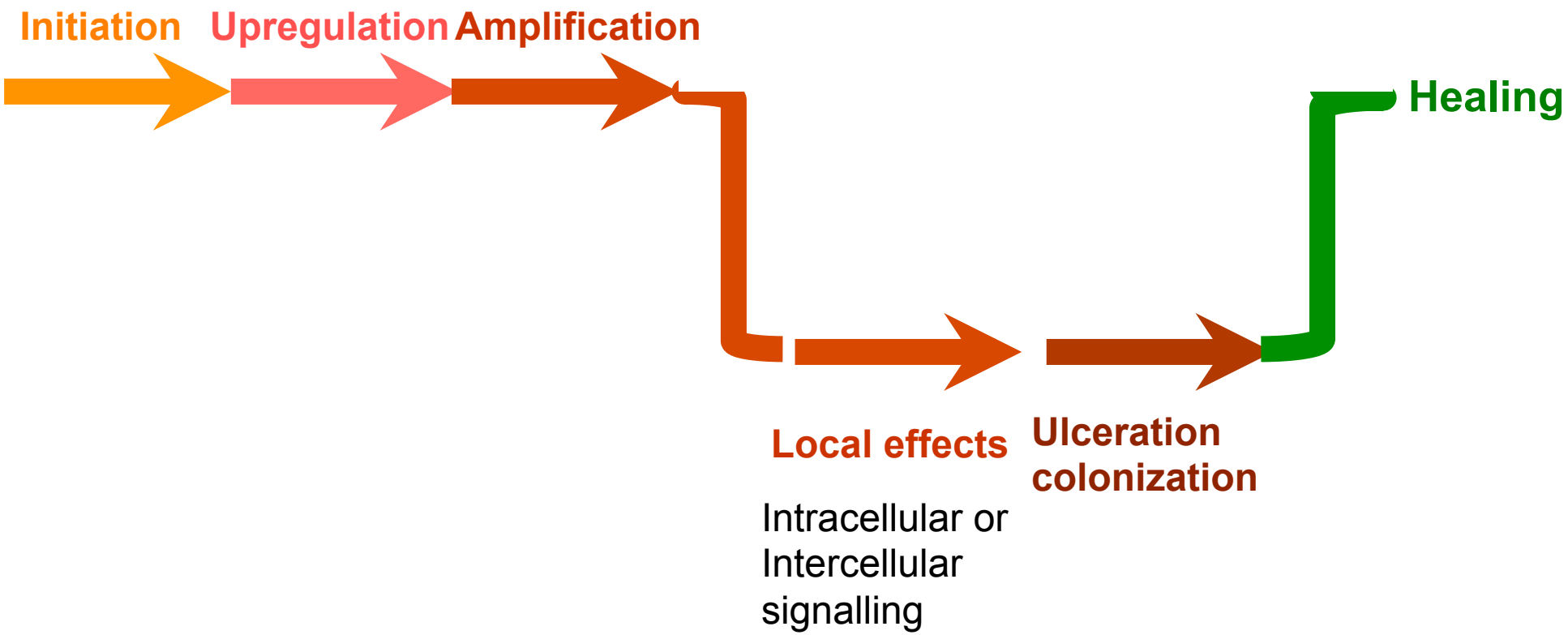



Initiation
Upregulation
Amplificatio
Healing
Local effects
Intracellular or
Intercellular
signalling
Ulceration
colonization

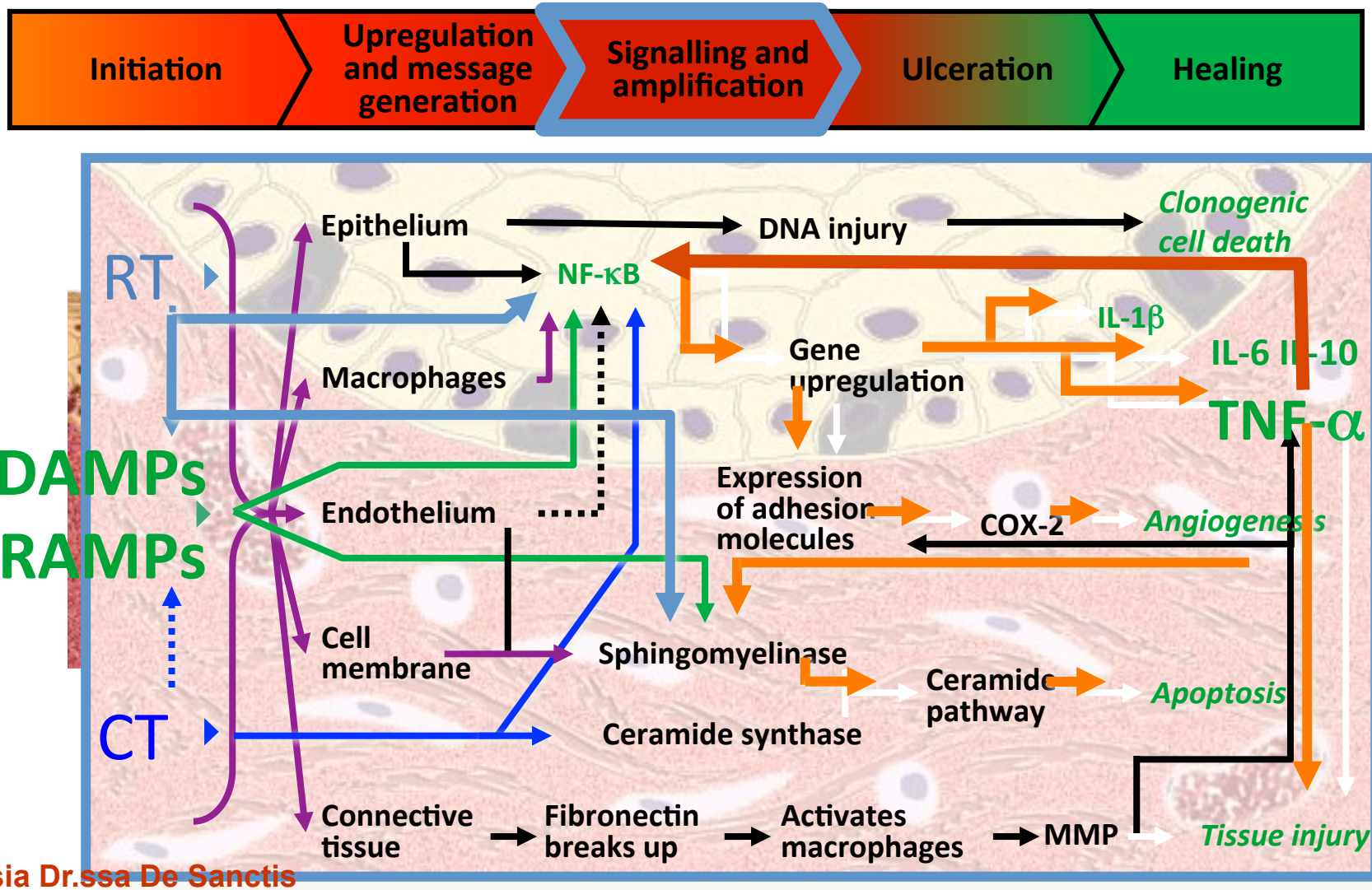
Simultaneous biological events in all tissues



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


Initiation
Upregulation
Amplification
Healing
Local effects
Intracellular or
Intercellular
signalling
Ulceration
colonization

Biological Cross-talk and signal amplification



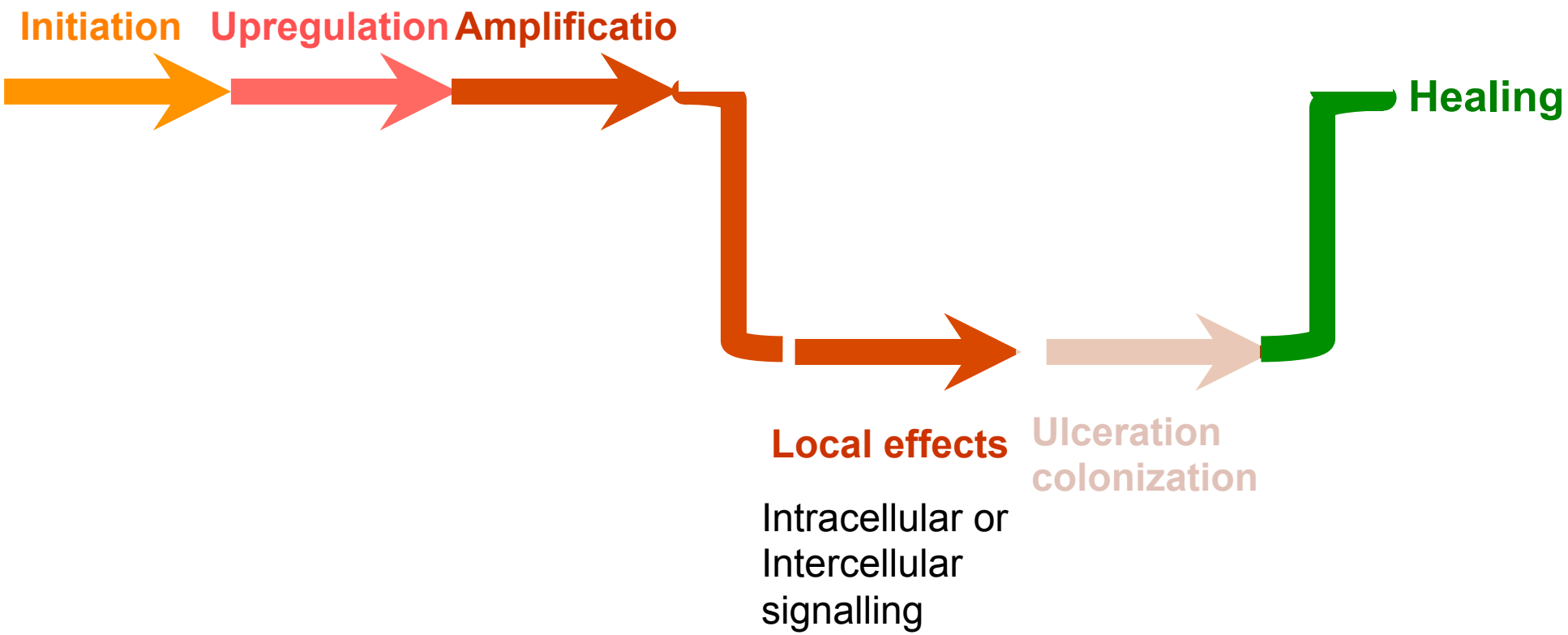
Cortesia Dr.ssa De Sanctis

dermatitis **mucositis**

xerostomia

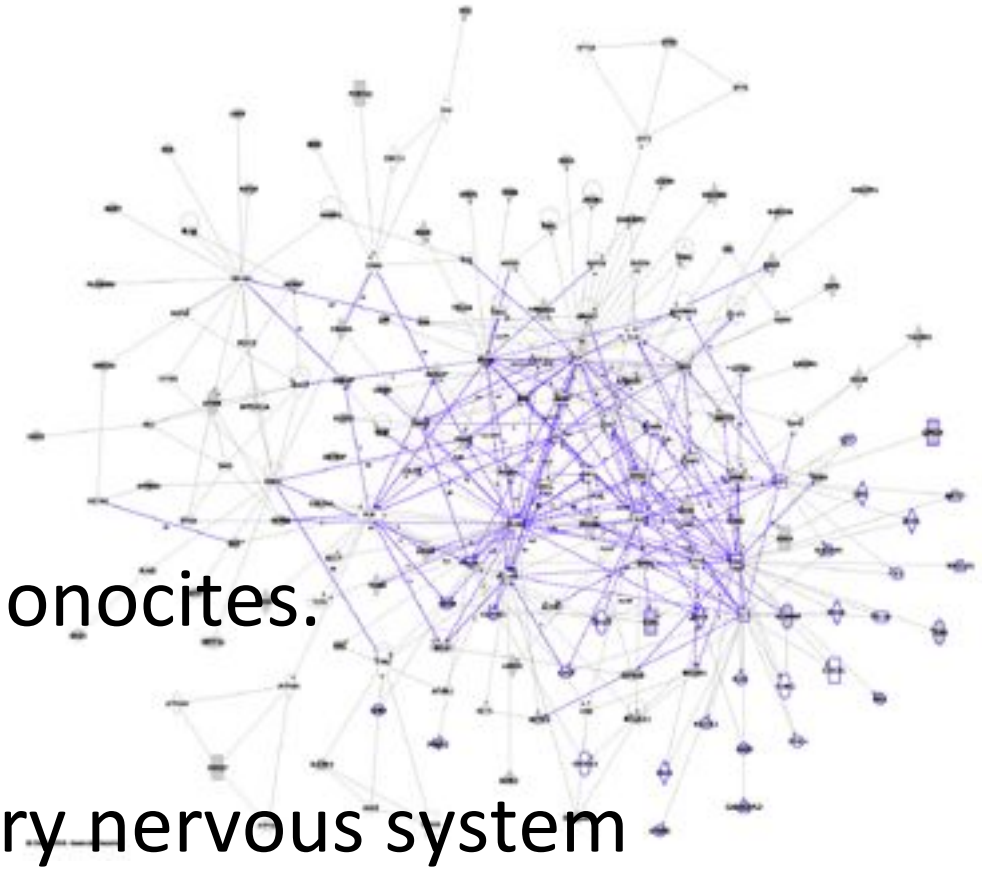
pain

dysphagia


Initiation
Upregulation
Amplificatio
Healing
Local effects
Ulceration
colonization
Intracellular or
Intercellular
signalling

Signalling amplification endocrine-like effects

- NFkB, TNFa, IL-1b and IL-6 bloodstream level
- Genetic changes in peripheral blood monocites.
- Activation of sensory nervous system



Fatigue Cachexia

dermatitis mucositis

xerostomia

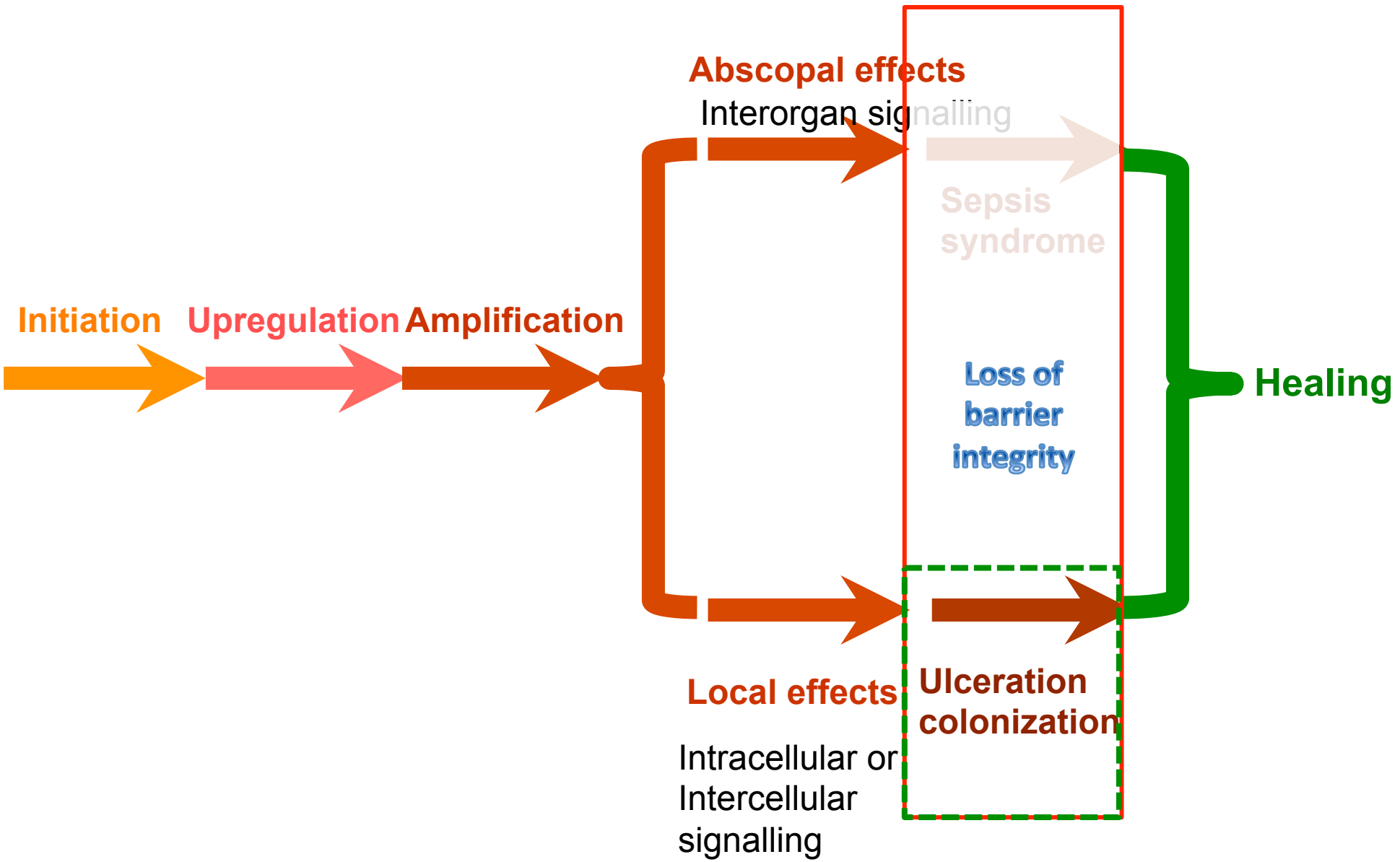
neutropenia

pain

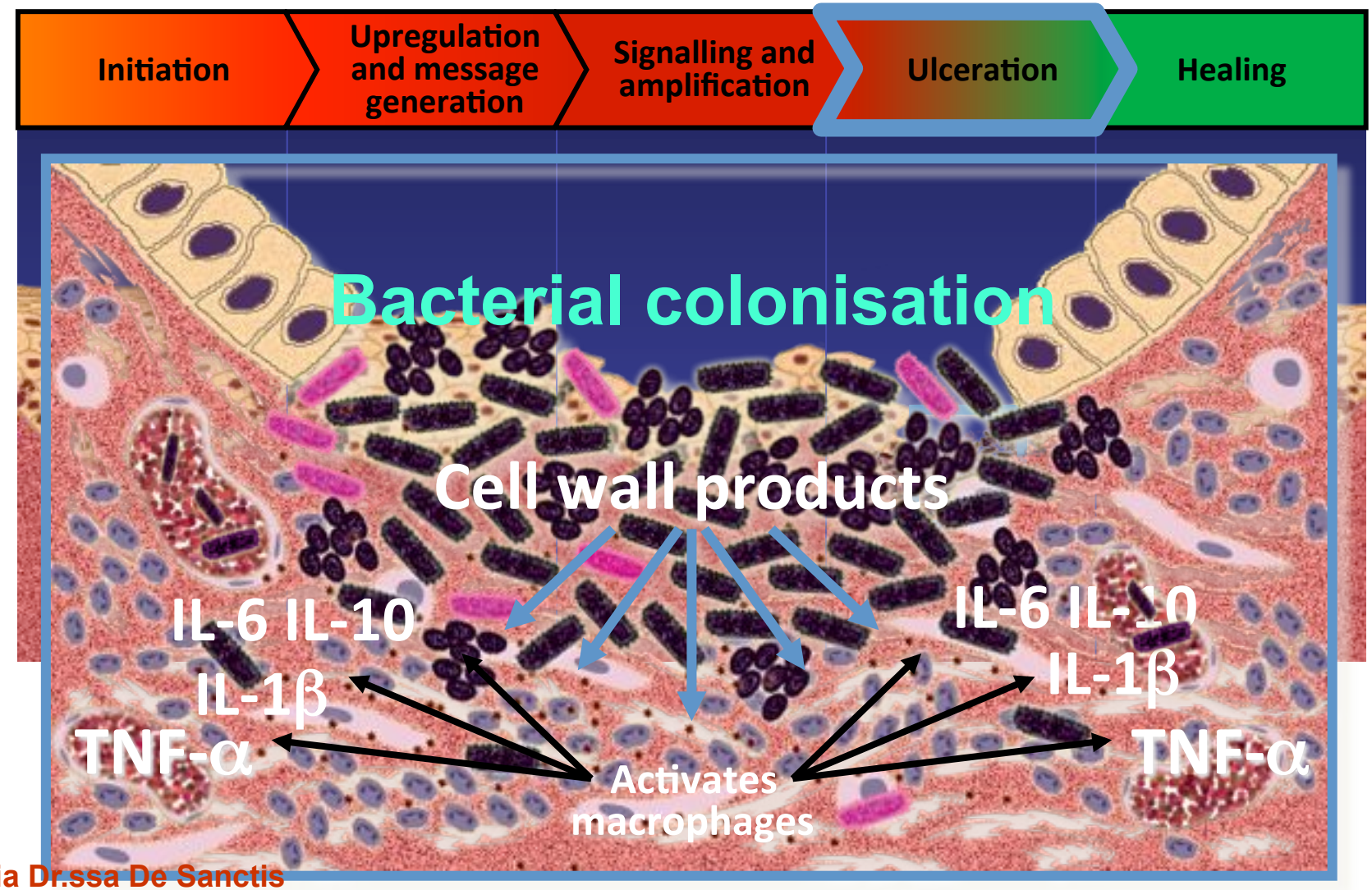
fever

dysphagia

SIRS


Abscopal effects
Interorgan signalling
Sepsis syndrome
Initiation
Upregulation
Amplification
Loss of barrier integrity
Healing
Local effects
Intracellular or Intercellular signalling
Ulceration colonization

Loss of barrier integrity with sepsis risk and pain

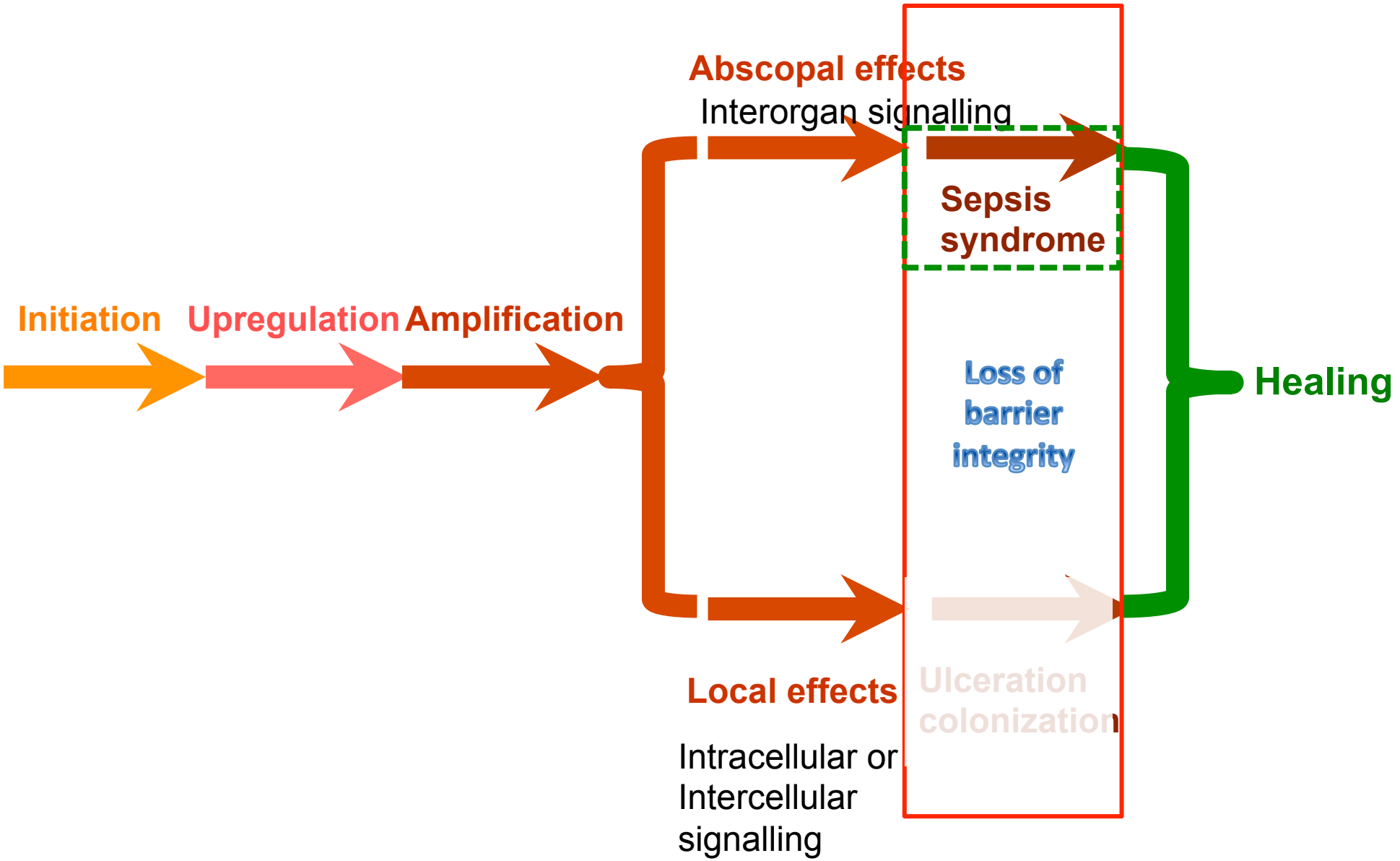


Cortesia Dr.ssa De Sanctis

ceration Phases

complication

Colonization

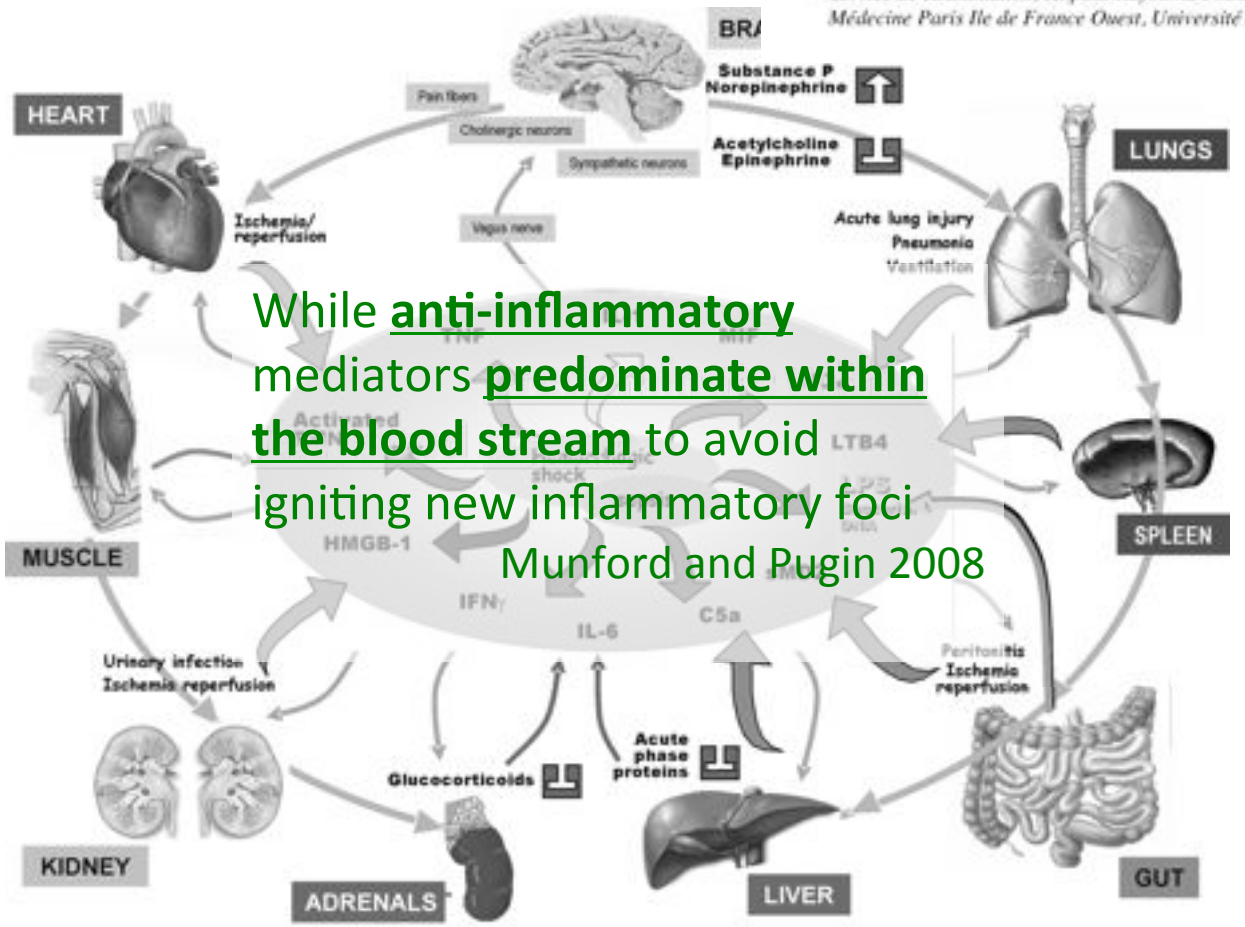

Abscopal effects
Interorgan signalling
Sepsis syndrome
Initiation
Upregulation
Amplification
Loss of barrier integrity
Healing
Local effects
Ulceration colonization
Intracellular or Intercellular signalling

Journal of Endotoxin Research, Vol. 12, No. 3, 2006

Compartmentalization of the inflammatory response in sepsis and SIRS

Jean-Marc Cavaillon[1], Djillali Annane[2]

[1]*Cytokines & Inflammation, Institut Pasteur, Paris, France*
[2]*Service 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.

dermatitis mucositis

xerostomia

pain

dysphagia

neutropenia

fever

SIRS

Fatigue Cachexia

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

Consensus conference on supportive care
in concurrent chemo-radiation of head and neck cancers

Daris Ferrari
Fabio Trippa
Giuseppe Sanguineti
Lisa Licitra
Paolo Bossi
Vitaliana De Sanctis
Anna Merlotti
Antonio Schindler
Daniela Alterio
Fausto Chiesa
Marco Merlano
Massimo Spadola
Nerina Denaro
Nicole Pizzorni
Orietta Caspiani
Sergio Riso
Valeria Zurlo
Antonello Lombardo
Francesco Moretto
Marco Benasso
Mario Grosso
Monica Rampino
Ombretta Ciotti
Fabiola Paiar
Graziella Pinotti
Maria Grazia Ghi
Salvatore Grisanti
Agostino Paccagnella
Alessandro Gava
Carla Ripamonti
Cecilia Gavazzi
Francesco Caponigro
Francesco Valduga
Giovanni Pavanato
Jessica Lops
Maria Cossu Rocca
Maria Soloperto
Almalina Bacigalupo
Aurora Mirabile
Elvio Russi
Fulvio Crippa
Gianmauro Numico
Andrea Bolner
Enzo Ruggeri
Giuseppe Azzarello
Mario Airoldi
Alessandra Majorana
Corrado Paganelli
Ester Orlandi
Federico Di Rosario
Giorgio Gastaldi
Lucia Vassalli
Michela Buglione
Piero Nicolai
Roberta Cavagnini
Robero Maroldi
Stefano A. Salgarello
Stefano Magrini

Le società scientifiche
AIOM
AIRO
AIOCC

Finalità della gestione della tossicità

- **La gestione delle tossicità ha l'obiettivo di ridurre le mortalità ….**

- **…ma cosa sappiamo circa la qualità della vita di questi pazienti? … e ….**

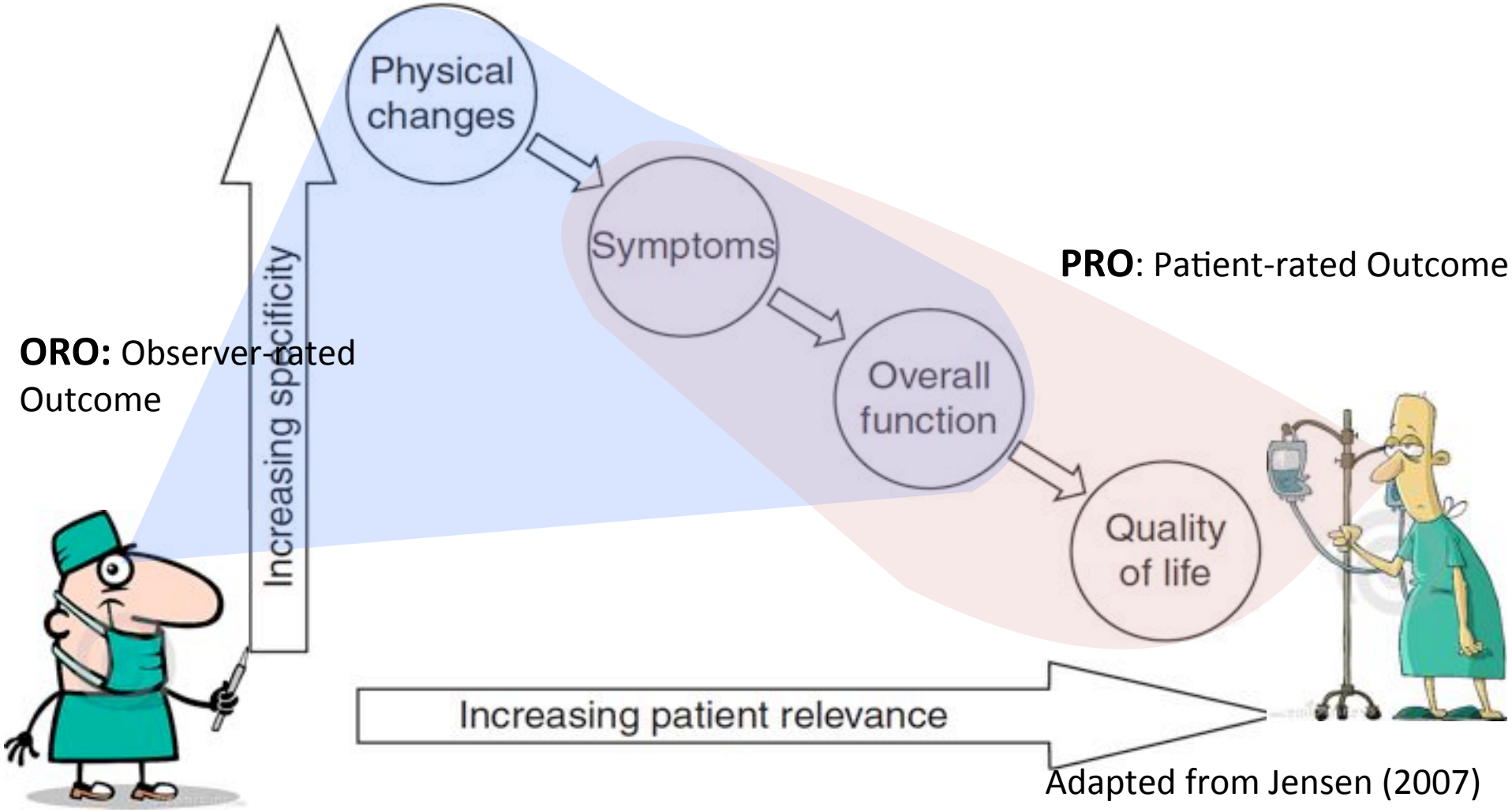
- **…come la misuriamo?**

Main topics

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

Come sono stimati I sintomi in letteratura?

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



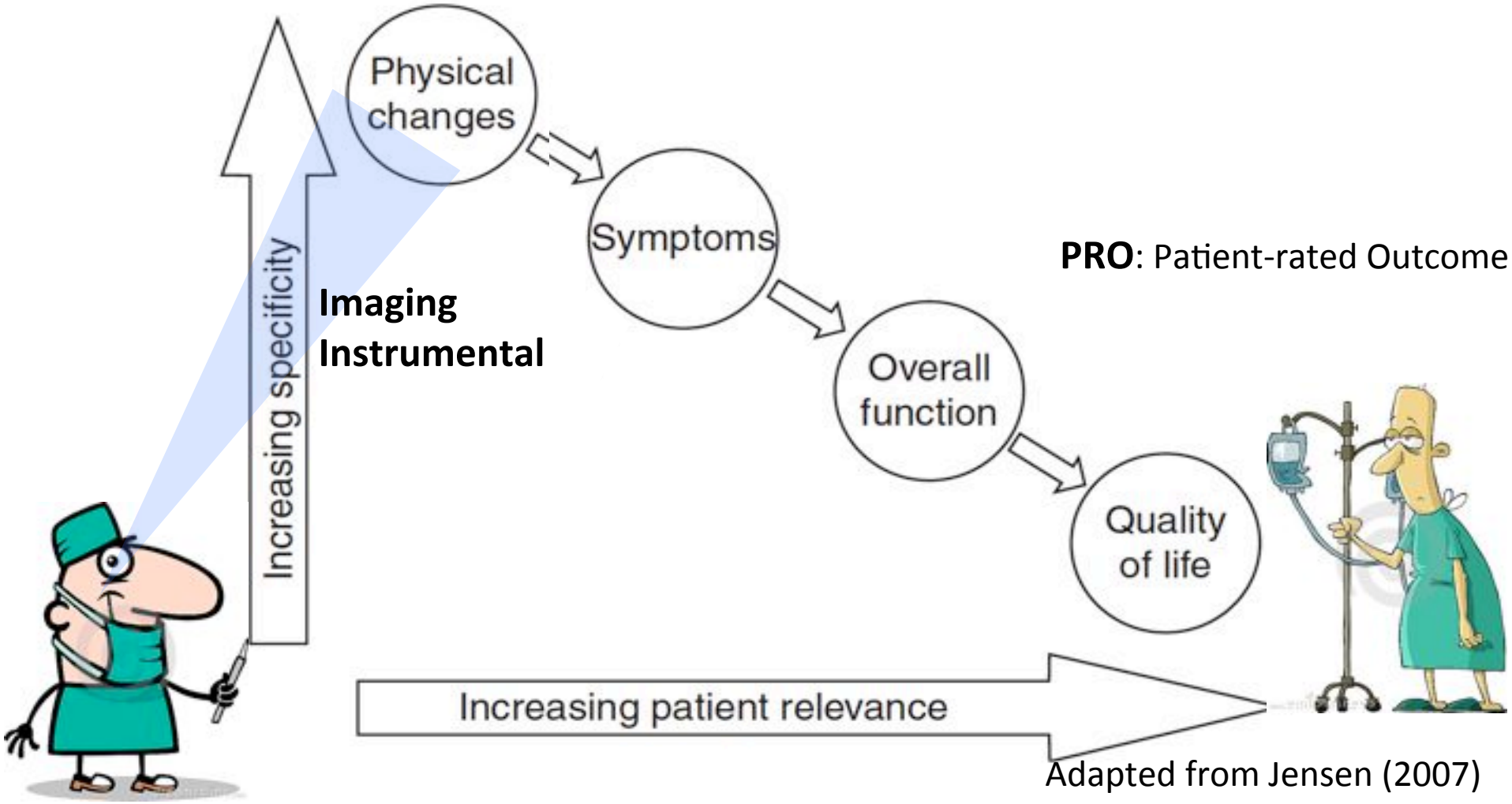
Adapted from Jensen (2007)

OBSERVER RATED

Biological and Physiological Variables

Wilson IB JAMA 1995

Valutazione analitica



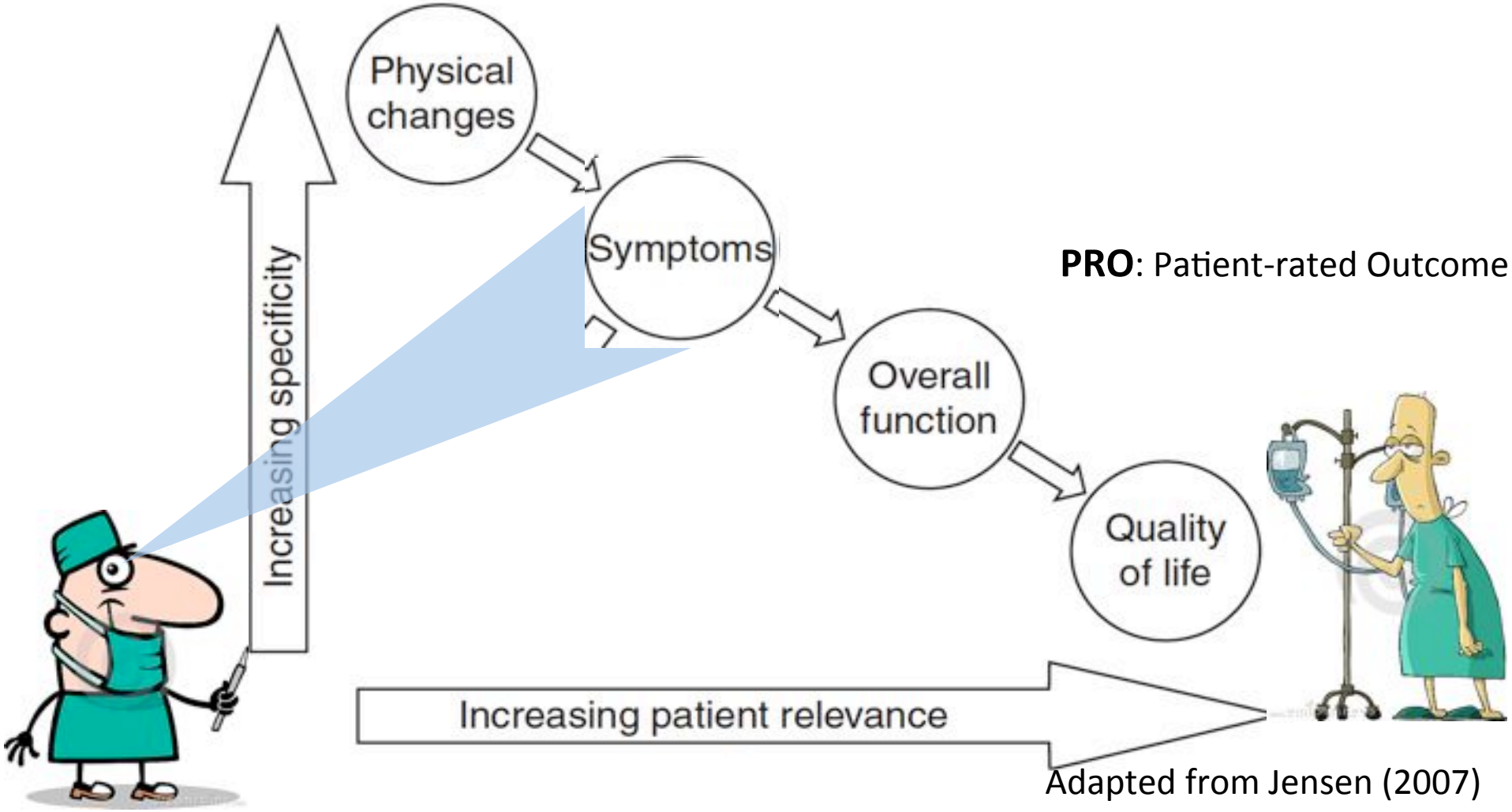
PRO: Patient-rated Outcome

Adapted from Jensen (2007)

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



PRO: Patient-rated Outcome

Adapted from Jensen (2007)

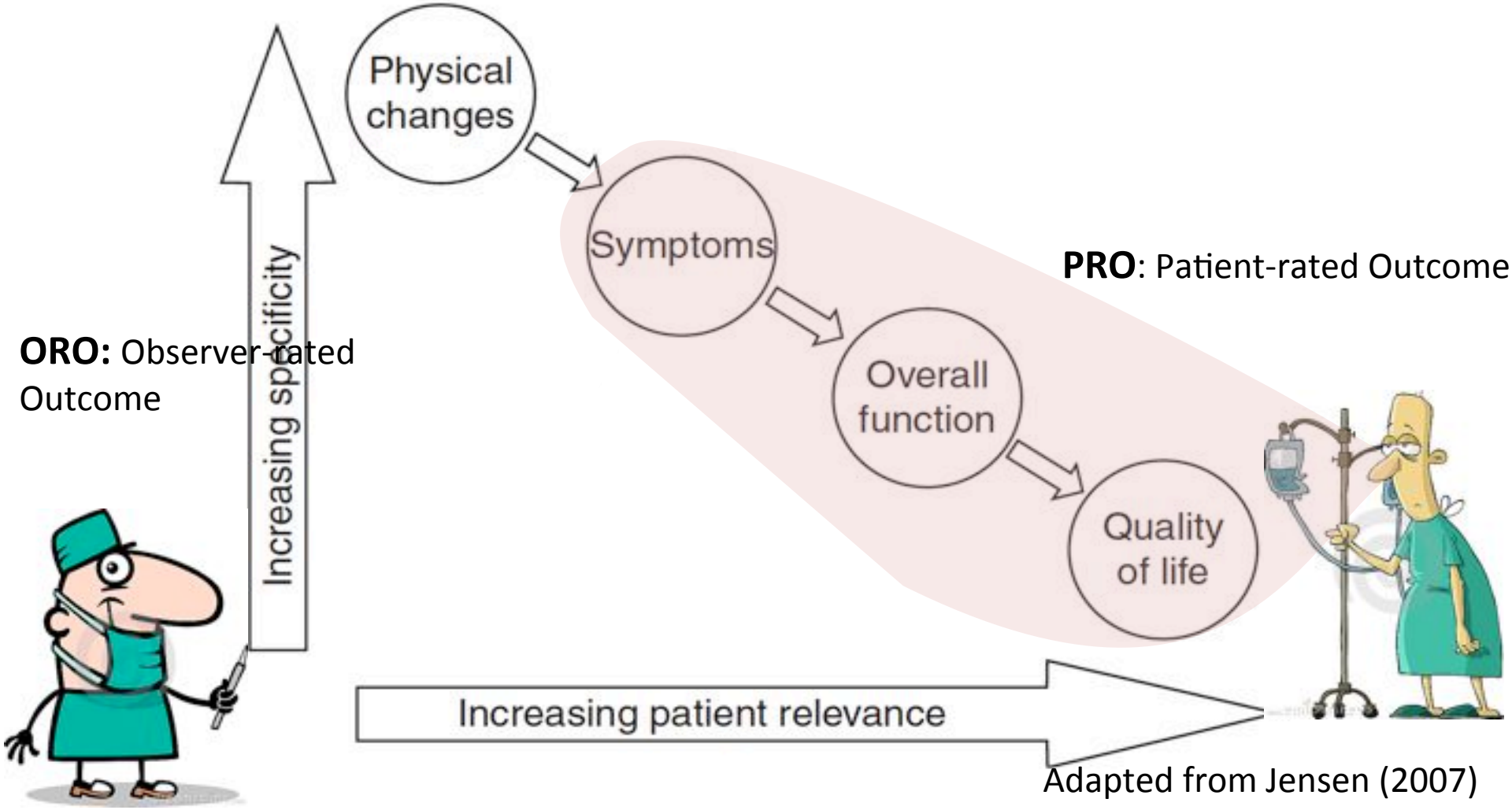
Observer-rated Subjective symptoms

- 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.



Adapted from Jensen (2007)

OBSERVER RATED

Biological and Physiological Variables

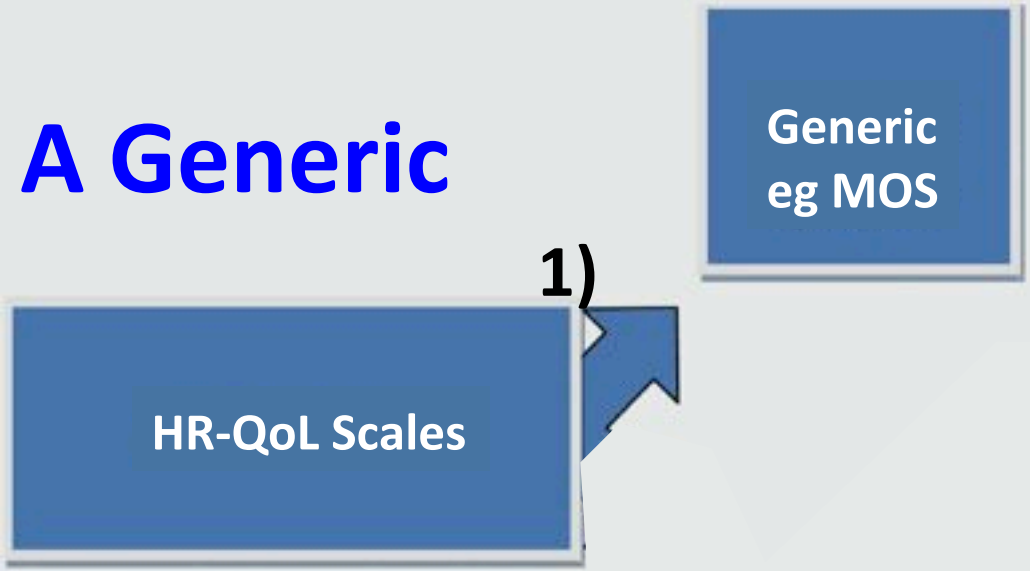
Quali le PRO scale?

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



Medical Outcome Study short Form
MOS-SF36

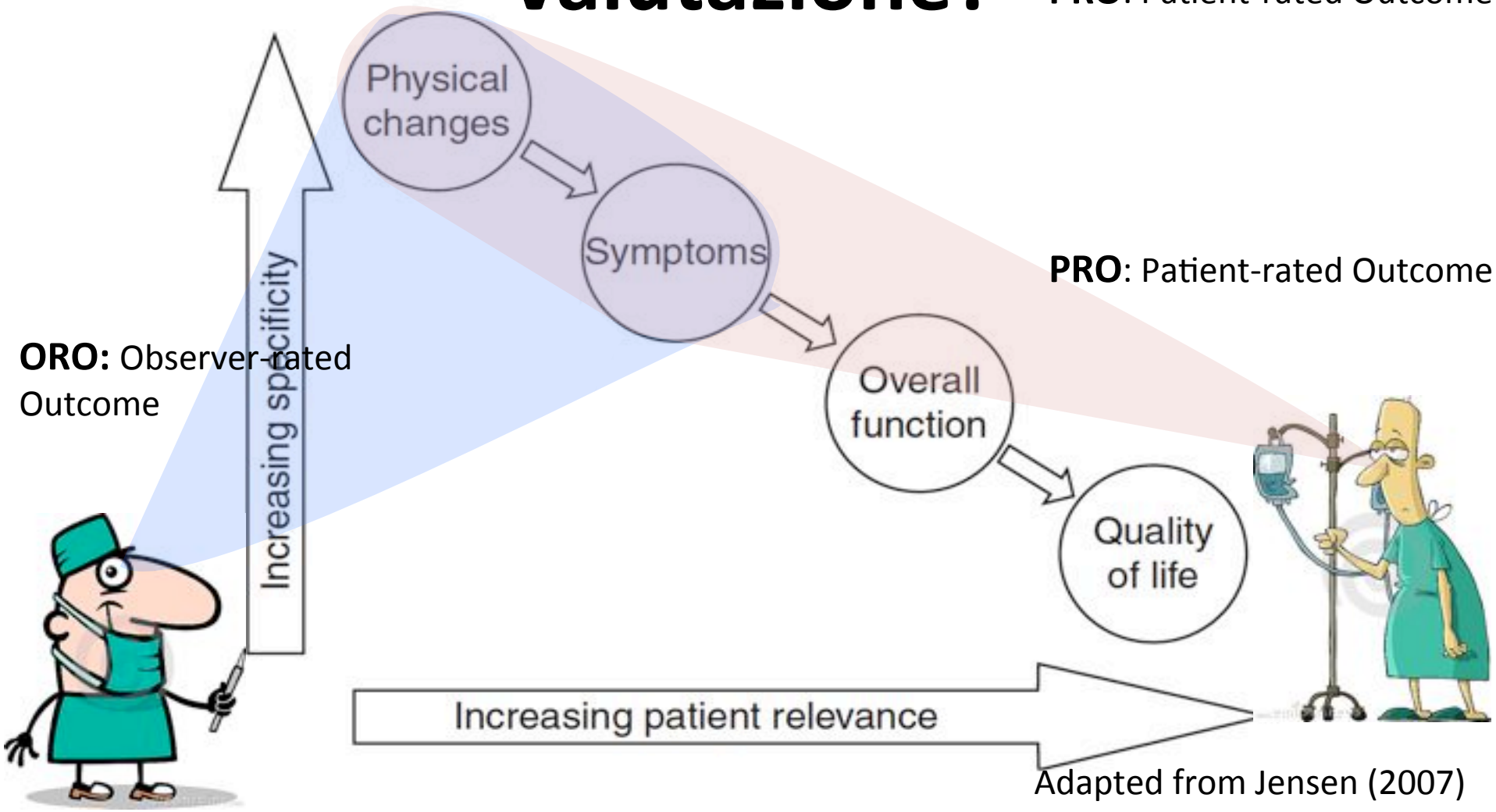
B Specific

PRO Tools

Sayed CTR 2009 Modified

Quali le relazioni tra i due tipi di valutazione?

PRO: Patient-rated Outcome



PRO: Patient-rated Outcome

ORO: Observer-rated Outcome

Adapted from Jensen (2007)

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

Jensen 2007

PRO

- EORTC C30
- H&N35

PRO

Warning:
Aspiration/Penetration & EORTC QLQ H&N35

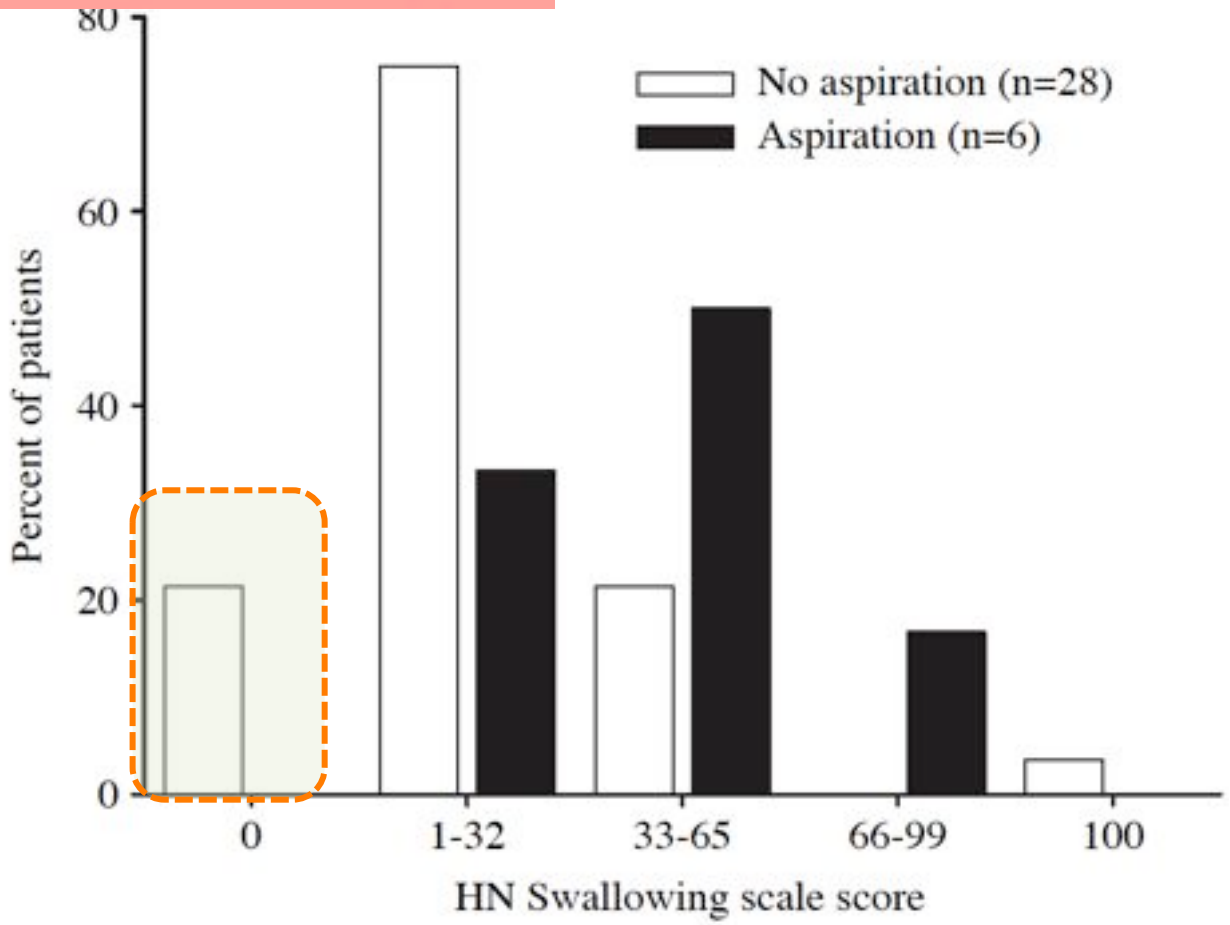
- ***Inadequate sensitivity, specificity, and predictive values of patient self- reporting with the EORTC QLQ-H&N35 scales*** have been identified in comparisons to the objective findings **of aspiration or penetration in patients undergoing FEES evaluation of swallowing**
  - (Jensen et al.2007b).

ma…..

Valore predittivo negativo fra

Disturbi di deglutizione/Aspirazione

0.94 (0.70; 1.0)

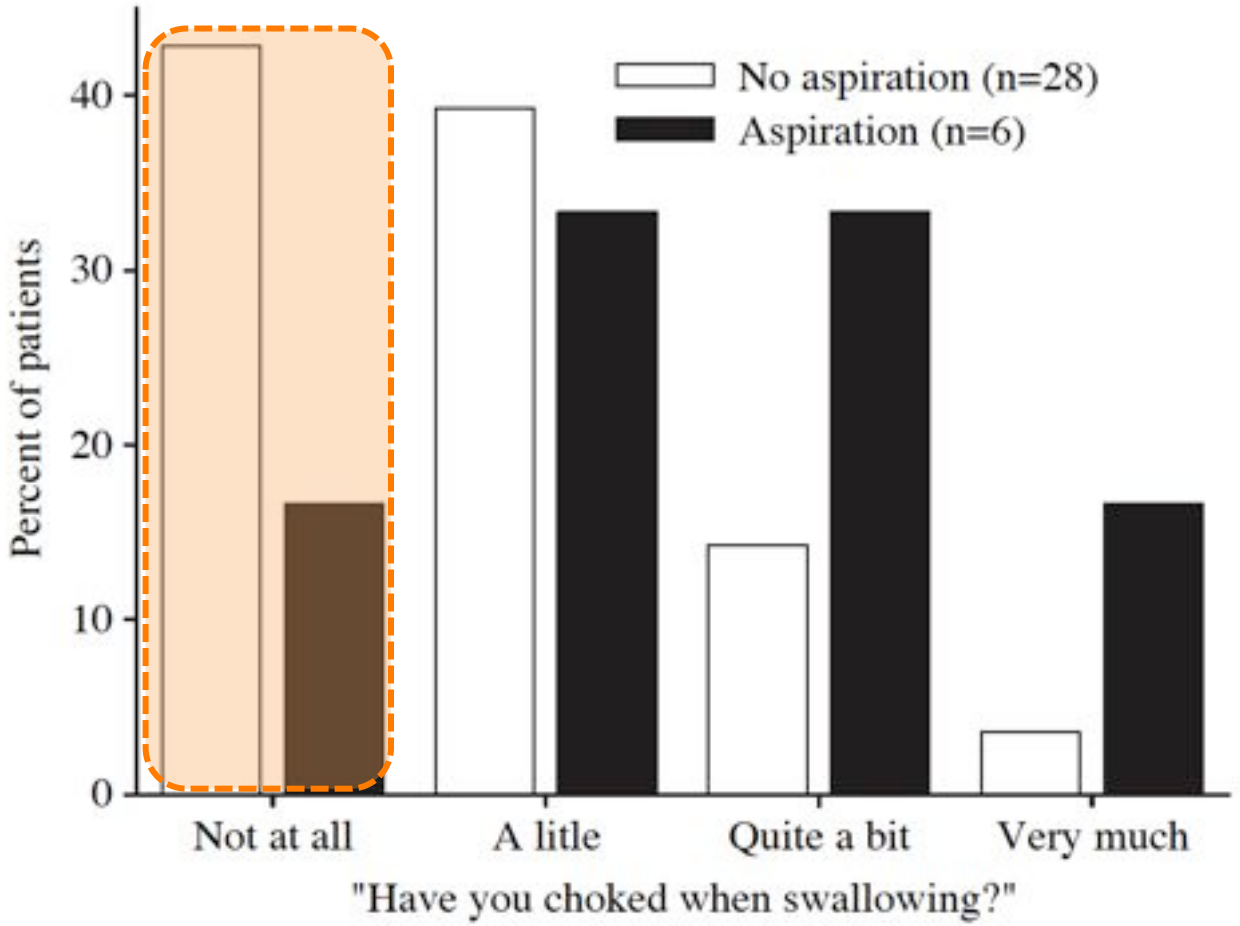


Jensen 2007

Valore predittivo negativo fra

“Chocking”/Aspirazione

0.92 (0.64; 1.0)

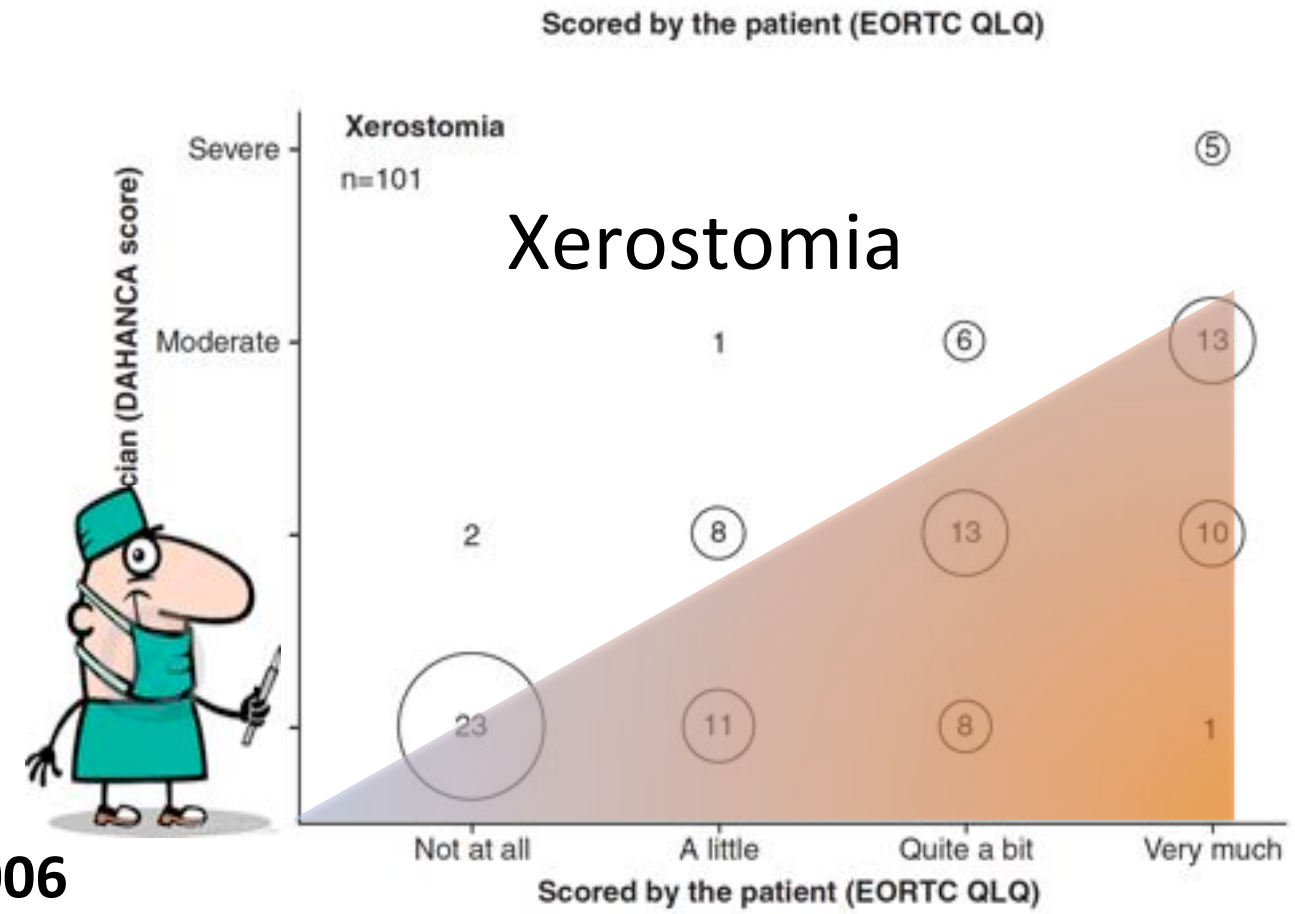


Jensen 2007

PATIENT REPORTED OUTCOME e PHYSICIAN ASSESSED TOXICITIES

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

MEASUREMENT



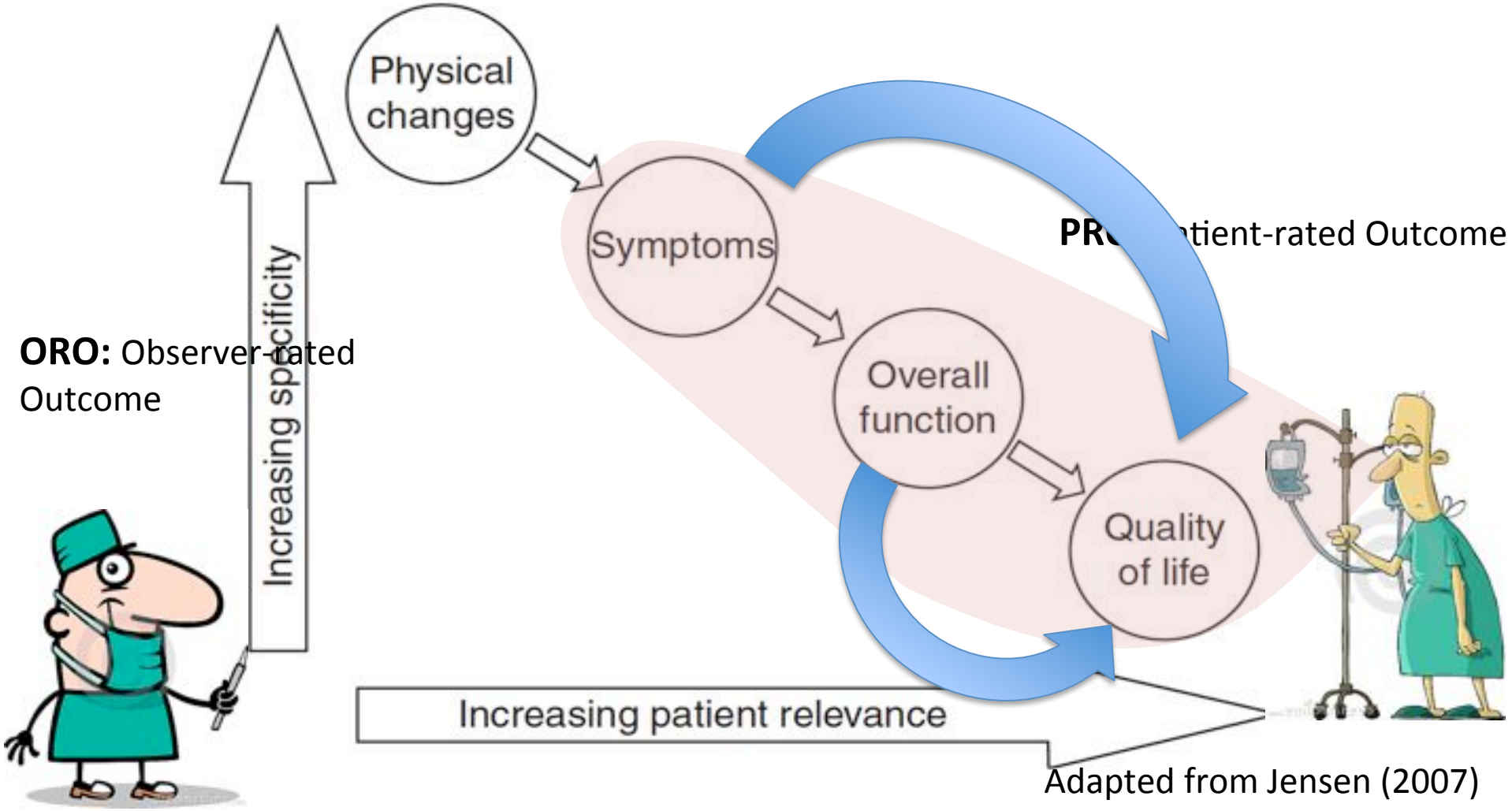
Xerostomia

Jensen 2006

Main topics

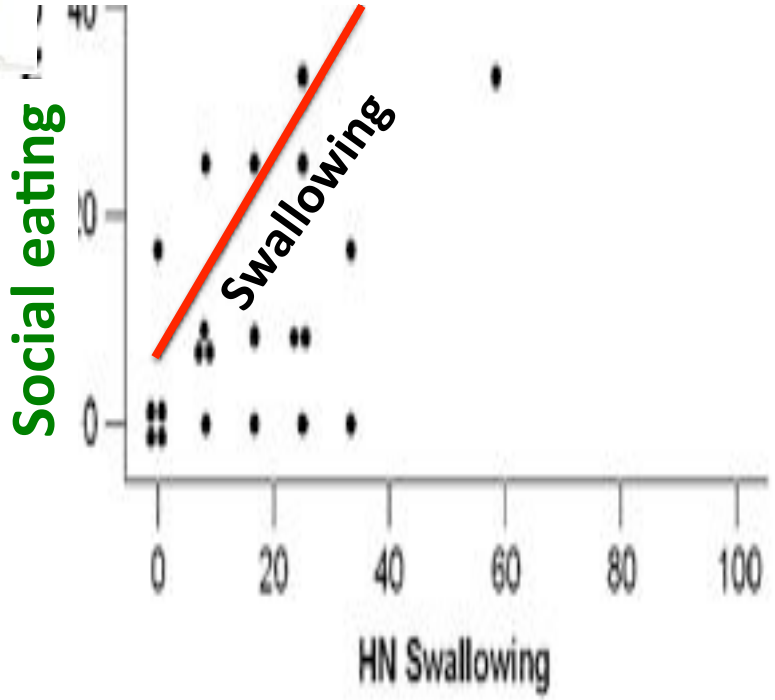
- Patogenesi delle tossicità
- Misurazione delle tossicità
- Inferenza delle tossicità sulla QoL

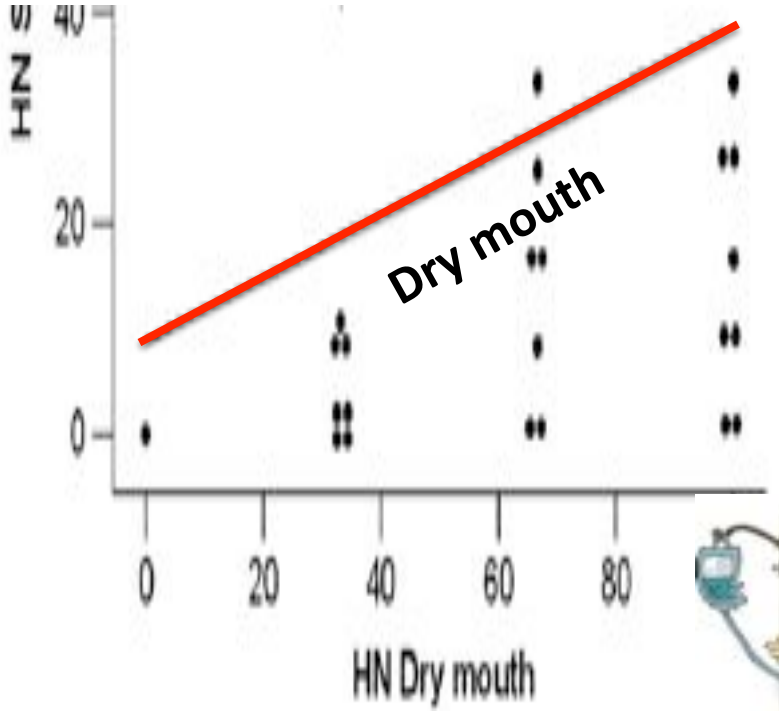
Relazione tra PRO-evaluated domains and HR-QoL



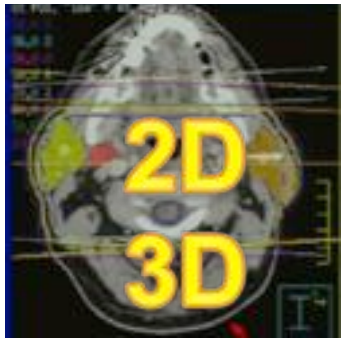
Adapted from Jensen (2007)

Swallowing dysfunction, dry mouth vs. HR-QoL

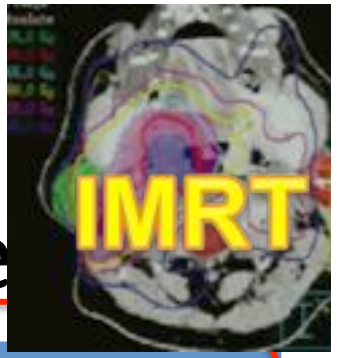




Swallowing had better correlation with overall QoL, physical function **and social eating scale** than all other H&N specific symptoms, e.g. xerostomia ***Jensen 2007***



Studi prospettici e randomizzati sul rinofaringe

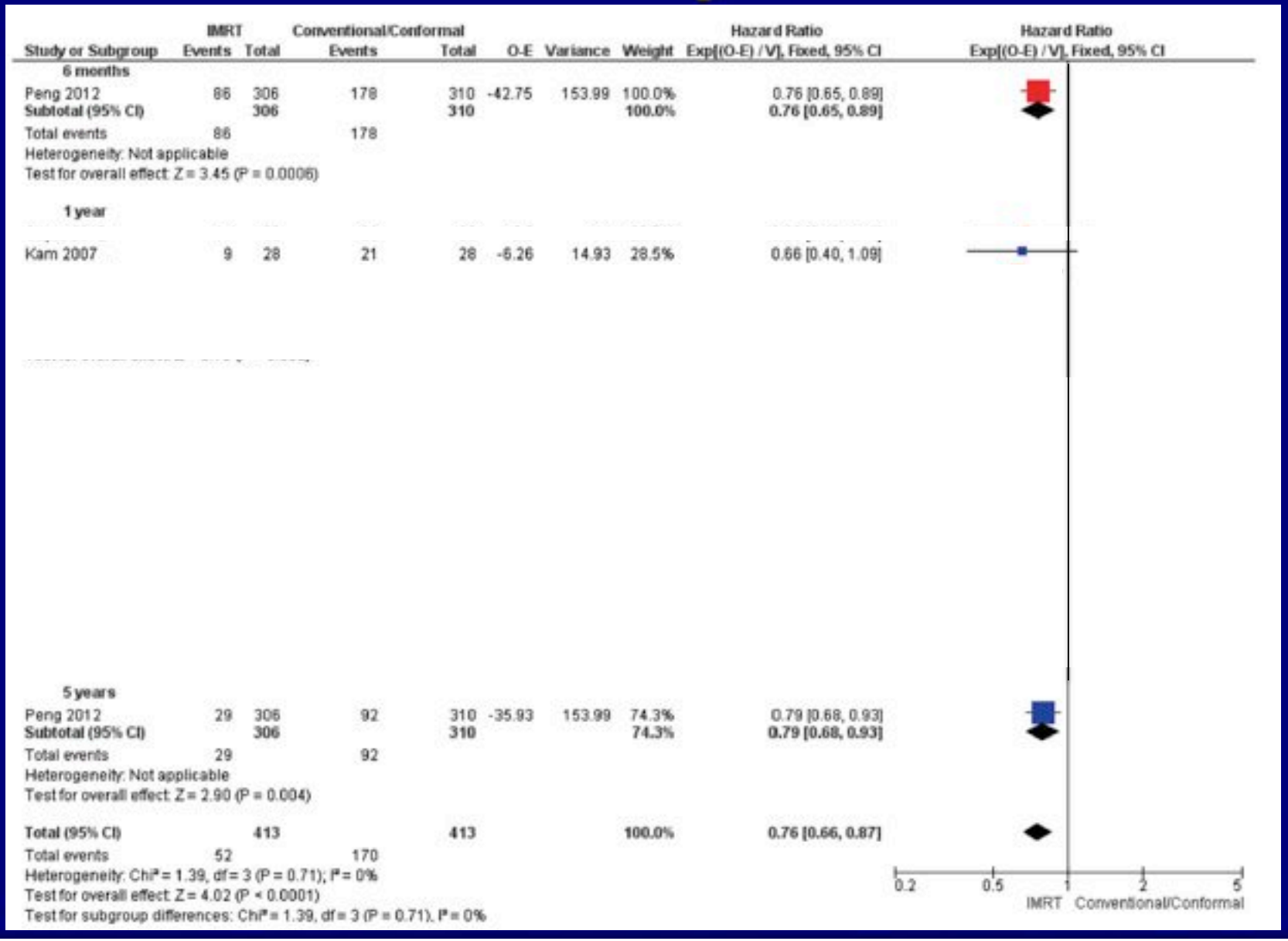


Authors	Treatment	N. pts	QoL	HN35	Xerostomia
			Randomizzati		
Pow 2006	IMRT	21	Function <.05	Swallowing Speech Sticky saliva	Salivary flow (analytic) (no-Observed rated)
	2D	24			
kam 2007	IMRT	28			1 years 39.3%
	2D	28			1 years 82.1%
Peng 2012	IMRT	306			5 years 9.5%
	2D	310			5 years 29.7%
			Prospettico		
Fang 2008	IMRT	203	Global Fatigue	Dry mouth	
	3D				

Risultati degli studi randomizzati e prospettici sul rinofaringe

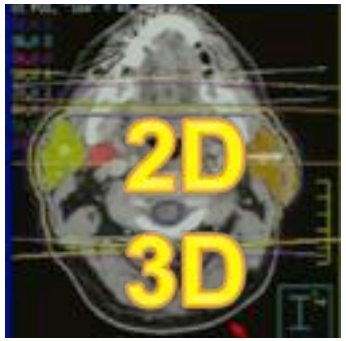
- Miglioramento della Xerostomia.

Xerostomia Improvement

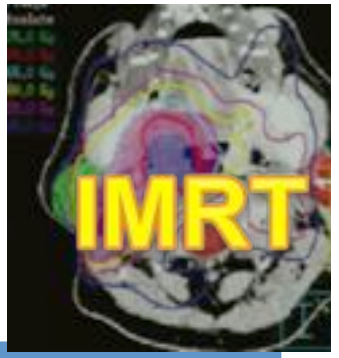


Risultati degli studi randomizzati e prospettici sul rinofaringe

- Miglioramento della Xerostomia
- **Miglioramento della QoL**



Studi prospettici e randomizzati sul rinofaringe



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Risultati degli studi randomizzati e prospettici sul rinofaringe

- Miglioramento della Xerostomia
- Miglioramento della QoL
- **Probabile miglioramento della sopravvivenza**

No difference in survival

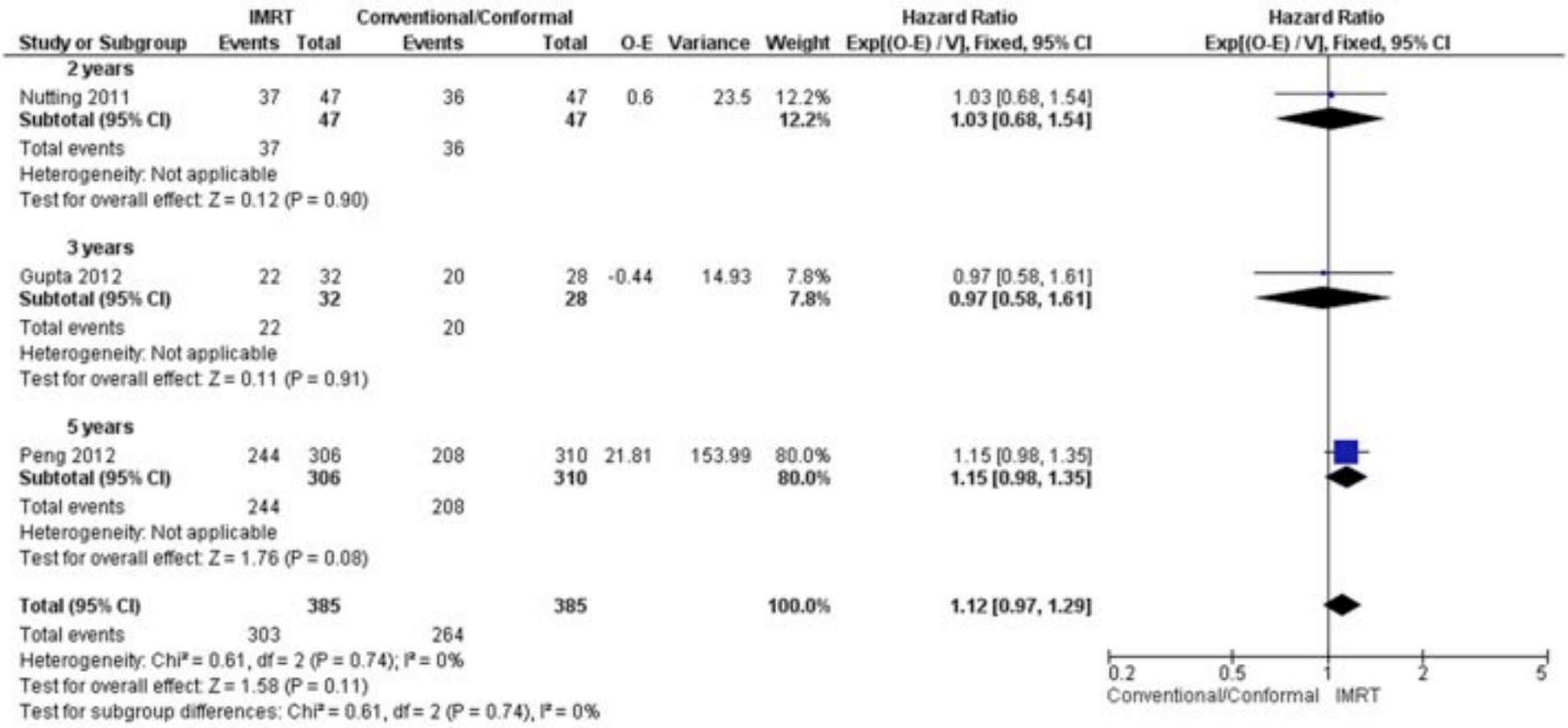

Fig. 4. Conventional/conformal RT versus IMRT and overall survival.

Comparative Effectiveness

- SEER-Medicare study of 3172 patients with head and neck radiotherapy
- 1,056 (33%) treated with IMRT
- Adjusted HR for CSS with IMRT (0.6-0.72)

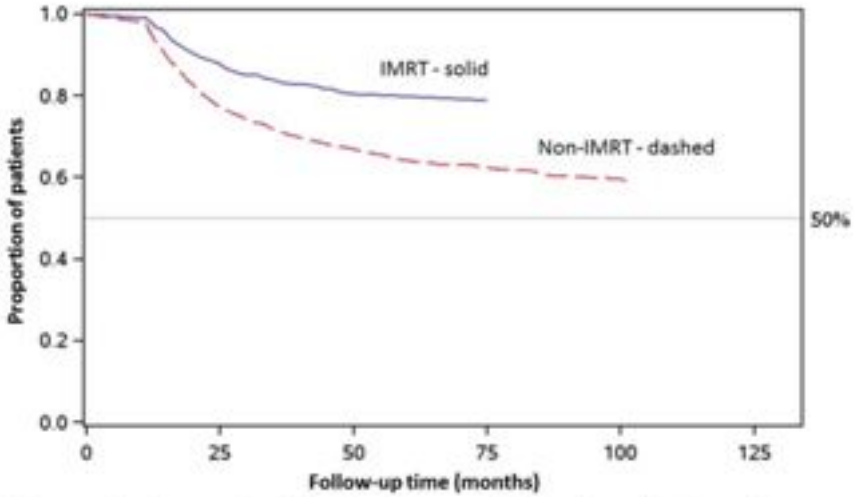

Figure 1. Impact of intensity-modulated radiation therapy (IMRT) on cause-specific survival. Kaplan-Meier curve depicting the cause-specific survival with time for patients treated with IMRT (dashed) compared to those treated with non-IMRT (solid).

Beadle BM Cancer 2014

Conclusion

- Ultimately, it is **highly unlikely that any additional randomized trials will be performed on IMRT versus more conventional techniques**, and thus **analyses of its value and cost-effectiveness** hinge on
  - the clear xerostomia benefits,
  - potentially improved global quality-of-life, and
  - questionable survival gains.

- 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