Impact of cachexia and malnutrition on **cancer treatment decisions**:

- Adapt dosing of anticancer treatment
- Anticancer treatment to improve cachexia

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Musclemass (Sarcopenia) is associated with more toxicity, poorer OAS & poor QoL

Oncologist «promise» anticancer treatment improves cancer-related symptoms

1 Case challenge of anticancer treatment and palliative interventions patient value based

7 Facts

Sarcopenia	→ OAS	→ Tox
Anticancer Tx	→ Muscle	→ S-NIS
	→ Goals	→ RR & QoL
	→ Cachexia	

3 Questions and state-of-the-art answers

. Dose reduction in SP because of worse OAS?
. Dose reduction in SP preventing toxicity?
. How give anticancer treatment in cachexia?

Ms V, Italian, mid fifties; no comorbidities, BMI 32

2/2014	Locally advanced, non-operable pancreatic corpus Adenocarcinoma, pT4 cN0 (0/2), cM0; biliodigestive Anastomosis Roux-Y
4-9/14	6 x FOLFIRINOX, PR; wait; 5/15 CT PR; 6/15 PD
9-9/15	6 x FOLFIRINOX, PR, Hepatosteatosis
9-11/15	4 x FOLFIRINOX, PD primary Tumor under Chemo well tolerated, minimal fatigue, no febrile NP
12/15-3/16	3 x Gem/nab-Paclit., PT 9→3 cm^2, liver met 1→3
3/16-5/16	3 x Gem/nab-Paclit., PT 3.2 cm^2, liver multiple PD adequately tolerated, fatigue

CA19-9 8.4.16: 28, 22.4.: 56, 20.5.: 145, 31.5.: 356

PDL1-Expression membranous <1%, DNA mismatch repair preserved

→ ***Palliative Oncology referral in refractory disease***

5-6/2016 5 Visits Palliative Oncology Outpat in 4 weeks; CA19-9 7.6. 544, 14.6. 702

Pain 6/10, Fatigue 7/10 (emotional, physical), Anorexia 8/10, Nausa 2/10, Anxiety 2/10, Depression 4/10, no breathlessness

Pain syndrome abdominal (6/10), no risk factors, eating-related
→ Increasing doses Oxycodone/Naloxone, Oxyc, Novamin

Cachexia, weight loss 8%/5 mts, anorexia (8/10), no dysgeusia, early satiety, minimal nausea, CRP 12, Alb 32
→ combination laxatives, prokinetics, education eating

Illness- / prognosis-understanding moderate, unknow liver mets
→ education spectrum wks to many mts, pat wants «all» if QOL

Preparation for end-of-life
→ Legacy work, finish business, living will, testament
→ marriage daughter in 7/16 italy, family important

What would you do next? 6/2016 PS1

6/2016 St.Gallen no Phase I option, consider capec/gem
Second opinion Zurich: consider nal-Iri, SIRT

23.6. FOLFIRINOX, cachexia & inflammation-adapted dose
Physical activity & strenght training, protein-rich food

5./18.7. FOLFIRNIOX, 14.7. Opioid stop, CA 19-9 412, CINP 1

20.7.-7.8. Marriage in Italy, dancing, eating; 8.8. CA19-9 215
8./24.8. FOLFIRINOX (#20/21), G1 Fatigue, Tc nadir 59
5.9. CA19-9 582, CT PT SD, liver PD, LN retrop PD; PS1

7.9. Discussion phase I (SAKK 67/15), required 1 mts wait
13.9. New pain cevical, CA 19-9 856, MRI Clivus metastasis
21.9-6.10. Radiotherapy Skull Base 12x3 Gy. CA 19-9 7400

12.10. More pain, Oxycodone/Naloxone 40, Pregabaline 50, Dexamethasone 4mg
PS 2, 9% weight loss in 1 month, Fatigue, if Dexam reduced 2mg → Pain
Good illness understanding, PS2.

What shall we do? Will symptoms improve again with Chemo?

13.10. FOLFIRINOX (4000/600, 200, 100), CA19-9 7400>4680
Fatigue G2 day 4-9, CINP G1, sweating better

27.10. FOLFIRINOX (Dose Reduction: 3500/500, 100, 50), CA19-9 7520>9830
11.11. FOLFIRINOX (4000/700, 250, 160), CA199 13100>5130

25.11. no opioids, 1 mg Dex, weight stable (min. edema), PS1
CINP G1, Tc 53, Bili 21; 4 KCL → aldosterone 25mg;
Pat wants celebrate family christmas → wants chemo

25.11. FOLFIRINOX (4000/700, 280, 100) CA199 6650>3700

1.-10.12. Hospital for Cholangitis, Gc nadir 2.9, Tc 39; Liver diffuse metas, Bili 94, Antibiotics, Ascites punction, no opioids

14.12. outpat, KPS 50, pain abdominal right, Bili 117, CRP 84
CA19-9 11400; Ciproflox/Metronidazol. Fenta td 12mcg
alert, clear, wants again anticancer treatment (helped), Fatigue 9/10
Husband, daughter prepared both for death & christmas

15.12. FOLFIRINOX (#26) (3000/500, 140, 100)

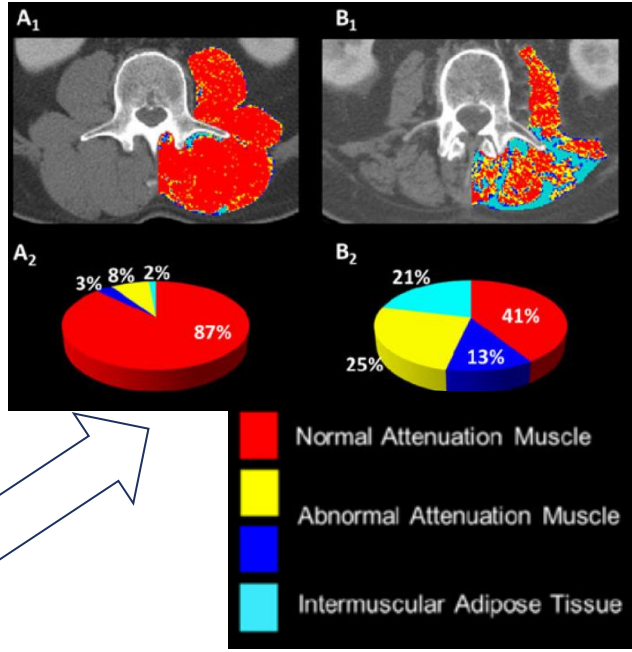
20.12. Hospitalisation Pain abdominal, weakness
Ascites 2000ml (relief), Dexamethasone (no relief)
hepatorenal syndrome (Bili 222, Crea-Cl 36), worsening
CRP 77 → 51, CA 19-9 11’400 → 3200 (day 8)
no neutropenia, no bleeding

23.12. Family from Italy (mother, brother) visit dying patient
24.12. Psychooncology support for family
26.12. Patient dies peacefully with family members around

Would we (who is we?) do this same management again?	YES / NO
Was this aggressive End-of-Life Care?	YES / NO
Was this Patient-Centered Integrated Oncology & Palliative Care ?	YES / NO
Palliative Oncology (double boarded)?	YES / NO

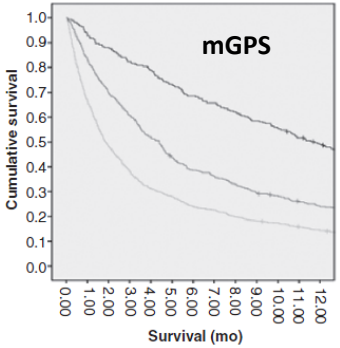
Impact on Survival

- **P**erformance **S**tatus (abundant data, various tumors)
- **Weight Loss** abundant data[1](mixed with starvation)
- **Weight loss & BMI**[2] (BMI: available reserves)
- Low **MiniNutrAss**[3] (intake, WL, mobil, psych, Di, BMI)
- **Muscle mass** (SarcoPenia)[4]
- **Muscle Attenuation**[4] (catabolism, hypo-anabolism)
- **Inflammation** (CRP) & Albumin[5] / Lymphocytes[6]



- $\text{CRP} \leq 10\text{mg/L} = 0$
- $\text{CRP} > 10\text{mg/L} = 1$
- $\text{CRP} > 10\text{mg/L and albumin} < 35\ \text{g/L} = 2$

***m**odified **G**lasgow **P**rognostic **S**core*[4]



More factors
. WL+SP+MA [4]
. WL+BMI+CRP [2]
→ worse OAS

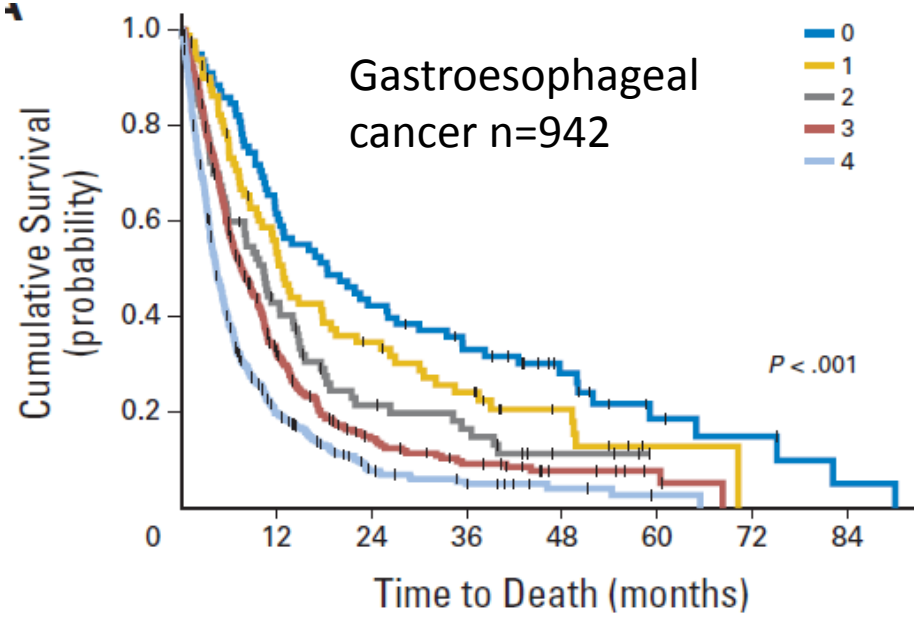
1: Bozzetti F Crit Rev HemOnc 2013;173 // 2: Martin L JCO 2015;90 // 3: Caillet P Clin Nutr 2016 Dec 18 // 4: Martin L JCO 2013;1539 // 5: Laird BJ Clin Cancer Res 2013;5456 // 6:Jafri BMC Cancer 2013;158

Cancer-Associated Weight Loss: Survival, Grading System

Weight Loss (%) \ BMI (kg/m²)	28	25	22	20
2.5	0	0	1	1	3
6	1	2	2	2	3
11	2	3	3	3	4
15	3	3	3	4	4
	3	4	4	4	4

Weight Loss (%) \ BMI (kg/m²)	28	25	22	20		
2.5	21.5	19.9	15.7	13.5	8.4	17.3
6	14.2	11.9	10.5	10.6	7.8	11.3
11	10.7	9.2	6.8	6.7	4.7	7.5
15	8.1	8.1	6.2	5.4	4.4	6.2
	7.1	4.8	4.7	3.7	4.1	4.4
	13.1	10.2	8.1	6.1	4.7	Overall

8160 cancer pts, multivariable analysis (age, sex, cancer site, stage, PS). Independent validation sample 2963 pts
Survival mts depends both on WL% and BMI



Martin L et al. J Clin Oncol 2015;33:90-99

Skeletal muscle density (SMD) is an independent predictor of diffuse large B-cell lymphoma outcomes treated with rituximab-based chemoimmunotherapy

		Multivariate analysis		
	Variable	Hazard ratio	95% CI	*p*-Value
PFS	R-IPI score 1–2	1.29	0.29–5.75	0.74
	R-IPI score 3–5	4.20	0.98–17.88	0.05
	Sex, male	0.98	0.60–1.61	0.95
	Low SMD	1.56	0.90–2.71	0.11
OS	R-IPI score 1–2	2.18	0.28–16.74	0.45
	R-IPI score 3–5	6.26	0.84–46.4	0.07
	Sex, male	1.23	0.76–2.02	0.40
	Low SMD	2.52	1.40–4.54	0.002

In DLBCL patients watch protein intake and physical function

May consider also early Pall Care
El Jawahri JCO 2016

Who are the patients?

R-IPI	
0	18 (8%)
1	44 (20%)
2	48 (21%)
3	58 (26%)
4	40 (18%)
5	16 (7%)

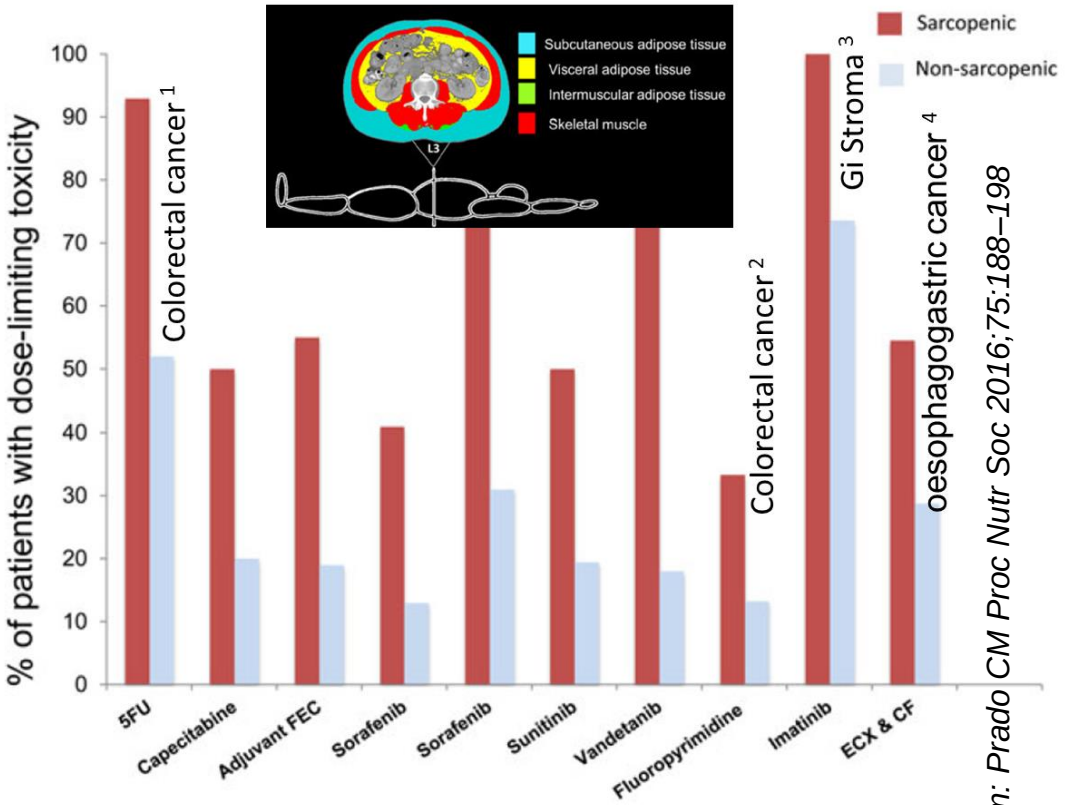
Complete response	168 (75%)
Partial response	41 (18%)
Stable disease	2 (0.1%)
Progressive disease	13 (6%)

Chu MP J Cachexia Sarcopenia Muscle 2016 Nov 21

F2 Sarcopenia → Toxicity

Sarcopenia is associated with anticancer tx toxicity and perioperative complications

Amini N J GI Surg 2015; **19**: 1593-1602
Wagner D World J GI Surg 2016; 8: 27-40



Graph from: Prado CM Proc Nutr Soc 2016;75:188–198

1: Prado CM et al. Clin Cancer Res 2007;13,3264–8
2: Barret M et al. Nutr Cancer 2014;66: 583–9
3: Moryoussef F et al. JCSM 2015;6,343–50
4: Tan BH et al. Eur J Surg Oncol 2015; 41, 333–8

Why is this association?

- Pharmacokinetics ?
- Inflammation (hepatic fct)?
- other cachexia mediators?

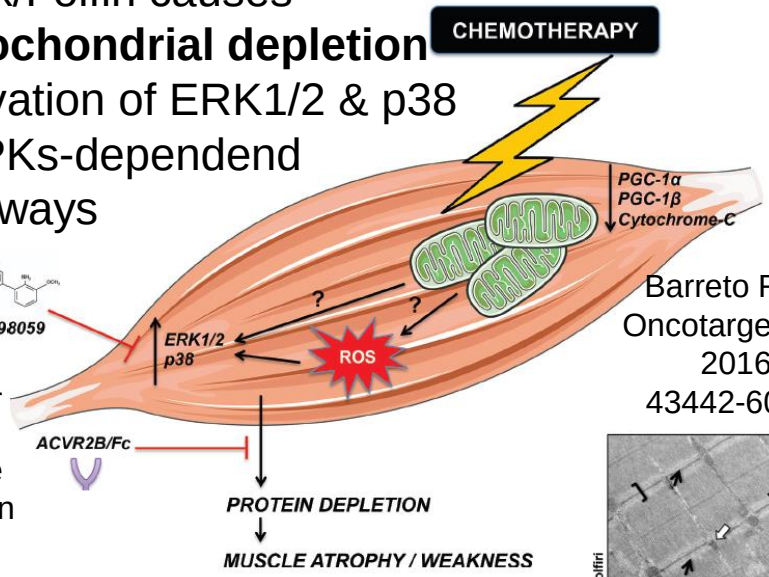
Another example (of many):

84 NSCLC pts afatinib
(55% 2nd, 38% 3rd, 7% 4th line)
G3/4 diarrhea 39%, mucositis 29%, overall GI-Tox 56%
Lower LBM & BMI: DLT 71% vs 19%

Arrieta O Oncologist 2015;20:967-74

F3 Anticancer treatment → Impact on Muscle

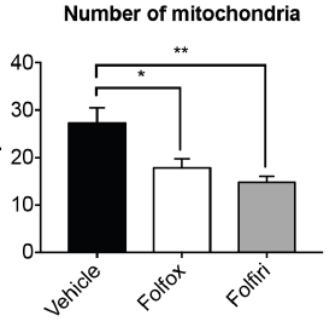
Folfox/Folfiri causes
. **mitochondrial depletion**
. activation of ERK1/2 & p38 MAPKs-dependend pathways

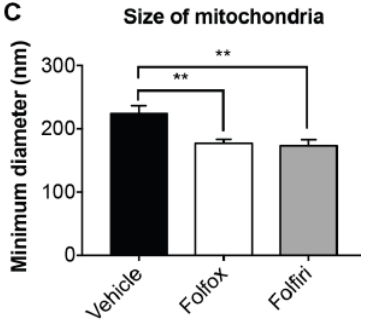


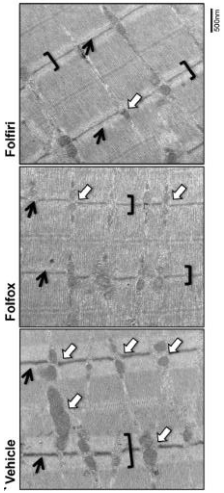
MEK-1 Inhibitor

Soluble Activinin Rec 2B

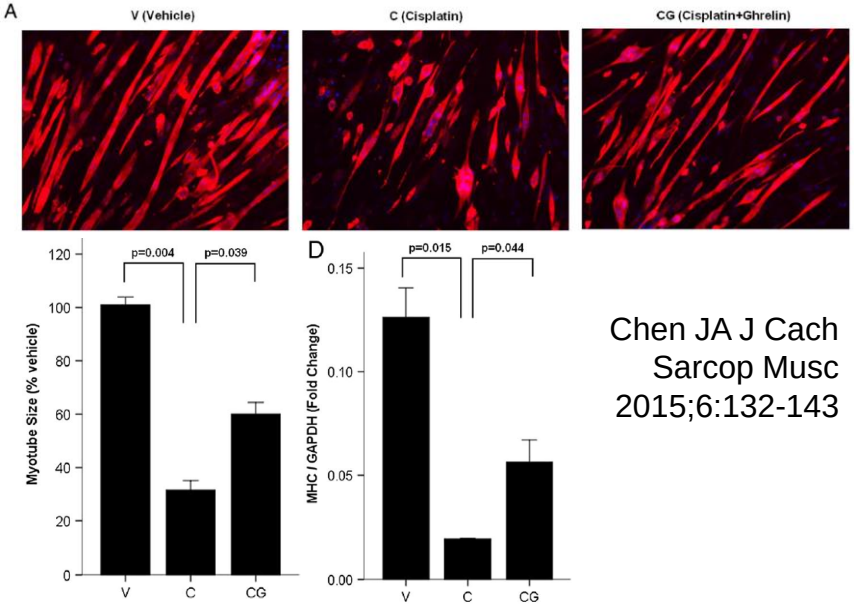
Barreto R Oncotarget 2016; 43442-60







Cisplatin (& tumor) causes muscle atrophy
. downregulate **Akt**, **myoD**, myogenin
. upregulate **proteolysis** (UbP), **Myostatin**
. Ghrelin may partially reverse effects



Chen JA J Cach Sarcop Musc 2015;6:132-143

Chemo → **inflammation, oxidative stress**

Sultani M Chemother Res Pract 2012;490804
Chen JA J Cach Sarcop Musc 2015;6:132-143

Muscle wasting associated with the long-term use of mTOR inhibitors

Drug use	
Everolimus alone	12
Temsirolimus alone	8
Disease	
Renal cell carcinoma	18
Pancreatic neuroendocrine tumor	2
Gender	
Male	16
Female	4
Age in years (median)	65.5 (45-83)
Duration of therapy in months (mean)	14.1±2.1
CT interval in months (mean)	14.4±2.0
Baseline BMI category (kg/m^2)	
Normal (18.5-24.9)	13
Underweight (<18.5)	5
Overweight (25.0-29.9)	2

Parameter	Prior to the start of the treatment	Following at least 6 months of treatment	95% confidence interval	P-value
Body weight (kg)	55.5	54.4	-2.9 to 0.8	0.262
SAT index (cm^2/m^2)	35.1	36.4	-6.3 to 8.8	0.722
VAT index (cm^2/m^2)	31.5	43.8	-0.2 to 24.7	0.053
TAT index (cm^2/m^2)	66.6	80.2	-6.0 to 33.1	0.163
SMT area at (cm^2)	137.3	124.6	-22.0 to -3.3	0.011[a]
SMI (cm^2/m^2)	50.2	43.8	-11.7 to -1.0	0.022[a]
Lean body mass (kg)	47.2	43.1	-6.9 to -1.3	0.007[a]
Serum albumin (g/dl)	3.7	3.5	-0.6 to 0.0	0.091
CRP (mg/dl)	2.8	5.3	-0.6 to 5.5	0.105

SMT skeletal muscle tissue; SMI: SM index (corrected for hight)

Also data for sorafenib: promote muscle wasting (8% in 12 mts) by proteolytic systems

Toledo M J Cach Sarcop Musc 2016;7:48-59
Antoun S et al. J Clin Oncol 2010;28:1054-60

→ Indication for monitoring protein intake, physical activity

Gywali B Molec Clin Oncol 2016;5:641-6

F4 Anticancer treatment
→ causing Secondary Nutrition Impact Symptoms

Anticancer treatments can cause a lot of secondary nutrition impact symptoms, these data are not well reported, but clinical reality

- Stomatitis, Xerostomia, Taste alterations
- Nausea/vomiting, stomach pain
- GI mucositis, Diarrhea, Constipation
- Endocrine abnormalities, etc,

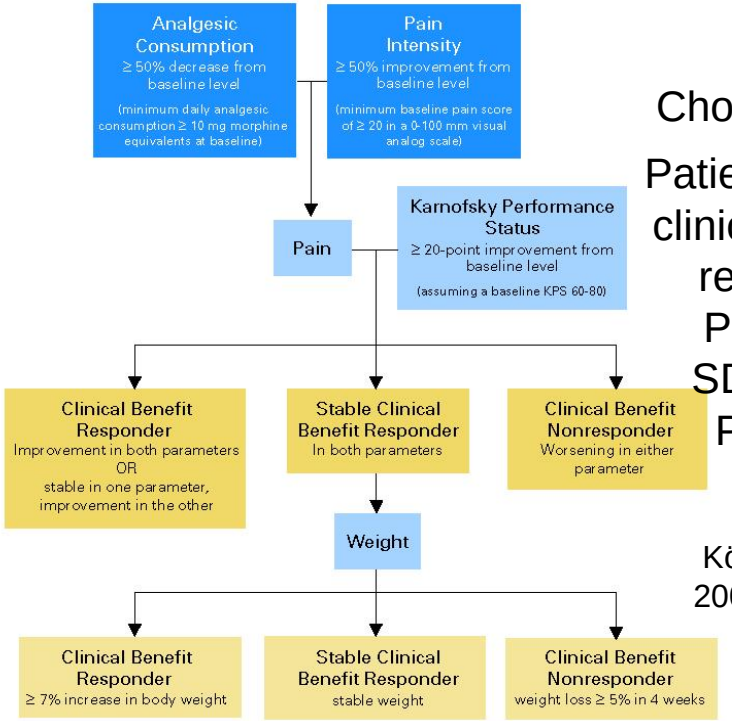
Systematic review (Medline 2005-16: n=24)

Chemotherapy-related digestive symptoms likely to impair nutritional status:
dry mouth, nausea/vomiting, stomach pain, diarrhea and constipation

Caillet P Clin Nutr 2016 Dec 18

F5 Anticancer treatment
→ explicit goals to improve cancer-related symptoms

Clinical trials with primary endpoint cancer-related symptoms & syndromes are still rare



Cholangio-Ca

Patient-derived clinical benefit response
PR: 7/10
SD: 16/24
PD: 2/5

Köberle D JCO 2008;26:3702-8

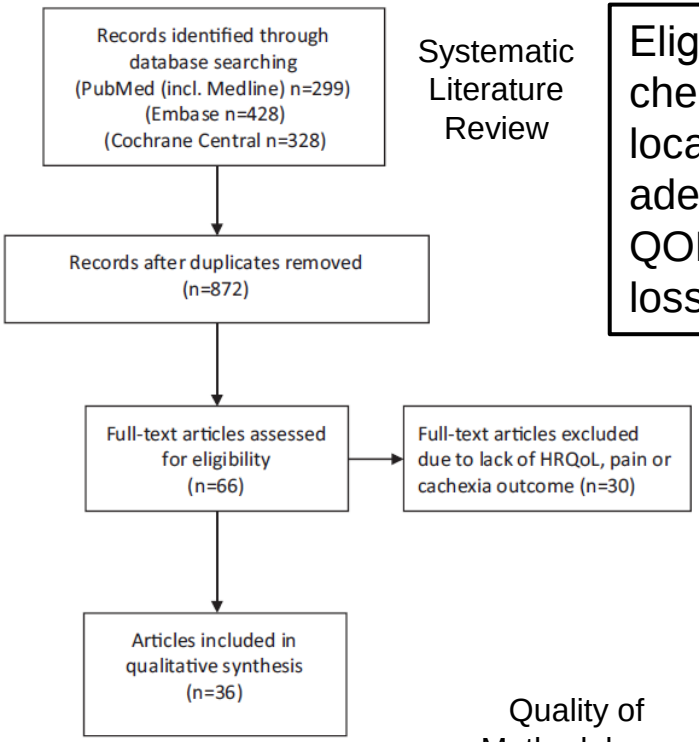
Tumor-Response and Symptom-Alleviation
example: Lung cancer (Cisplatin & Vindesin vs Gemcitabine)

	Response ($N = 34$)			Stable disease ($N = 44$)			Progression/non eval ($N = 91$)[a]		
	N_{eval}	N_{impr}	PR	N_{eval}	N_{impr}	SD	N_{eval}	N_{impr}	PD
Cough	33	22 (67%)		39	24 (62%)		57	13 (23%)	
Dyspnea	31	17 (55%)		35	20 (57%)		64	13 (20%)	
Pain	26	13 (50%)		34	19 (56%)		57	15 (26%)	
Haemoptysis	19	13 (68%)		24	18 (75%)		30	10 (33%)	
Anorexia	34	20 (59%)		44	17 (39%)		68	11 (16%)	
Fatigue	34	17 (50%)		43	17 (40%)		66	7 (11%)	
Overall symptom control	32	19 (59%)		40	22 (55%)		62	14 (23%)	
Normal daily activities	32	15 (47%)		40	16 (40%)		45	2 (4%)	
Overall quality-of-life	32	13 (41%)		40	16 (40%)		42	1 (2%)	
Symptoms better		41-67%			39-62%			2-23%	

→ Individual improvement of symptoms despite tumor-growth
→ Symptom deterioration despite tumorshrinking

Vansteenkiste J
Lung Cancer
2003;40:191-9

7 Anticancer treatment → improvement of Cancer Cachexia



Systematic Literature Review

Eligible: ≥18y; RCT n ≥ 100; chemotherapy or targeted therapy; locally adv or met **pancreatic** adenocarcinoma; patient-reported QOL, pain or cachexia (weight loss) as endpoints

Eight studies reported on weight change, data were inadequately reported. No studies significant differences in favor of one treatment arm.

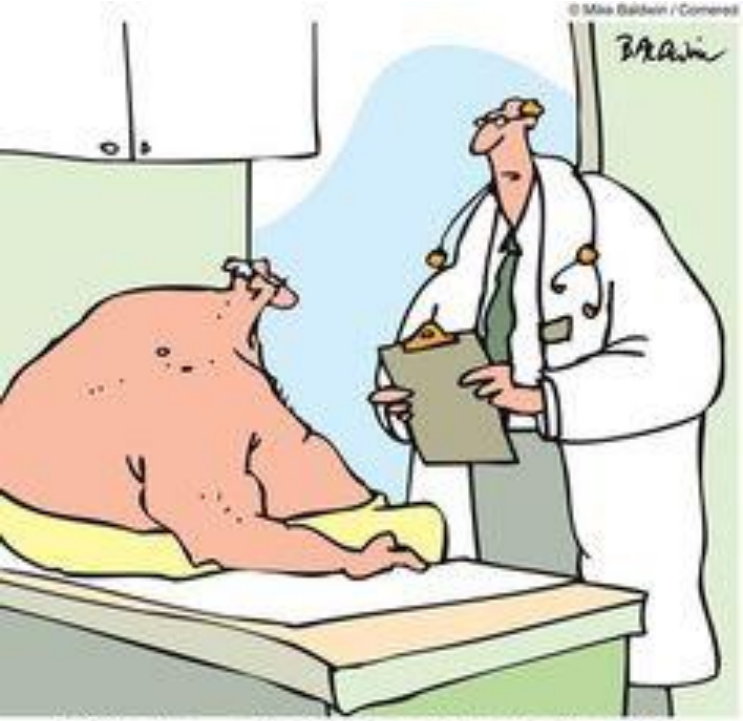
Health-related quality of life issue	
Conceptual	
A priori hypothesis stated	5 (22%)
Rationale for instrument reported	5 (22%)
Measurement	
Psychometric properties reported	23 (100%)
Cultural validity verified	23 (100%)
Adequacy of domains covered	23 (100%)
Methodology	
Instrument administration reporte	7 (30%)
Baseline compliance reported	12 (52%)
Timing of assessments documente	23 (100%)
Missing data documented	19 (83%)
Interpretation	
Clinical significance addressed	8 (35%)
Presentation of results in general	16 (70%)

Quality of Methodology: moderate

Kristensen A Crit Rev Onc/Hemat 2016;99:286–298

"The effect on cachexia (weight loss) was rarely and inadequately evaluated, and cannot be determined from the current literature"

→ May be true for other tumor types



"You've got six months, but with aggressive treatment we can help make that seem much longer."

Musclemass (Sarcopenia) is associated with more toxicity, poorer OAS & poor QoL

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Sarcopenia	→ OAS	→ Tox
Anticancer Tx	→ Muscle	→ S-NIS
	→ Goals	→ RR & QoL
	→ Cachexia	

3 Questions and state-of-the-art answers

. Dose reduction in SP because of worse OAS?

. Dose reduction in SP preventing toxicity?

. How give anticancer treatment in cachexia?

Dose reduction (DR): paucity of data

[1] 12'472 pts 2012, **10% DR <60d start.** 15-17% taxanes & cDDP, 11% 5-FU, 7% Capecit.

[2] (Neo-) adjuvant breast cancer tx (n=123). **40%** needed **DR** (73.4% [68-94], **17% for CINP**. Risk fct: diabetes, african-amer, paclitaxel.

[3] 86 pts DLBCL ≥ 6 x R-CHOP. Relativ avg dose **intensity** (±85%) 2y **OAS** 67% vs 93%, p=.011

[4] **Primary DR** in 500 pts (73y [**65-91**]; 36% curative) **15%** curative, **25%** palliative chemotx (p=.005). Factors: age, pall only: comorbidity (cancer, liver/kidney), NOT KPS.

[5] 55/76 mNSCLC pts erlotinib skin rash ≥G2, retrospective Data. **24 DR vs 31 no DR. PFS** 341 vs 70, **OS** 566 vs 202 d (p<.001). DR: no smoker, female, EGFR mutated, G3 rash.

1: Casadei GA Oncotarget 2016;7:40719-24
2: Bhatnagar B Springerplus, 2014;3:366-72
3: Utsu Y Ann. Hematol 2016;95:41-7
4: Gajra A J Geriatr Oncol, 2015:6;133-40
5: Takashima, N Onkologie 2012;35:747-52

- DR seems to be performed *usually* in many patients responding to toxicity[1,2]
- DR in curative Tx: done *after* toxicity[2]
  → important to maintain Dose Intensity[3]
- DR may be *in-vivo* dose optimization[4]
  → toxicity as signal of individual effect, no impact on survival
- Primary DR
  - in older cancer pts due to Sarcopenia?
  - in palliative pts when co-morbidity
  -not performed according to KPS

Q1 Primary dose reduction in sarcopenic / cachectic patients if survival is the main goal?

- Currently not recommended, paucity of data (needs trials)

To do practically:

- Monitor weight (and edema), BMI, nutritional intake
- Monitor Symptoms (ESAS) and Toxicity
- Prescribe protein-rich food, maybe Oral Nutritional Supplements
- Prescribe Physical Activity and Strenght Training
- Educate Patient (and family)

Check ESPEN – Guidelines (Arends J et al. Clin Nutr 2016 Aug 6

Q2 Primary dose reduction in sarcopenic / cachectic patients if quality of life / minimizing toxicity is the main goal?

- In adjuvant settings currently not recommended, needs clinical trials
- In palliative intent anticancer treatment: consider secondary uptitration

. **age** *over-treatment risk*
64% elderly pts solid tumor: severe toxicity by polychemotherapy[1]
under-treatment risk
Advanced NSCLC el-pts less tx despite clear evidence (OAS, Sy)[2]

. **PS** PS3/4 NSCLC pts not recommended, but performed often[3]

. **CRP** may consider DR if CRP high and suspected hepatic dysfunction

. **CoM** Comorbidities, renal function (too low s-crea in sarcopenia)

1: Versteeg KS et al. Ann Oncol 2014:1914-8 // 2: Gridelli C Clin Lung Cancer 2015;16:325-33; Presley C Cancer J 2015;21:392-7; Quoix E Lancet 2011;378:1079-88; Kale MS Am JCO;2015 // 3: Tisnado D JOP 2016;**12**:653-62

Q3 How to give and monitor anticancer treatment in the sarcopenic / cachectic patient?

- Assess and treat malnutrition (S-NIS) before you start anticancer tx
- Assure patient & family member understanding of cachexia mechanism
- Careful decisonal process (session 1)
  - define expected effect (symptom, weight, function) as goal
  - prediscuss how to deal with toxicity & burden of anticancer treatment
- Prescribe physical function (2-3 x / week, 15min moderate) and strenght training (2-3 x/week, upper & lower extremity, 12 repetitions x 2 80% max)
- Every visit (weekly) check on nutritional intake, # meals, type of food
- Monitor proactively toxicity (session 1)
- Prevent toxicity: nausea/vomiting, mucositis, constipation, diarrhea
- Monitor effect (tumormarker if any, physical fct, symptoms, tumor size)

“You’ve come to the right place, Ms. Colburne. I specialize in futile treatment”

Take home

Assess always risk factors for toxicity: weight loss (& edema), low BMI, CRP/NLR, anorexia

Include in the decisional process of anticancer treatment clear, measurable goals and illness & prognosis understanding

May empower patients, if chemo, also physical activity and protein-rich food, but this is also a research question (MENAC)

Thank you

florian.strasser@kssg.ch