EVIDENCE BASED CONFOUNDING FACTORS IN THE ASSESSMENT OF ORAL MUCOSITIS

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Faculty Disclosure

	No, nothing to disclose
x	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Astra Zeneca, Roche, MSD	x	X						

Agenda

- The importance of confounding factors (CFs) in clinical trials

- Patient-related CFs
- Disease-related CFs
- Treatment-related CFs

- Outcome measures as source of bias

The importance of confounding factors (CFs) in clinical trials

- The internal validity of a study depends on the extent to which biases have been accounted for

- Underestimation or overestimation of the true association exposure → outcome
- Selection bias
- Information bias
- **Counfounding**

Confounding Factors

- Variables that may compete with the exposure (intervention we are studying) in explaining the outcome of a study

…therefore, CFs may mask or falsely demonstrate an «apparent» association

- (Un)equal distribution of CFs is key in quality of clinical trials!

Patient-related CFs

- Age
- Gender
- Oral hygiene
- Nutritional status (BMI)
- Comorbidities
- Drugs
- Smoking
- Salivary secretory function
- Genetic factors

Treatment-related CFs

- Previous treatments: surgery (extent, reconstruction), previous radiotherapy (RT)
- Dose, field of radiation
- RT technique
- Treatment interruptions
- Systemic therapy dose-intensity

Disease-related CFs

- Subsite
- Different pathogenesis: the example of HPV status in oropharyngeal cancer
- Inflammatory cytokines by the tumor itself

Patient-related CFs

- Nutritional status (BMI)

Table 3. Factors associated with severe adverse effects ($n = 74$)

	Diarrhea		Mucositis		TGI toxicity		Dose reduction	
	n (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
Gender								
Female	46.3	.21	37	.07	68.5	.06	64.8	.12
Male	30		15		45		45	
Age, years								
≥60	42.5	.91	22.5	.08	55	.17	62.5	.56
<60	41.2		41.2		70.6		55.9	
ECOG								
0–1	40.3	.4	**26.9**	**.03**	**58.2**	**.04**	59.7	.9
2–3	57.1		**71.4**		**100**		57.1	
Weight, kg								
≤58.6	48.8	.18	**43.9**	**.008**	**73.2**	**.03**	65.9	.21
>58.6	33.3		**15.2**		**48.5**		51.5	
Body mass index, kg/m^2								
≤24.3	32.5	.08	40	.07	62.5	.94	62.5	.56
>24.3	29.7		20.6		61.8		55.9	
Body surface, m^2								
≤1.7	41.8	.98	**41.8**	**.001**	67.3	.12	**67.3**	**.02**
>1.7	42.1		**0**		47.4		**36.8**	
Nutritional status								
Malnourished	46.5	.34	39.5	.06	**72.1**	**.04**	**74.4**	**.002**
Well-nourished	35.5		19.4		**48.4**		**38.7**	

Patient-related CFs

- Nutritional status (BMI)

Research Article

The Effects of Compliance with Nutritional Counselling on Body Composition Parameters in Head and Neck Cancer Patients under Radiotherapy

"…to evaluate the effects of compliance of patients with individual dietary counselling on toxicity of treatment"

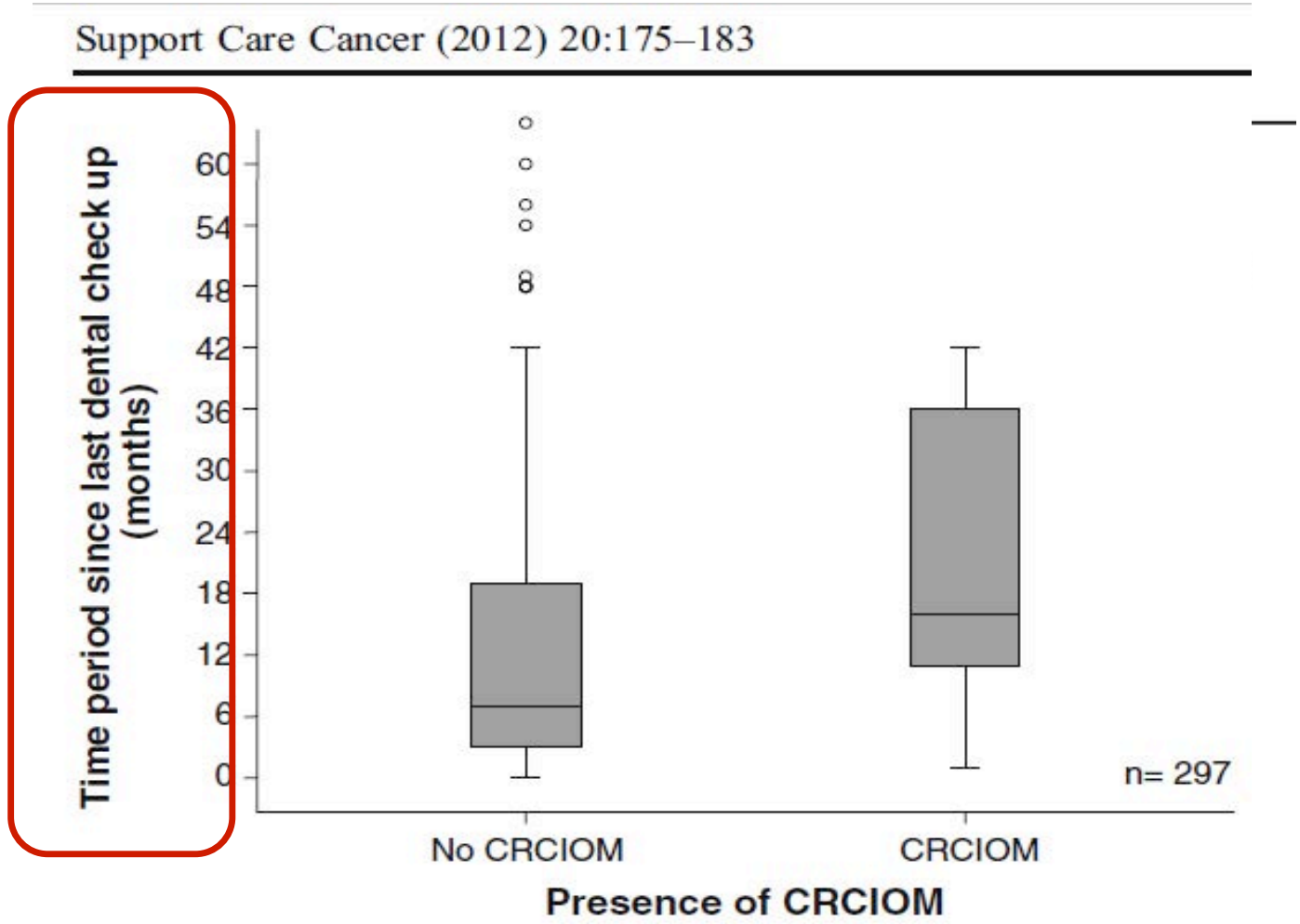
TABLE 4: Severity of mucositis with respect to compliance.

	Compliant patients		Noncompliant patients	
	n	%	*N*	%
Light mucositis ($n = 30$)	16	53.3	14	46.7
Heavy mucositis ($n = 18$)	2	11.1	16	88.9

Chi-square; $p = 0.009$.

Patient-related CFs

- Oral hygiene



Patient-related CFs

- Smoking status

Support Care Cancer (2012) 20:175–183
DOI 10.1007/s00520-011-1107-y

ORIGINAL ARTICLE

Prevalence of clinically relevant oral mucositis in outpatients receiving myelosuppressive chemotherapy for solid tumors

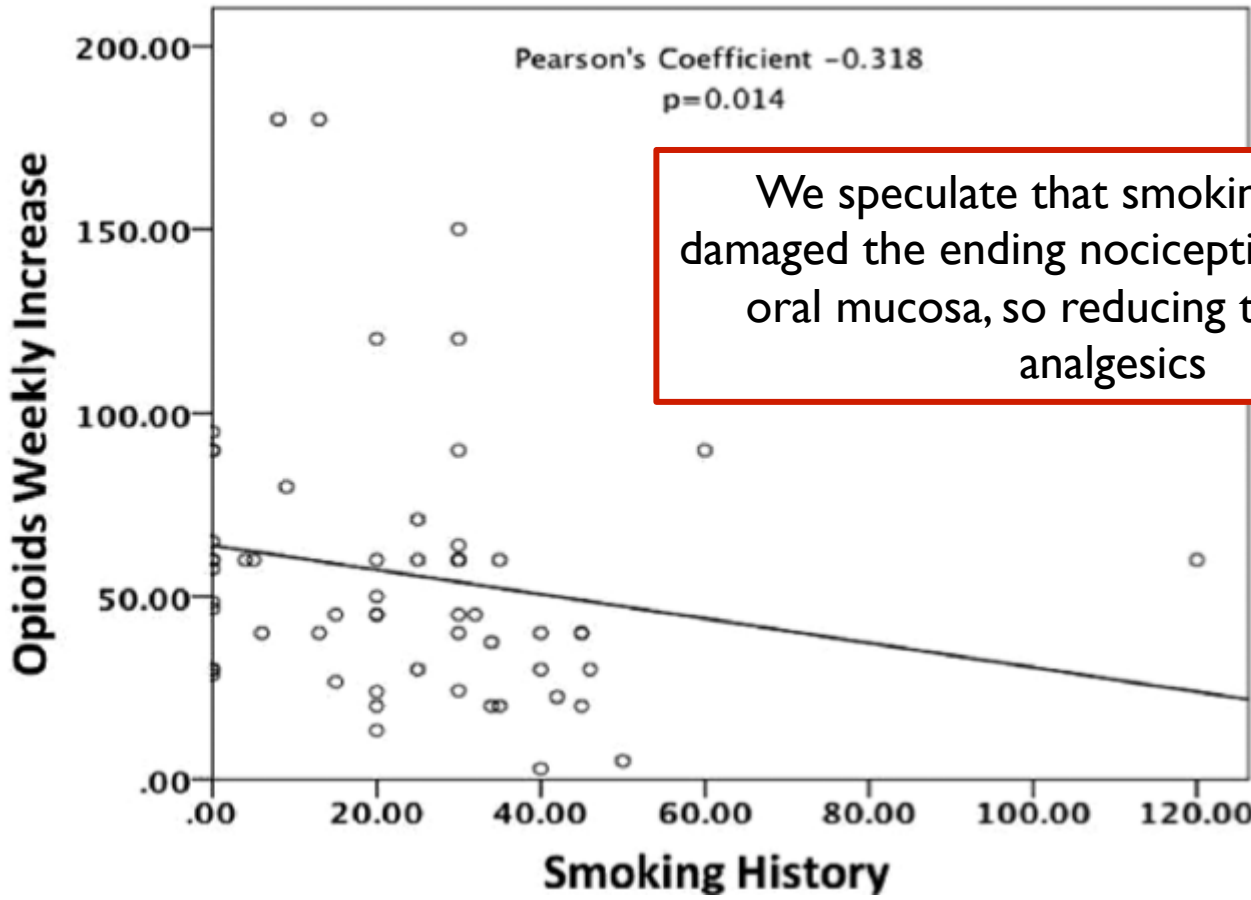
Stefan Wuketich · Stefan A. Hienz · Christine Marosi

Associations of predefined risk factors with CRCIOM

Overall, 55 patients (18.5%) were current smokers at the time of the examination. CRCIOM was found in 4.5% of the non-smoking patients. In contrast, among smoking patients, the prevalence was 12.7% ($p<0.05$).

Patient-related CFs

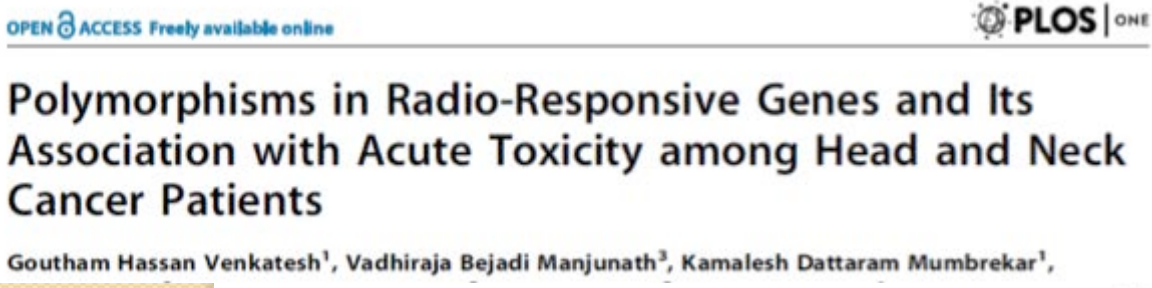
- Smoking status and mucosal-associated pain



We speculate that smoking may have damaged the ending nociceptive fibers of the oral mucosa, so reducing the need for analgesics

Patient-related CFs

- Genetic factors



OPEN ACCESS Freely available online

PLOS | ONE

Polymorphisms in Radio-Responsive Genes and Its Association with Acute Toxicity among Head and Neck Cancer Patients

Goutham Hassan Venkatesh[1], Vadhiraja Bejadi Manjunath[3], Kamalesh Dattaram Mumbrekar[1],

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 4, pp. 1187–1195, 2009

0360-3016/09/$–see front matter
doi:10.1016/j.ijrobp.2008.08.073

BIOLOGY CONTRIBUTION

ACUTE NORMAL TISSUE REACTIONS IN HEAD-AND-NECK CANCER PATIENTS TREATED WITH IMRT: INFLUENCE OF DOSE AND ASSOCIATION WITH GENETIC LYMORPHISMS IN DNA DSB REPAIR GENES

* Kim De Ruyck, Ph.D.,* Frédéric Duprez, M.D.,† Liv Veldeman, M.D.,†

Radiotherapy and Oncology 99 (2011) 356–361

ELSEVIER

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Clinical radiobiology

Association between single nucleotide polymorphisms in the XRCC1 and RAD51 genes and clinical radiosensitivity in head and neck cancer

Nicola Pratesi [a], Monica Mangoni [b,*], Irene Mancini [a], Fabiola Paiar [b], Lisa Simi [a], Lorenzo Livi [b], Sara Cassani [b], Michela Buglione [c], Salvatore Grisanti [d], Camillo Almici [e], Caterina Polli [f], Calogero Saieva [g],

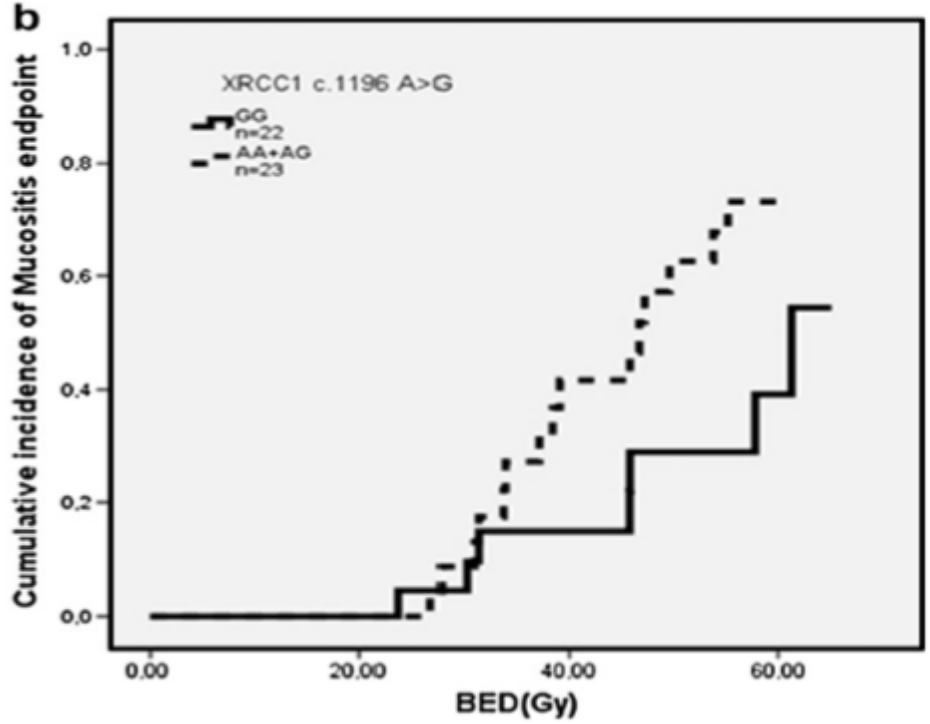
Patient-related CFs

- Genetic factors

Table 5. Multivariate analysis for CAT and NBN polymorphisms with radiation-induced oral mucositis in presence of alcohol among head and neck cancer patients.

Gene name	Genotype	Oral mucositis ≤2 (n = 66)	Oral mucositis >2 (n = 54)	Adjusted Odds ratio	95% CI	p- value
CAT (rs7943316)	TT	21	25	Reference		
	TA	39	21	0.463	0.199–1.076	0.074
	AA	6	8	1.675	0.427–6.575	0.460
NBN (rs1805794)	GG	24	16	Reference		
	CG	36	23	1.275	0.531–3.062	0.587
	CC	6	15	4.728	1.384–16.151	**0.013**

Patient-related CFs



The risk of mucositis was significantly increased in patients with XRCC1-399Gln allele genotypes both in chemo-radiotherapy ($p = 0.035$, HR = 1.72, CI = 1.03–2.86) and in radiotherapy alone ($p = 0.049$, HR= 2.50, CI = 0.97–6.47) groups.

Patient-related CFs

- Genetic factors

→ Identifying the genetic profiles associated with an enhanced or reduced risk for OM could be an important issue in assessing potentially confounding factors

→ However, large variability, conflicting results

→ Looking for rare alterations with high effects or more frequent ones with small effects?

Treatment-related CFs

- Radiation

Clinical Oncology 28 (2016) e216–e219

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Short Report

Does Dose to an Oral Mucosa Organ at Risk Predict the Duration of Grade 3 Mucositis after Intensity-modulated Radiotherapy for Oropharyngeal Cancer?

S. Yahya *, H. Benghiat *, P. Nightingale †, M. Tiffan

Clinical Oncology 29 (2017) 263–273

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

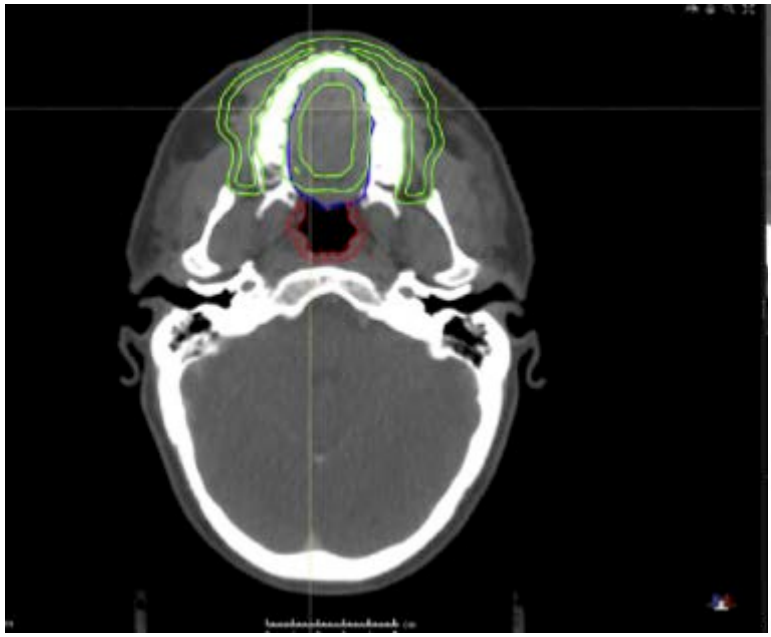
Original Article

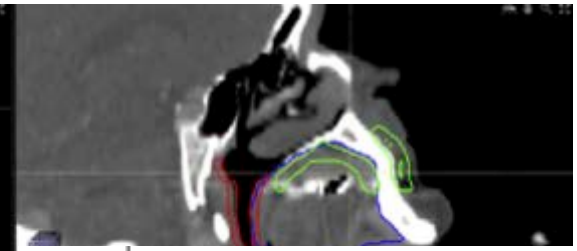
Normal Tissue Complication Probability (NTCP) Modelling of Severe Acute Mucositis using a Novel Oral Mucosal Surface Organ at Risk

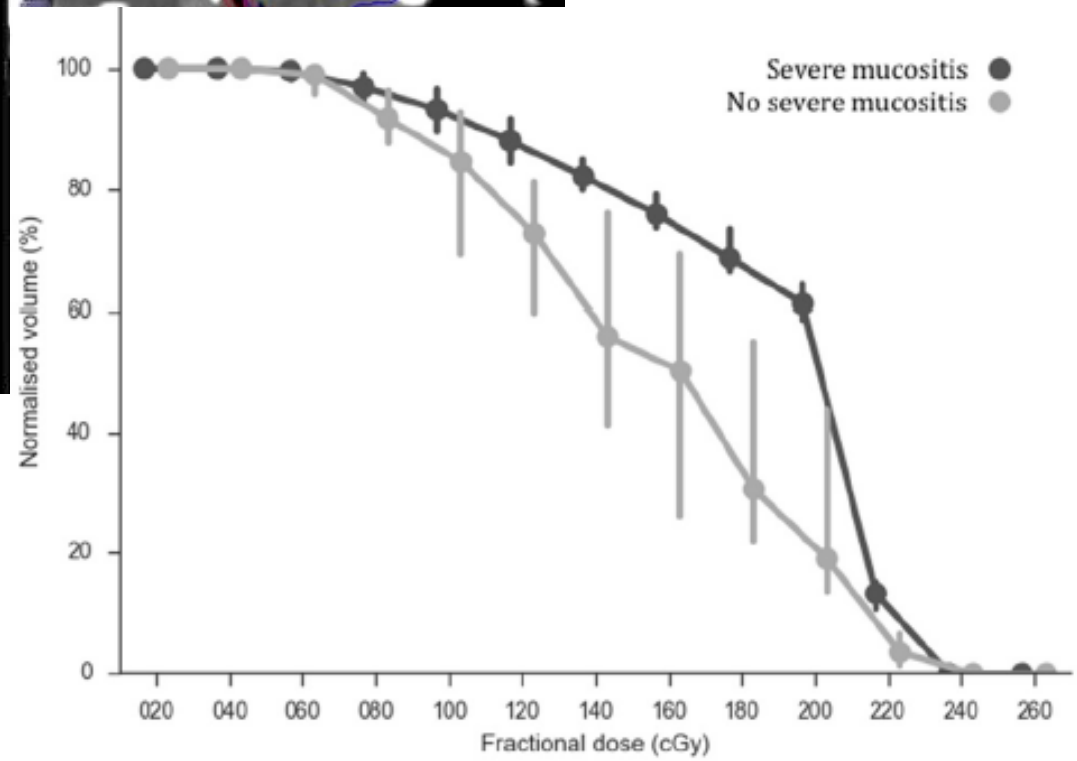
J.A. Dean *, L.C. Welsh †, K.H. Wong †, A. Aleksic †, E. Dunne †, M.R. Islam †, A. Patel †,

Treatment-related CFs

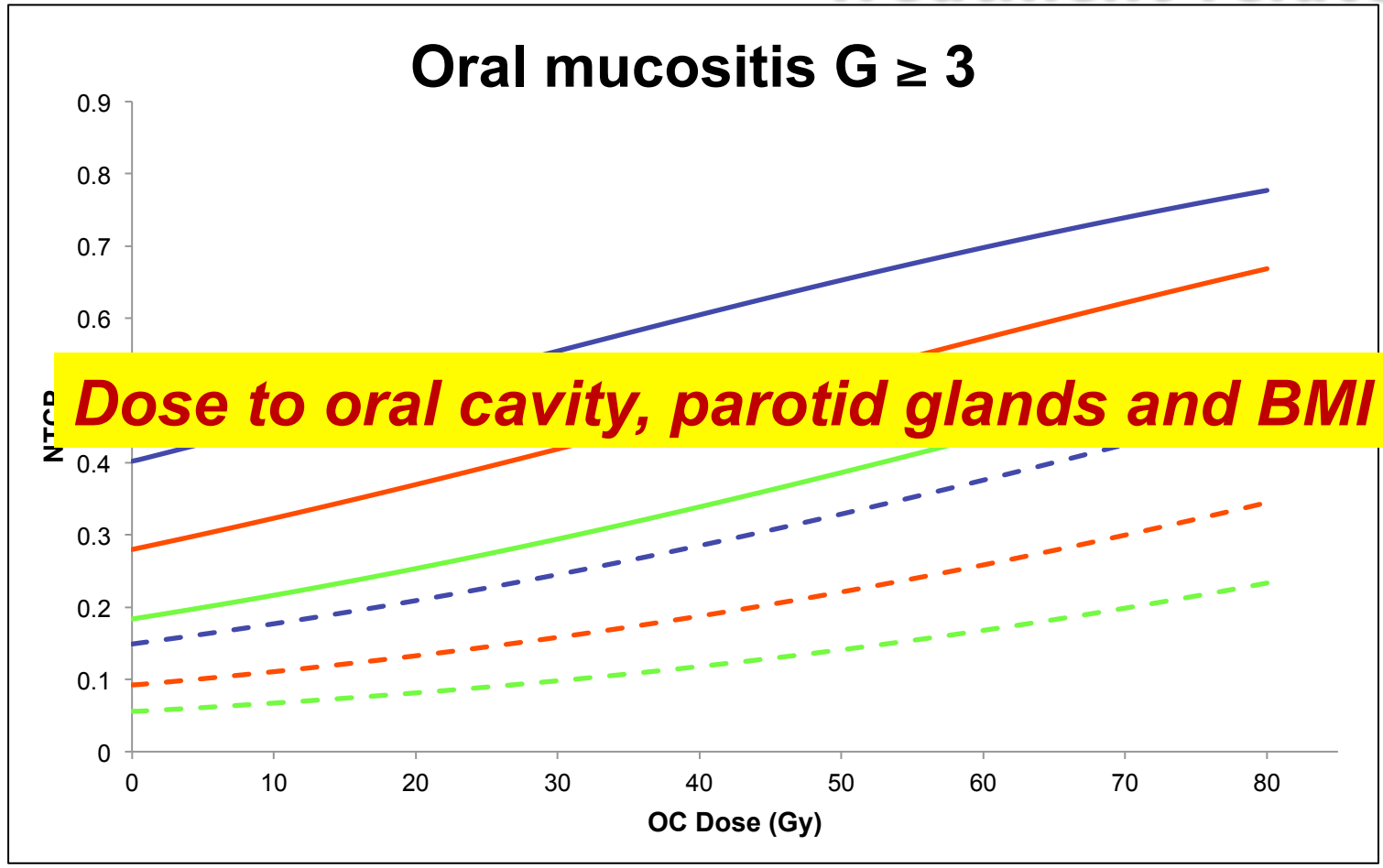
- Radiation







Treatment-related CFs



Dose to oral cavity, parotid glands and BMI

Probability of Grade ≥3 acute oral mucositis as a function of dose to OC, dose to combined (c)PG and BMI.

Orlandi , Canceropole Meeting, 2017

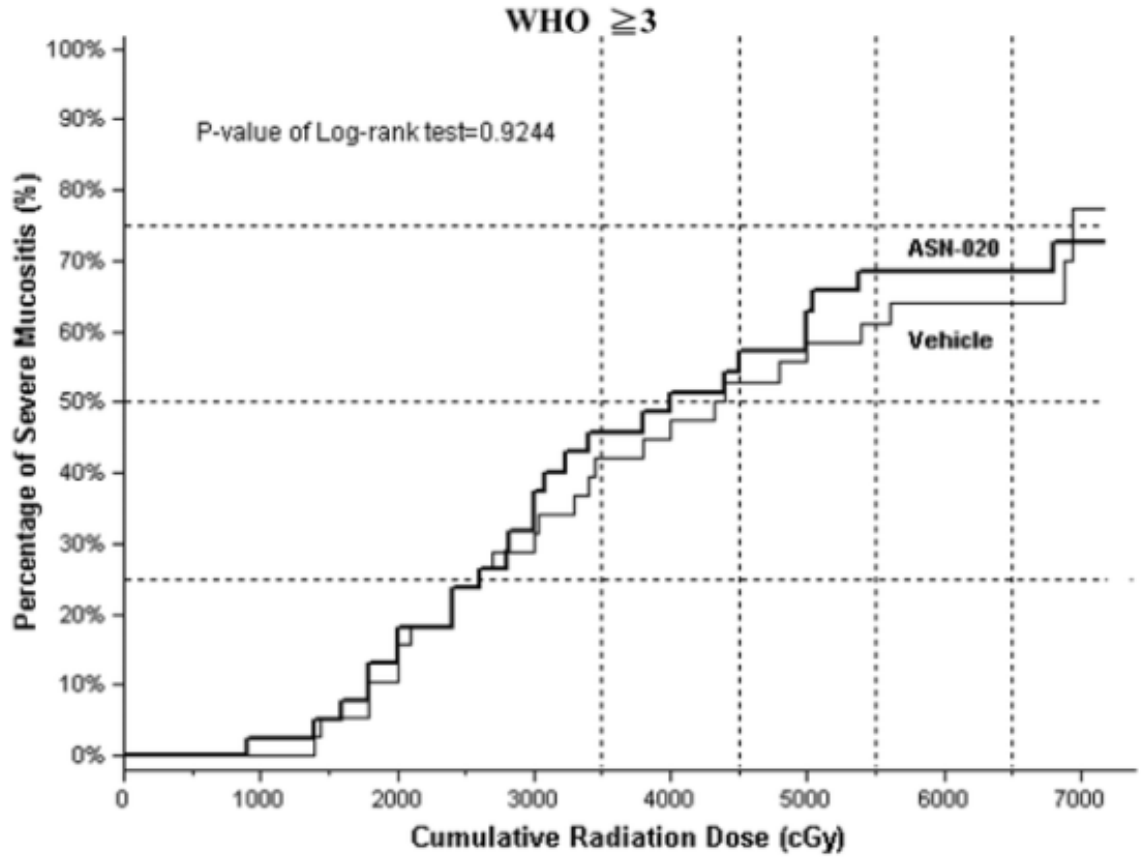
Treatment-related CFs

- Treatment interruption

- Ex: clinical trial for prevention of OM with 5% phenylbutyrate mouthwash (ASN-020), vs placebo in patients with HNC on CCRT
- Main endpoint: OM assessed by physicians or pts

Treatment-related CFs

Figure S1. Physician-rated cumulative incidence of severe mucositis World Health Organization (WHO) grade ≥ 3 (A) and Oral Mucositis Assessment Scale (OMAS) ≥ 2 (B).



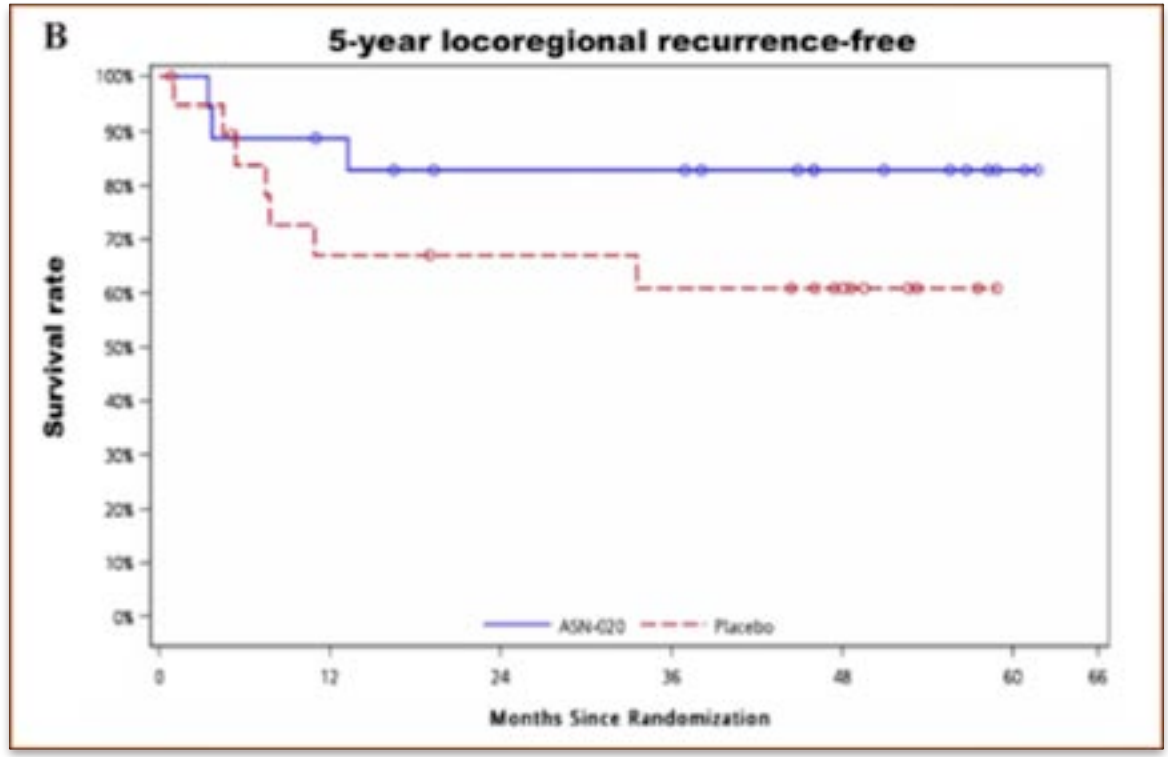
Treatment-related CFs

- However, more patients in the placebo group deviated from the treatment plan, in the form of **multiple, unplanned, short breaks from RT** after 30 Gy.
- No difference in Tx interruption between the two arms of the original study was initially detected as the protocol considered interruption "any stop > 7 days"!!!

Treatment-related CFs

Cumulative RT breaks ≥5 days, WHO ≥2, OMAS (ulcerative score at the worst site) ≥2

Cohorts	ASN-020		Placebo	*p* value
ITT[a]	5% (2/40)	≠	35.0% (14/40)	0.0015
Modified ITT[b]	5.4% (2/37)		36.8% (14/38)	0.0014
PP[c]	9.5% (2/21)		44.0% (11/25)	0.0194
Modified PP[d]	7.1% (2/28)		36.4% (12/33)	0.0068



Disease-related CFs

- The role of HPV pos vs HPV neg cancer

Oral Oncol. 2014 September ; 50(9): 869–876. doi:10.1016/j.oraloncology.2014.06.010.

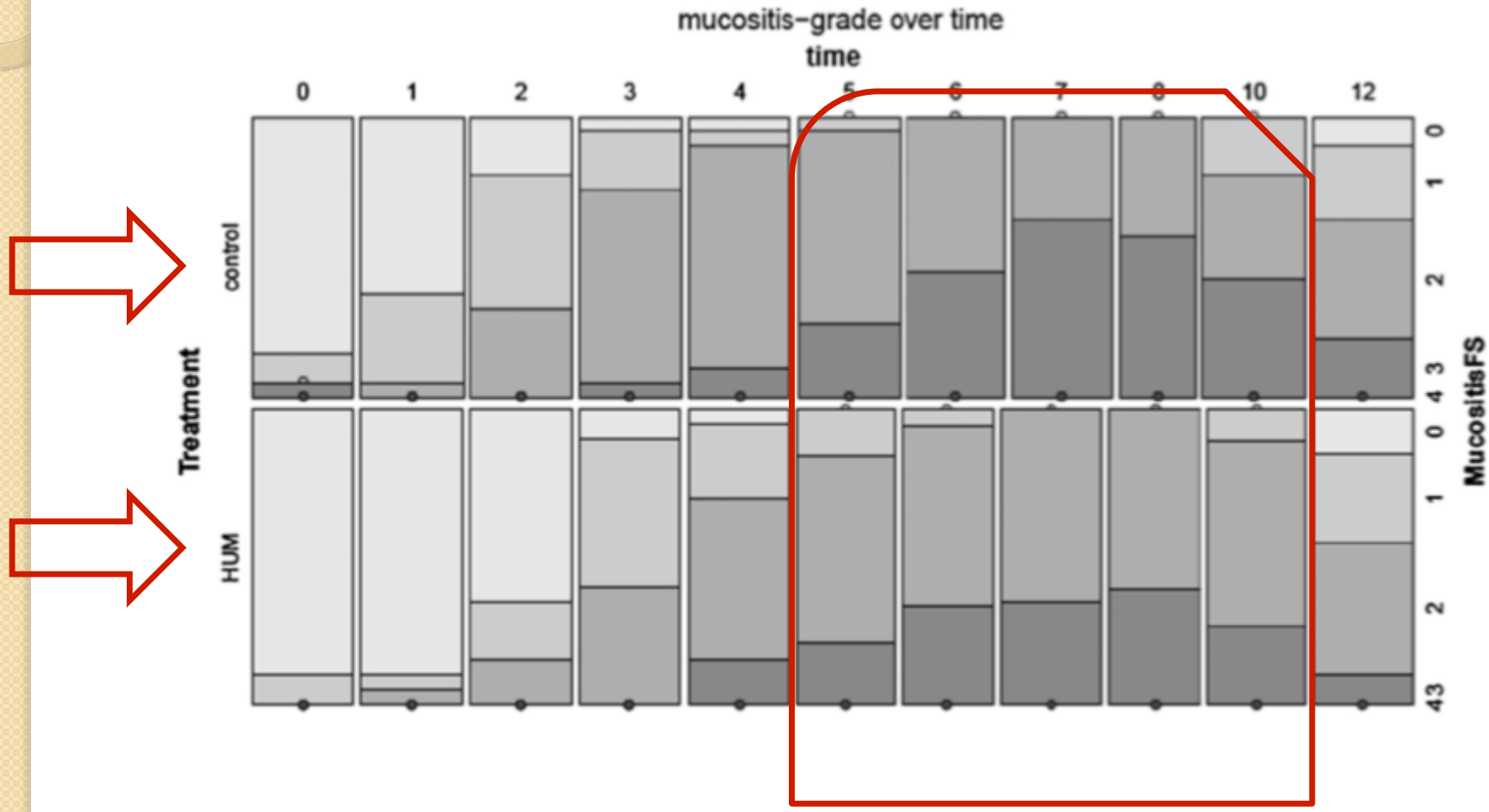
Retrospective analysis of the impact of HPV status and smoking on mucositis in patients with oropharyngeal squamous cell carcinoma treated with concurrent chemotherapy and radiotherapy

M. Vatca[a,e], J.T. Lucas Jr.[b], J. Laudadio[c,1], R.B. D'Agostino[d,e], J.D. Waltonen[e,f], C.A.

HPV-positive *patients had a 6.86-fold increase in the risk of having severe, grade 3–4 mucositis.*
This effect was preserved after adjusting for patient smoking status, nodal stage, RT technique and RT maximum dose

Just to complicate… environmental factors!

- Humidification!



What about the next future?

- Tailoring the risk on microbioma?

EBioMedicine 18 (2017) 23–31

Contents lists available at ScienceDirect

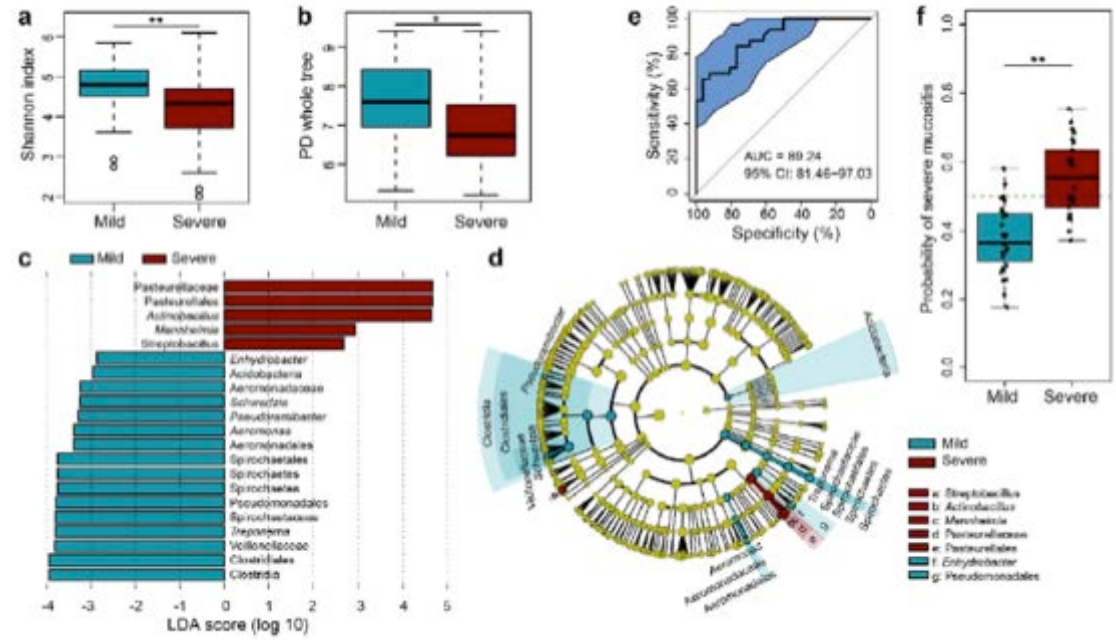
EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

The Potential Effect of Oral Microbiota in the Prediction of Mucositis During Radiotherapy for Nasopharyngeal Carcinoma

Xiao-Xia Zhu [a,1], Xiao-Jun Yang [b,1], Yi-Lan Chao [a], Hui-Min Zheng [c], Hua-Fang Sheng [c], Hai-Yue Liu [c],



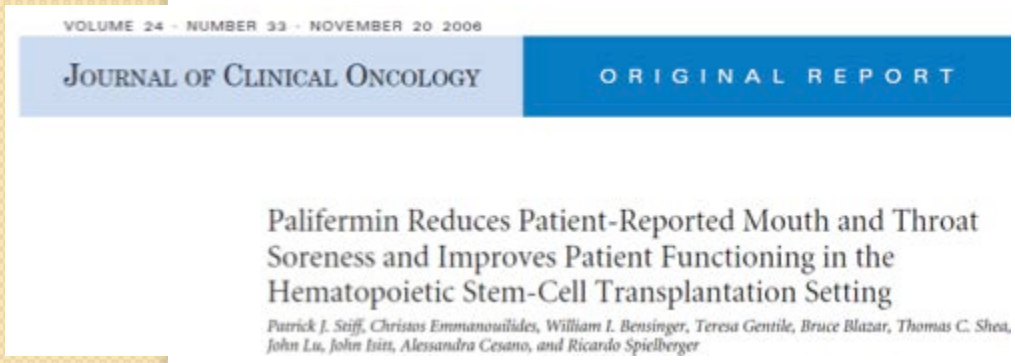
Comparison of bacterial diversity of oropharyngeal samples from the mild and severe subgroups at the phase of RTOG 1–2 OM

Confounding factors in methods of OM assessment: PRO vs Phys assessed

The case of palifermin and the value of PRO:

hematopoietic stem-cell transplantation

head and neck cancer



VOLUME 24 · NUMBER 33 · NOVEMBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Palifermin Reduces Patient-Reported Mouth and Throat Soreness and Improves Patient Functioning in the Hematopoietic Stem-Cell Transplantation Setting

Patrick J. Stiff, Christos Emmanouilides, William I. Bensinger, Teresa Gentile, Bruce Blazar, Thomas C. Shea, John Lu, John Isitt, Alessandra Cesano, and Ricardo Spielberger

VOLUME 29 · NUMBER 20 · JULY 10 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Palifermin Reduces Severe Mucositis in Definitive Chemoradiotherapy of Locally Advanced Head and Neck Cancer: A Randomized, Placebo-Controlled Study

VOLUME 29 · NUMBER 20 · JULY 10 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Palifermin Decreases Severe Oral Mucositis of Patients Undergoing Postoperative Radiochemotherapy for Head and Neck Cancer: A Randomized, Placebo-Controlled Trial

Both trials were positive according to physician-assessed mucositis

hematopoietic stem-cell transplantation

head and neck cancer

Palifermin significantly reduced the intensity and duration of WHO grade 3 and 4 mucositis in respect to placebo

A different result was obtained when employing PRO (OMDQ or OMWQ)

hematopoietic stem-cell transplantation

The OMDQ was able to detect a statistically significant improvement of patient self-reported MTS

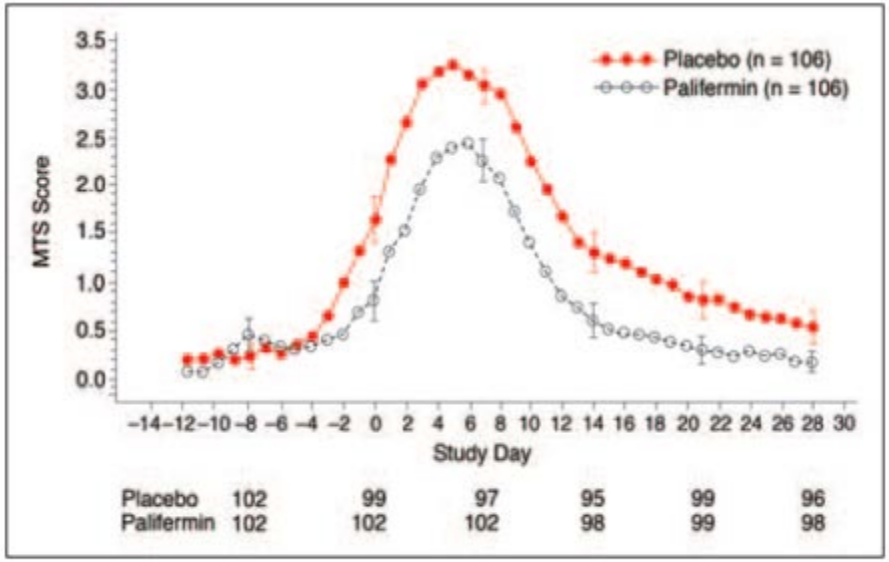
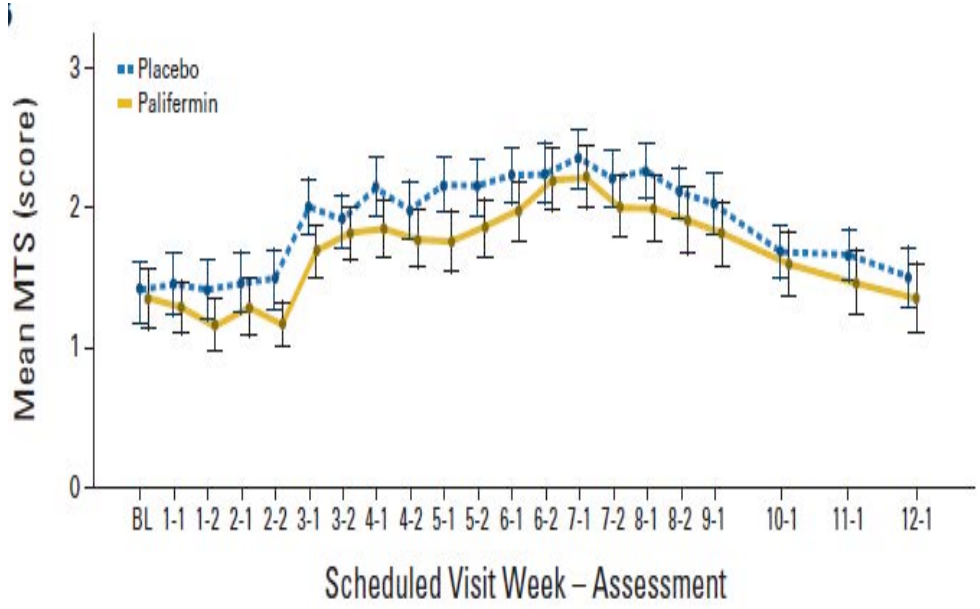


Fig 4. Mouth and throat soreness (MTS) scores (placebo *v* palifermin). Vertical lines represent 95% CIs.

head and neck cancer

The benefit of palifermin in physician-assessed mucositis was not paralleled by a better patient-reported outcome



Solutions

- Trying to correct the analyses for as many CFs as possible (tailored to the kind of disease and studied treatment approach)
- Building a comprehensive prognostic model to help stratyfing pts at baseline
- Adopting PRO instruments of assessment as well as physician-assessed

Thanks for your attention!

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